Original Article

The Prognostic Factors in Endometrial Cancers Treated with Radiotherapy: Retrospective Analysis

Radyoterapi Uygulanan Endometriyal Kanserlerinde Prognostik Faktörler: Retrospektif Analiz

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ABSTRACT

Introduction: Endometrial cancer is mostly diagnosed in the early stages and has a good prognosis. Surgery has main role in the treatment of patients with endometrial cancer and adjuvant radiotherapy (RT) is administered in certain risk groups. In this retrospective study, we analyzed the factors affecting the prognosis of patients with endometrial cancer who underwent RT.

Materials and methods: A total of 181 patients who were diagnosed with endometrial cancer were included in the study. Based on the prognostic factors, risk groups were recorded as low, intermediate, high-intermediate, high risk, and advanced/metastatic. Patients' overall survival (OS) was calculated using Kaplan– Meier method.

Results: Median age was 60 years (range, 28–82). The number of patients who received adjuvant RT alone, RT and chemotherapy, and chemotherapy alone were 77 (42.5%), 65 (36%), and 39 (21.5%), respectively. Median OS was 12.4 years (range, 0.1-21). Except for the advanced/metastatic risk group, OS was better in all the other risk groups who received RT alone ($p<0.001$).

Discussion: Risk groups (based on prognostic risk factors), p53, and treatment applied (RT alone) are the significant prognostic indicators for patients received adjuvant therapy in endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

Keywords: Chemotherapy, endometrial cancer, prognosis, radiotherapy

ÖZET

Giriş: Endometriyal kanser çoğunlukla erken evrelerde teşhis edilir ve iyi bir prognoza sahiptir. Endometriyal kanserli hastaların tedavisinde cerrahi tedavi temeldir ve belirli risk gruplarında adjuvan radyoterapi (RT) uygulanmaktadır. Bu retrospektif çalışmada, RT uygulanan endometriyal kanserli hastalada prognozu etkileyen faktörler inceledi.

Gereç ve yöntemler: Çalışmaya endometriyal kanser tanısı almış toplam 181 hasta dahil edildi. Prognostik faktörlere göre risk grupları düşük, orta, yüksek-orta, yüksek riskli ve ileri/metastatik olarak kaydedildi. Hastaların genel sağkalımı (GS), Kaplan-Meier yöntemi kullanılarak hesaplandı.

Bulgular: Ortanca yaş 60'tı (28-82). Tek başına adjuvan RT, RT ve kemoterapi ve tek başına kemoterapi alan hasta sayısı sırasıyla 77 (%42,5), 65 (%36) ve 39 (%21,5) idi. Ortanca GS 12.4 yıldı (0.1-21). İleri/metastatik risk grubu dışında diğer tüm risk gruplarında, tek başına RT alan hastalarda GS daha iyi bulundu ($p<0.001$).

Tartışma: Endometriyal kanserli hastalarda adjuvan tedavi alanlarda; risk grupları (prognostik risk faktörlerine göre), p53 ve uygulanan tedavi (yalnız RT) önemli prognostik göstergelerdir. RT'ye adjuvan kemoterapi eklenmesi prognozu olumsuz etkilemektedir.

Anahtar kelimeler: Endometriyal kanser, kemoterapi, prognoz, radyoterapi

First Received: 26.01.2023, Accepted: 17.03.2023 doi: 10.5505/aot.2023.02779

Introduction

Endometrial cancer is the most common gynecological cancer among women living in developed countries [1]. Most of the endometrial cancer patients are post-menopausal at the time of diagnosis, while the rate of disease in premenopausal period is only 25% [2]. Majority of the patients present with early-stage according to International Federation of Gynecology and Obstetrics (FIGO) at the time of diagnosis and survival time has been reported approximately 90% in these patients due to favorable prognosis [3]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) (including regional lymph node dissection or not) is the definitive management for early-stage endometrial cancer, but not for locally advanced or metastatic disease.

Numerous previous studies have identified the important prognostic factors in endometrial carcinoma. These are tumor stage, patient age, histological type, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. Additionally, prognostic effects of p53 and ki67 on endometrial cancer have been shown by certain studies, however, it has not been established clear enough yet. [6,7]. Risk groups that have different prognoses have been identified based on the prognostic factors and adjuvant management is set according to this classification [4,5,8].

Adjuvant management of endometrial cancer includes radiotherapy (RT), chemotherapy and/or hormonal therapy in patients who have certain risk factors [9]. RT plays a significant role in the treatment of endometrial cancer and commonly administered in postoperative setting; however, definitive RT may be considered for patients who are medically inoperable or in case of local recurrence. Treatment decision with adjuvant RT is related to certain risk factors, such as higher tumor grade, deep myometrium invasion, and lymphovascular invasion [9]. In this retrospective study, we analyzed the risk factors affecting the prognosis of patients with endometrial cancer who received adjuvant therapy.

Patients and Methods

A total of 203 patients who were diagnosed with endometrial cancer and referred to the Department of Radiation Oncology between January 2010 and January 2020 were included in the retrospective study. Twenty-one patients were excluded from the study because of unavailable medical records. The study was approved by the local ethics committee (Date: 15.11.2022, Decision Number: 2022/289502) and conducted by principles of the Helsinki Declaration 2013.

Surgical procedure was TAH+BSO with or without pelvic and paraaortic lymph-adenectomy. Histopathology of the tumor, FIGO stage (2009), lymph node status, depth of myometrial invasion, tumor grade, lymphovascular invasion and metastatic sites were recorded. Risk groups according to these prognostic factors were recorded as in Table 1[8].

Percentage of cells presenting with positive nuclear staining was expressed as ki67 and p53 scores. Ki67 positivity was defined as positive ki67 staining in >40% of tumor cells and p53 positivity was defined as positive p53 staining in >25% of tumor cells [10].

Number of patients treated with adjuvant and definitive RT were 77 (42.5%) and three (1.7%), respectively. Consecutive chemo-therapy was administered to 36% (n=65) of the patients who received adjuvant RT. Simultaneous chemoradiotherapy was administered to one patient. Thirty-nine patients (21.5%) received chemotherapy alone. Radiation fields en-compassed tumor bed and regional nodes with a treatment dose of 45-50.4 Gy in adjuvant setting. Total dose was 70-75 Gy with brachytherapy in patients who underwent definitive treatment.

Table 1 Risk groups of endometrial carcinoma

Risk group	ESMO-ESGO-ESTRO consensus
Low risk	Endometrioid endometrial cancer, grade 1–2, <50% myometrial invasion, without lymphovascular space invasion
Low- intermediate risk	Endometrioid endometrial cancer, grade 1–2, ≥50% myometrial invasion, without lymphovascular space invasion
High- intermediate risk	Endometrioid endometrial cancer, grade 3, <50% myometrial invasion, any lymphovascular space invasion Endometrioid endometrial cancer, grade 1–2, with unequivocally lymphovascular space invasion, any myometrial invasion
High risk	Endometrioid endometrial cancer, grade 3, ≥50% myometrial invasion, any lymphovascular space invasion Stage II–III endometrioid endometrial cancer, no residual disease Stage I-III non-endometrioid endometrial cancer (serous, clear cell, or undifferentiated carcinosarcoma)
Advanced/metastatic	Stage III with residual disease and, stage IVa Stage IVb

ESGO, European Society of Gynecological Oncology
ESMO, European Society for Medical Oncology
ESTRO, European Society for Radiation Oncology

Overall survival (OS) was defined as the period (years) from the time of the patient's diagnosis until the last visit or death.

Statistical analysis

Statistical analyses were done using SPSS (Statistical Package for Social Sciences) for Windows 23.0 IBM SPSS Statistics, New York, USA). P value less than 0.05 was defined statistically significant. Data measurements were represented by the mean, median and range. Categorical data were expressed as frequency and percentage, and chi-square test was used for comparison between groups. Patients' OS was determined using Kaplan– Meier method. Multivariate Cox regression model was used to determine the independent prognostic predictors of survival with the variables which were statistically significant by univariate Cox regression model.

Results

Median age was 60 years (range, 28–82). The predominant histologic subtype was endometrioid adenocarcinoma in 69.1% of the patients. Median tumor size was 4.5 cm (range, 0.3-16). Lymphovascular invasion was detected in 39.2% of the patients and hormone receptor was positive in 64.6%. Most of the patients were with high risk disease (42.5%). p53 and Ki67 positivity were 32.5% and 67.8%, respectively. The clinico-pathologic characteristics of the patients receiving adjuvant therapy are shown in Table 2.

Advanced age (over 70 years) was associated with deep myometrial invasion (17.9% vs. 6.8%), advanced stage (42.9% vs. 18%), and higher rates of grade 2 and 3 tumors (78.4% vs. 57.3%) ($p<0.04$).

Non-endometrioid histology was associated with deep myometrial invasion (48.1% vs. 31.1%), advanced stage (42.6% vs. 12.9%), grade 3 tumor (50% vs. 25.6%), p53 positivity (53.3% vs. 7.9%), and hormone receptor negativity (29.3% vs. 2.2%) ($p<0.04$).

In addition, deep myometrial invasion was associated with lymph node involvement (29.1% vs. 9.4%), lymphovascular space invasion (55.6% vs. 26.5%), advanced stage (65.7% vs. 31.4%) and grade 3 tumor (40.5% vs. 16.7%) ($p<0.03$).

Table 2 The clinicopathologic characteristics of the patients

Characteristic	All patient % (n)	RT alone % (n)	CT+RT % (n)	CT alone % (n)
Histologic type				
Endometroid	69.1 (125)	55.2 (69)	31.2 (39)	13.6 (17)
Papillary serous	10 (18)	5.6 (1)	55.6 (10)	38.9 (7)
Carcinosarcoma	6.6 (12)	16.7 (2)	25 (3)	58.3 (7)
ESS	6.6 (12)	16.7 (2)	41.7 (5)	41.7 (5)
Other types	7.7 (14)	21.4 (3)	57.1 (8)	21.4 (3)
T stage				
T1a	19.9 (36)	52.8 (19)	30.6 (11)	16.7 (6)
T1b	38.7 (70)	51.4 (36)	35.7 (25)	12.9 (9)
T2	22.1 (40)	50 (20)	42.5 (17)	7.5 (3)
T3	7.7 (14)	14.3 (2)	50 (7)	35.7 (5)
T4	8.8 (16)	-	25 (4)	75 (12)
Unknown	2.8 (5)			
FIGO stage				
I	56.4 (102)	54.9 (56)	34.3 (35)	10.8 (11)
II	20.4 (37)	48.6 (18)	43.2 (16)	8.1 (3)
III	9.4 (17)	17.6 (3)	47.1 (8)	35.3 (6)
IV	12.2 (22)	-	27.3 (6)	72.7 (16)
Unknown	1.7 (3)			
Tumor grade				
I	11 (20)	55 (11)	35 (7)	10 (2)
II	44.8 (81)	56.8 (46)	33.3 (27)	9.9 (8)
III	23.2 (42)	33.3 (14)	40.5 (17)	26.2 (11)
Unknown	21 (38)			
LVI				
Positive	39.2 (71)	38 (27)	43.7 (31)	18.3 (13)
Negative	47.5 (86)	50 (43)	31.4 (27)	18.6 (16)
Unknown	13.3 (24)			
LN metastasis				
Positive	22.1 (40)	2.5 (1)	65 (26)	32.5 (13)
Negative	60.2 (109)	56.9 (62)	26.6 (29)	16.5 (18)
Unknown	17.7 (32)			
Risk categories				
Low	11 (20)	65 (13)	25 (5)	10 (2)
Low-intermediate	13.8 (25)	68 (17)	20 (5)	12 (3)
High-intermediate	19.3 (35)	42.9 (15)	51.4 (18)	5.7 (2)
High	42.5 (77)	41.6 (32)	39 (30)	19.5 (15)
Advanced/metastatic	12.2 (22)	-	31.8 (7)	68.2 (15)

ESS, Endometrial stromal sarcoma; *LN*, Lymph node; *LVI,* Lymph-vascular invasion; *CT*, Chemotherapy; *RT*, Radiotherapy

Ki67 positivity was correlated with advanced stage, grade 3 tumor, hormone receptor negativity, lymph node involvement, and paraaortic metastasis ($p<0.04$), and p53 positivity was correlated with non-endometroid histology, hormone receptor negativity, and advanced stage ($p<0.02$).

Locoregional recurrence and/or distant metastasis occurred in 50 patients (27.6%). Lymphatic recurrences were seen in abdominal paraaortic, pelvic and mediastinal nodal regions in 12 (6.6%), 6 (3.3%) and seven patients (3.9%), respectively. Vaginal recurrence was seen in only three patients (1.7%).

Median OS was 12.4 years (range, 0.1-21), and 5- and 10-year survival rates were 70.5% and 56.8%, respectively. Patients with high and advanced/metastatic risk had shorter OS (Figure 1). Except for the advanced/metastatic risk group, survival was better in the all of the other risk groups who received RT alone (Table 3).

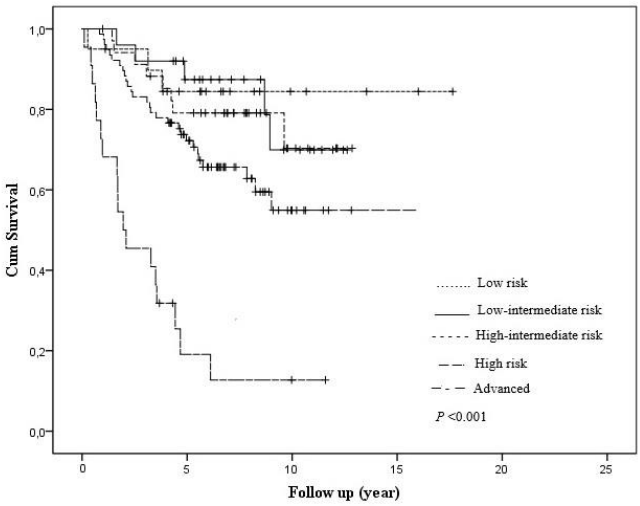

Figure 1. Overall survival by risk groups

Table 3. Median for Survival Time

				95% CI		
Risk group	Treatment	Time (year)	SE	Lower	Upper	*P value*
LIR	RT alone	16.5	1.5	13.3	19.8	0.004*
	RT-CT	9.5	1.7	6.1	12.5	
	CT	6.4	2.5	1.2	11.3	
HIR	RT alone	11.8	0.7	10.6	13.6	0.041*
	RT-CT	7.2	0.8	5.8	9.2	
	CT	5.6	1.3	3.4	7.8	
High risk	RT alone	12.5	0.4	10.8	13.2	0.042*
	RT-CT	6.7	0.7	5.7	8.4	
	CT	6.2	1.3	11.2	8.6	
Advanced	RT-CT	5	1.5	2	7.8	0.26
	CT	2.8	0.9	1.3	4.1	

HIR, High-intermediate risk; LIR, Low-intermediate risk; CT, Chemotherapy; RT, Radiotherapy; CI, Confidence interval; SE, Standard error
* P<0.05 was regarded statistically significant

Table 4 Cox regression analysis for prognosis

	Univariate			Multivariate		
Variable	HR	95%CI	P value	HR	95%CI	P Value
LNI (Yes vs No)	2.87	1.6-5.02	<0.001	0.77	0.39-1.49	0.44
Stage	1.97	1.6-2.4	<0.001	2.84	1.21-6.64	0.02*
PAND (Yes vs No)	2.14	1.25-3.65	0.006	0.54	0.12-2.49	0.43
PANM (Yes vs No)	2.6	1.3-5.2	0.007	1.07	0.20-5.70	0.94
Tumor size (≤4 cm vs >4 cm)	1.99	2.08-3.7	0.03	1.35	0.35-5.26	0.67
Age (≤70 vs >70)	1.05	1.02-1.08	0.04	0.65	0.10-4.25	0.66
P53 (≤25% vs >25%)	1.02	1.01-1.03	<0.001	0.16	0.05-0.53	0.003*
Ki67 (≤40% vs >40%)	3.18	1.44-7.02	0.004	0.41	0.08-1.95	0.26
Histology	1.3	1.12-1.5	0.001	0.84	0.44-1.62	0.60
Treatment	3.07	2.2-4.26	<0.001	4.39	1.65-11.70	0.003*
Risk groups	1.99	1.48-2.68	<0.001	0.29	0.11-0.79	0.02*

CI: Confidence interval; *HR*: Hazard Ratio; LNI, Lymph node involvement; PAND, Paraaortic node dissection; PANM, Paraaortic node metastasis
* *P<0.05* was regarded statistically significant

Prognosis was not found associated with lymphovascular space invasion (p= 0.08), extra-nodal spread (p= 0.6), and tumor grade (p= 0.2) by the univariate analysis. In the multivariate analysis, p53 (p= 0.003), tumor stage (p = 0.002), risk groups (p=0.02) and the treatment administered (adjuvant RT alone) (p<0.001) were significantly associated with prognosis. The results of univariate and multivariate analyses for prognosis are shown in Table 4.

Discussion

Endometrial cancer is predominantly diagnosed at earlier stages and has a good prognosis. Only 15–20% of the patients with endometrial cancer present with high-risk disease/distant metastases and poor prognosis. Surgery is the cornerstone of the endometrial cancer treatment and consists of TAH+BSO with or without pelvic and paraaortic lymphadenectomy [11]. Major factors affecting the prognosis of endometrial cancer have been established by previous studies and defined as age, tumor stage, histolopathology, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. After surgery, indications for adjuvant treatment are commonly related to these clinicopathological risk factors. In this study, factors affecting the prognosis of endometrial cancer were analyzed in patients received adjuvant therapy and it was found that tumor stage, and treatment applied (RT alone) were associated with prognosis in multivariate analysis.

Importance of RT in the adjuvant management of endometrial cancer was established by multiple studies. Recent studies have been concentrated upon the high-intermediate and high-risk diseases, whereas the adjuvant treatment in low-risk endometrial cancer is not indicated [8]. In our study, patients with high and high-intermediate risk diseases who received RT alone had a better prognosis than the patients who received chemotherapy with RT or chemotherapy alone. Addition of chemotherapy to RT also affected survival negatively in other risk groups except for the advanced/metastatic risk group.

The correlation between advanced age and poor prognosis is well established. The adverse impact of advanced age on worse progress of the disease is often explained by frequency of aggressive histology and advanced disease at diagnosis. Treatment with less aggressive regimens are another reason of the shorter survival in elderly patients [12]. In the present study, advanced stage, non-endometrioid histology and grade 2, 3 tumors were more frequent in patients over 70 years of age.

According to the FIGO annual report, serous and clear cell histologic types present with more advanced stages which explains the poorer survival in patients with non-endometrioid histology [13]. In our study, non-endometrioid histology was associated with higher rates of deep myometrial invasion and advanced stage resulting in shorter survival.

Myometrial invasion more than the half of the myometrial wall is defined as deep myometrial invasion which increases the risk of relapse and results in worse outcome [14]. In the present study, deep myometrial invasion was associated with non-endometrial types, advanced stage, lymphovascular invasion and higher grade. As a result, deep myometrial invasion and/or advanced stage were associated with poor survival.

Lymph node involvement has a potent impact on the outcome of the endometrial cancer which decreases the 5- year disease-free survival time to 65% to 70% alone. Presence of pelvic nodal metastases is an important indicator for the involvement of paraaortic nodes which decreases the 5-year disease-free survival rates to 30% [15]. In our study, whole patients with involved paraaortic nodes had

also involvement in pelvic nodes. However, prognosis was similar in patients who had only pelvic or pelvic plus paraaortic nodal involvements.

Increased ki67 or p53 expression in endometrial cancer was associated with more aggressive clinicopathological features and these markers were reported as indicators of poor prognosis [6,7]. In the present study, both markers were also associated with negative prognostic factors.

Prognosis of endometrial cancer is mainly affected by tumor grade which has a strong correlation with depth of myometrial invasion and metastasis to the lymph nodes. Grade 3 tumor for all stages has been reported to be an independent factor in predicting poor survival in the FIGO annual report [13]. Lympho-vascular invasion is also an important prognostic factor and indicates pelvic recurrence and distant metastasis which results in poor survival [16]. However, in our study, lymphovascular invasion and tumor grade was not associated with prognosis.

In univariate analysis, age, stage, histology, ki67, p53, pelvic or paraaortic nodal involvement, paraaortic lymphadenectomy, adjuvant RT alone, and risk groups were statistically associated with prognosis, however, only p53, stage, risk groups, and adjuvant RT alone were found statistically significant in multivariate analysis. Other prognostic factors, lymphovascular invasion and tumor grade, were not significantly associated with prognosis.

Conclusion

Tumor stage, p53, risk groups (based on prognostic risk factors), and RT alone are the most important prognostic indicators for patients received adjuvant therapy in the postoperative setting of endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

REFERENCES

1. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002; 97(1): 72-81.
2. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol. 1984; 64(3): 417-20.
3. Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. Gynecol Oncol. 1990; 38(1): 99-104.
4. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000; 355(9213): 1404-11.
5. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004; 92(3): 744-51.
6. Lundgren C, Auer G, Frankendal B, Moberger B, Nilsson B, Nordstrom B. Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. Int J Gynecol Cancer. 2002; 12(1): 110-8.
7. Coronado PJ, Vidart JA, Lopez-asenjo JA, et al. P53 overexpression predicts endometrial carcinoma recurrence better than HER-2/neu overexpression. Eur J Obstet Gynecol Reprod Biol. 2001; 98(1): 103-8
8. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016; 26(1): 2-30.
9. Lybeert ML, van Putten WL, Brolmann HA, Coebergh JW. Postoperative radiotherapy for endometrial carcinoma. Stage I. Wide variation in referral patterns but no effect on long-term survival in a retrospective study in the southeast Netherlands. Eur J Cancer. 1998; 34(4): 586-90.
10. Ferrandina G, Ranelletti FO, Gallotta V, et al. Expression of cyclooxygenase-2 (COX-2), receptors for estrogen (ER), and progesterone (PR), p53, ki67, and neu

protein in endometrial cancer. Gynecol Oncol. 2005; 98(3): 383-9.
11. van den Heerik A, Horeweg N, de Boer SM, Bosse T, Creutzberg CL. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. Int J Gynecol Cancer. 2021; 31(4): 594-604.
12. Bishop EA, Java JJ, Moore KN, Walker JL. Pathologic and Treatment Outcomes Among a Geriatric Population of Endometrial Cancer Patients: An NRG Oncology/Gynecologic Oncology Group Ancillary Data Analysis of LAP2. Int J Gynecol Cancer. 2017;27(4):730-7.
13. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006; 95 Suppl 1: S105-43.
14. Carien LC, Gini FF. Endometrial cancer. In: Joel ET, Robert LF, Jeff MM, editors. Gunderson & Tepper's Clinical Radiation Oncology. 5th ed. Philadelphia: Elsevier; 2021. p. 1213-1242.
15. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991; 40(1): 55-65.
16. Bosse T, Peters EE, Creutzberg CL, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015; 51(13): 1742-50.

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Doi: 10.5505/aot.2023.02779

Original Article

Investigation of the Effect of Adjuvant Endocrine Treatment on Depression, Sleep Quality and Sexual Function in Hormone Receptor-Positive Early-Stage Breast Cancer

Hormon Reseptör Pozitif Erken Evre Meme Kanserinde Adjuvan Hormonal Tedavinin Depresyon, Uyku Kalitesi ve Cinsel Fonksiyon Üzerine Etkinliğinin Araştırılması

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ABSTRACT

Aim: Questioning and recognizing depression, sleep and sexual dysfunctions in breast cancer patients improves the patients' quality of life. We aimed to evaluate the effects of adjuvant endocrine treatment and other variables on depression, sleep quality and sexual dysfunction in patients with early-stage breast cancer.

Materials and Methods: Our study was performed with the participation of 105 patients who were diagnosed with hormone receptor positive, early stage (stage I-III) breast cancer and at least 3 months followed by the medical oncology outpatient clinic. Sociodemographic form, Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI) and Female Sexual Function Index (FSFI) were used as data collection tools.

Results: According to the results obtained in our study, 55.8% patients had depression, 60.6% patients had poor sleep quality, 77.1% had poor sexual function. A tendency to sexual dysfunction was observed in patients with PR positivity and it was found to be statistically significant (P=0.005). There was a strong ($p<0.001$) correlation between the PSQI and BDI values of the patients. There was no significant relationship between different endocrine therapy agents (tamoxifen/anastrozole/letrozole) in patients with depression, sleep and sexual dysfunction ($p> 0.05$).

Conclusion: In our study, we found a tendency to depression, sleep disturbance, and sexual dysfunction in most patients. It was found that sleep disorders and sexual dysfunction increased in patients with depression. It was also statistically significant that hormone receptor status could affect sexual function. Therefore, symptoms related to depression, sleep and sexual problems should be questioned in patients followed up with a diagnosis of breast cancer.

Key Words: Breast cancer, endocrine treatment, BDI, PSQI, FSFI

ÖZET

Giriş ve Amaç: Meme kanseri hastalarında depresyon, uyku ve cinsel işlev bozukluklarını sorgulamak ve tanımak hastaların yaşam kalitesini iyileştirmektedir. Erken evre meme kanserli hastalarda adjuvan endokrin tedavisi ve diğer değişkenlerin depresyon, uyku kalitesi ve cinsel işlev bozukluğu üzerine etkilerini değerlendirmeyi amaçladık.

Yöntem ve Gereçler: Çalışmamız, hormon reseptörü pozitif, erken evre (evre I-III) meme kanseri tanısı almış ve medikal onkoloji polikliniğinde en az 3 ay takip edilen 105 hastanın katılımıyla gerçekleştirildi. Veri toplama aracı olarak sosyodemografik form, Beck Depresyon Envanteri (BDI), Pittsburgh Uyku Kalitesi İndeksi (PSQI) ve Kadın Cinsel İşlev İndeksi (FSFI) kullanıldı.

First Received: 28.11.2022, Accepted: 02.05.2023 doi: 10.5505/aot.2023.24654

Bulgular: Çalışmamızda elde ettiğimiz sonuçlara göre hastaların %55.8'inde depresyon, %60,6'sında kötü uyku kalitesi, %77.1'inde cinsel işlev bozukluğu saptandı. PR pozitif olan hastalarda cinsel işlev bozukluğuna eğilim gözlendi ve istatistiksel olarak anlamlı bulundu (P=0,005). Hastaların PUKİ ve BDI değerleri arasında güçlü (p<0,001) bir korelasyon vardı. Depresyon, uyku ve cinsel işlev bozukluğu olan hastalarda farklı endokrin tedavi ajanları (tamoksifen/anastrozol/letrozol) arasında ise anlamlı bir ilişki yoktu (p> 0.05).
Tartışma ve Sonuç: Çalışmamızda çoğu hastada depresyon, uyku bozukluğu ve cinsel işlev bozukluğuna eğilim saptadık. Bazı sosyodemografik özelliklerin ve hormon reseptör durumunun cinsel işlevselliği etkileyebileceği ortaya çıktı. Bu nedenle meme kanseri tanısı ile takip edilen hastalarda bu belirtilerin sorgulanması ve değerlendirilmesi önemlidir.

Anahtar Kelimeler: meme kanseri, hormonoterapi, depresyon, uyku, cinsel fonksiyon

Introduction

Breast cancer is the most common type of cancer in women, and it is a disease that has heterogeneous features both biologically and clinically [1].

From the moment of the diagnosis of breast cancer, it creates a crisis that affects the patient's life in different aspects such as physical, psychological, spiritual, and social. In this crisis, some reactions are common in every patient, regardless of age, ethnicity, and stage of the disease [2].

Adjuvant endocrine treatment reduces recurrence and increases survival rates in receptor-positive tumors [3]. However, endocrine treatments (eg ovarian suppression, SERMs such as tamoxifen) reduce estrogen levels and can modulate the central nervous system by their estrogen antagonist actions, which can inhibit serotonergic mechanisms in the brain, causing mood and sleep disturbances [4, 5]

Also, side effects of tamoxifen are known as hot flashes, vaginal dryness, cataracts, thromboembolism, and increased risk of endometrial cancer [6]. These side effects may also reduce the patient's interest and desire for sexual life.

Sexual problems observed in women with breast cancer may be the result of anxiety and depression experienced when diagnosed with cancer, as well as side effects of surgery, chemotherapy, radiotherapy, and endocrine treatment [7].

Depression and anxiety are very common in breast cancer patients, which could reduce adherence to the treatment, and is associated with significant functional impairment and increased risk of mortality [8]. Despite all these harms and high frequency; depression, insomnia, and sexual problems that occur in patients can be ignored by both healthcare professionals and researchers. In this context, emphasizing the importance of the follow-up and treatment of depression, sleep and sexual dysfunctions in early-stage breast cancer patients receiving endocrine treatment can improve the quality of life of patients by struggling against the poor quality of life.

Therefore, in this study, we aimed to evaluate the effects of adjuvant endocrine treatment and other variables on depression, sleep quality, and sexual dysfunction in patients with early-stage breast cancer.

Materials and Methods

Our study is conducted between September 2018 and March 2020 with the participation of 105 patients who were diagnosed with hormone receptor-positive early-stage (stage I-III) breast cancer who were receiving endocrine treatment for at least 3 months and still receiving in the department of oncology of our hospital.

The inclusion criteria of the study are being 18 years of age and older, being diagnosed with stage I-III breast cancer according to the TNM Staging System, having received endocrine treatment for at least 3 months, volunteering to participate in the study. Patients were selected regardless of their previous chemotherapy or radiotherapy history, and patients with distant organ metastasis were not included in the study.

This study is a cross-sectional study conducted to detect depression, sleep quality, and sexual dysfunction in women with breast cancer who are receiving endocrine treatment. The questionnaires were administered in a single interview by interviewing the patients one-on-one and taking verbal consent from the patient, paying attention to the principle of voluntary participation. Cancer type and stage, chemotherapy, radiotherapy information is obtained from the patient file.

Potential study participants were approached at the oncology outpatient clinic. The heads and interns of clinics of oncology were informed about the study by one of the researchers. In this way, the interns became able to answer questions if the participants would ask. The investigators explained the purpose of the study to patients who met the inclusion criteria, and face to face questionnaire was administered after obtaining the consent of the patients. They were assured of their anonymity and of confidentially, and they were told that they could drop out at any time. The subjects were administered three questionnaires that look around 20 to 30 min to complete. The data collected from patients and questionnaire forms were preserved in the research folder in the paper. Sociodemographic form, Beck Depression Inventory, Pittsburgh Sleep Quality Index (PSQI), and Female Sexual Function Index (FSFI) were used as data collection methods. The study was approved by the institutional ethics committee. All procedures performed under the national research committee's ethical standarts and Helsinki declaration updated in 2013.

Methods of Assessment

Beck Depression Inventory (BDI)

The main version of the scale was prepared by Beck et al. [9]. In this study, the 1978 version of the Beck form adapted by Hisli was used [10].

There are 21 questions with four options for each in the Beck Depression Inventory form. The patient is asked to select and mark the sentence that best describes how the person felt in the last week, including the day of the questionnaire, and each item gets a score between 0 and 3. The highest score that can be obtained on the scale is 63. In this study revise Beck depression inventory was used. According to the Beck Depression Inventory (BDI-II) scoring system, 0–13 points indicate minimal depression, 14-19 points indicate mild depression, 20-28 points indicate moderate depression and 29-63 indicate severe depression [9].

Pittsburgh Sleep Quality Index (PSQI)

PSQI is a self-report measure that evaluates sleep quality and disorder over one month period. According to the Pittsburgh Sleep Quality Index (PSQI), a global PSQI score ≤5 indicates ''good sleep quality'', and >5 indicates ''poor sleep quality''. PSQI, which is an effective tool used to measure sleep quality in cancer patients, was developed by Buysse et al. in 1989. Reliability and validity studies in our country were performed by Ağargün et al. (1996) [11].

Female Sexual Function Index (FSFI)

Female Sexual Function Index is a Likert-type scale consisting of 19 items developed by Rosen et al. to evaluate female sexual functions. The scale was created by the researchers who developed the sexual functions of women in the last month, 6 subgroup scores, and FSFI score calculation scale, and it is made according to a scoring index [12]. The Turkish validity and reliability analysis of the scale were conducted by Öksüz and Malhan (2005). In the study performed by Taş et al. in 2006 in Turkey the functional status; If FSFI score is >30, it is stated as good, if between 23-29 it is stated as medium, if <23 it is stated as bad [13]. (Table 1)

Statistical methods

IBM SPSS (Statistical Programme for Social Scientists) version 20.0 (IBM Corp., Armonk, Newyork, USA) program was used for the statistical analysis of the study. The Kolmogorov Smirnov test was used to evaluate the compatibility of the data for normal distribution. Continuous data matching to normal distribution were given as

Table 1. Female Sexual Function Index scoring chart [14].

FSFI domain	Questions	Score range	Factor number	Minimum score	Maximum score	Total score
Desire	1,2	1-5	0.6	1.2	6.0	
Arousal	3,4,5,6	0-5	0.3	0	6.0	
Lubrication	7,8,9,10	0-5	0.3	0	6.0	
Orgasm	11,12,13	0-5	0.4	0	6.0	
Satisfaction	14,15,16	0/1-5	0.4	0.8	6.0	
Pain	17,18,19	0-5	0.4	0	6.0	
Total score (FSFI score)				2.0	36.0	

Mean ± Standard Deviation, continuous data not matching to a normal distribution as Median (highest - lowest value or interquartile range), and categorical data as frequency (percentage). Mann Whitney U test was used to compare the data of two groups that did not match with the normal distribution between independent groups. Independent samples t-test was used to compare the data of two groups with normal distribution. Chi-square or Fisher's Exact test was used to compare independent categorical variables. Spearmen correlation test was used between BDI, PSQI and FSFI. All statistical tests were done bilaterally and $p < 0.05$ was considered statistically significant.

Results

The demographic characteristics of the patients included in the study are examined; 105 women were included in the study, and the median age of the individuals was 53 (34-79). 80% of the patients were married, 19% were divorced, and the median number of children they had was found to be 2 (0-9). The single patients didn't declare that they have sexual partners. 67% of the cases are housewives, 21% are retired and 17% continue to work actively.

When the patients were evaluated in terms of their menopausal status at the time of the interview, the menopausal status of seven patients was unknown, 61.9% were in the postmenopausal stage, 17.1% were in the premenopausal stage, and 14.3% were in the perimenopausal stage.

The surgery and pathology information of the patients included in the study are shown in Table 2 below.

Surgery type are unknown for four patients because data was missing. Tumor stage for 8 patients and Her2 value of nine patients are also unknown because data was missing. Perineural invasion is also unknown in 22 patients and extracapsular extension is unknown in 26 patients because pathological data could not be reached.

When the endocrine treatment agents taken by the patients were examined, 62 (59.6%) patients used tamoxifen, 29 (27.9%) patients used letrozole, and 13 (12.5%) patients used anastrozole. The median duration of endocrine treatment of the patients included in the study was followed for 24 months (3-120). Detailed data on Adjuvant treatments and their durations are shown in Table 3.

When we look at the BDI score information of the patients, 46.5% had minimal depression, 26.7% had mild depression, 24.7% had moderate depression, and 1.9% had severe depression. BDI value was below the median value of 10 in 55.8% of the patients, and above the median value of 10 in 44.2% of the patients.

When the sleep quality rates were examined, 41 (39.4%) patients had good and 63 (60.6%)

Table 2. Surgery and pathology information of patients

Number of patients		105
Surgery type, n (%)	Breast-Conserving Surgery (BCS)	33 (31,4)
	Modified Radical Mastectomy (MRM)	68 (64,8)
	unknown	4 (3,8)
Stage T, n (%)	T0	2 (1,9)
	T1	38 (36,2)
	T2	48 (45,7)
	T3	7 (6,7)
	T4	2 (1,9)
	unknown	8 (7,6)
Stage N, n (%)	N0	46 (43,8)
	N1	22 (21,0)
	N2	11 (10,5)
	N3	16 (15,2)
	unknown	10 (9,5)
ER, n (%)	positive	98 (93,3)
	negative	7 (6,7)
PR, n (%)	positive	93 (88,6)
	negative	12 (11,4)
Her-2, n (%)	positive	51 (48,5)
	negative	45 (42,9)
	unknown	9 (8,6)
Grade, n (%)	1	13 (12,4)
	2	39 (37,1)
	3	16 (15,2)
	unknown	37 (35,2)
LVI, n (%)	Yes	39 (37,1)
	No	49 (46,7)
	unknown	17 (16,2)
PNI, n (%)	available	15 (14,3)
	umavailable	68 (64,7)
	unknown	22 (21,0)

Table 2. continue next page

ECE, n (%)	Yes	21 (20,0)
	No	58 (55,2)
	unknown	26 (24,8)
Stage, n (%)	1A	24 (25,5)
	1B	22 (23,4)
	2A	25 (26,6)
	2B	3 (3,2)
	3A	8 (8,5)
	3B	12 (12,8)

T: Tumor, N: Lymph Node, ER: Estrogen Receptor, PR: Progesterone Receptor, Her2: Human Epidermal Growth Factor Receptor 2, LVI: Lymphovascular invasion, PNI: Perineural Invasion, ECE: Extracapsular Extension

patients had poor sleep quality. As a result, a tendency towards sleep disorder was observed in the patients who participated in the study.

When the FSFI scores of the patients were examined, low scores were found in the majority of the patients, and a tendency to sexual dysfunction was observed. According to the FSFI scores, 81 (77.1%) patients scored bad, 16 (15.2%) patients were found to be fair, and 8 (7.6%) patients scored well in terms of sexual function.

BDI, PSQI, and FSFI score information of the patients are summarized in Table 4.

When demographic characteristics of the patients with low and high BDI, PSQI, and FSFI scores were compared, no statistically significant relationship was found with the age, the number of children, social security, the menopausal status of the patients ($p>0.05$). However, the relationship between marital status and FSFI score was found to be statistically significant, and in 70% of married patients, sexual function was found to be poor ($p=0.04$).

When the patients' ER and PR positivity percentage rates were examined, no significant relationship was observed between the BDI scores and positivity percentage ($p=1.0$ for ER, $p=0.26$ for PR). However, although it was not statistically significant, a decrease in the ER percentage and an increase in the BDI score, that is, a tendency to depression, was observed ($p=0.06$). There was no significant effect of ER positivity ($p= 0.15$) and ER percentage ($p=0.35$) on sexual function. A tendency to sexual dysfunction was observed in patients with PR positivity and it was found to be statistically significant ($p=0.005$). There was no significant correlation between PR percentages and FSFI score ($p=0.55$).

No significant relationship was found between adjuvant chemotherapy, radio-therapy, trastuzumab, Luteinizing hormone releasing hormone (LHRH) treatment status, duration of treatment and BDI, PSQI and FSFI score values. There was no significant relationship between different endocrine therapy agents (tamoxifen/ anastrozole/ letrozole) in patients with depression, sleep and sexual dysfunction ($p> 0.05$). However, although not statistically significant, patients using aromatase inhibitors had a higher tendency to sleep disorder. Poor sleep quality was found in 29 (69%) of 42 patients using aromatase inhibitors. However, although not statistically significant, 90% of the patients who took aromatase inhibitors tended to sexual dysfunction.

Comparison of BDI, PSQI, and FSFI scores with adjuvant treatments is summarized in Table 5.

There was a strong correlation between PSQI and BDI ($p<0.001$), and a moderate inverse

Table 3. Adjuvant treatments and their durations

Adjuvant CT, n (%)	Yes	76 (72,4)
	No	28 (26,7)
	unknown	1 (1,0)
Adjuvant CT regimen, n (%)	Anthracycline and taxane	58 (55,2)
	Anthracycline	12 (11,4)
	Taxane	2 (1,9)
	Other	33 (31,4)
Adjuvant CT duration, the median day		149 (25-462)
Adjuvant trastuzumab, n (%)	Yes	32 (30,5)
	No	69 (65,7)
	unknown	4 (3,8)
Adjuvant RT, n (%)	Yes	81 (78,6)
	No	22 (21,4)
Adjuvant RT duration, the median day		35 (4-56)
Adjuvant Endocrine Treatment type, n (%)	Tamoxifen	62 (59.6)
	Letrozole	29 (27.9)
	Anastrozole	13 (12.5)
Adjuvant Endocrine Treatment duration, median month		24 (3-120)
Adjuvant LHRH, n (%)	Yes	10 (9,5)
	No	95 (90,5)

CT: Chemotherapy, RT: Radiotherapthy, LHRH: Luteinizing hormone releasing hormone

correlation (P=0.001) between FSFI-BDI scores. In summary, it was found that sleep disorders and sexual dysfunction increased in patients with depression. The correlation analysis of BDI, PSQI, and FSFI scores is summarized in Table 6.

Discussion

First of all, if we examine the results obtained with the Beck Depression Inventory, our first questionnaire, 44.2% of the patients tended to depression with a BDI score of 10 and above. In a study, results confirmed that side effects of endocrine treatment were significantly associated with anxiety and depression [8]. The prevalence of depression and anxiety in that study were 33.4% (133) and 13.3% (53), respectively. In another study by Weitzner et al., based on BDI questionnaires in a population of patients with 5 years of disease-free period, they found 29% depression among breast cancer patients. [15]. The reason why this rate was found to be higher in our study may be that our patient group consisted of patients who still received endocrine treatment and did not reach the disease-free period. In another study based on HADS (Hospital Anxiety and Depression Scale) score, comorbid depression was found in approximately one-quarter of all breast cancer patients, and this rate was estimated to be between 20% and 30% in early breast cancer and more than 50% in advanced and palliative stages [16]. Although all of the patients in our

Table 4. Beck, PSQI, and FSFI score information of the patients

Beck Depression score, median (min-max)		10 (0-33) if you want average 11,5±7,8
Beck Depression score, n (%)	Low	58 (55,8)
	High	46 (44,2)
	Minimal depression	47 (%46,5)
	Mild depression	27 (%26,7)
	Moderate depression	25 (%24,7)
	Severe depression	2 (%1,9)
PSQI score, median (min-max)		7 (1-16) if you want average 7.2 ±3.3
PSQI score, n (%)	Good	41 (39,4)
	Poor	63 (60,6)
FSFI score, median (min-max)		2,6 (2-34) if you want average 11,7±11,3
FSFI score, n (%)	Good	8 (7,6)
	Fair	16 (15,2)
	Bad	81 (77,1)

BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index,
FSFI: Female Sexual Function Index

Table 5. Comparison of BDI, PSQI, and FSFI Scores with Adjuvant Treatment.

	BDI	PSQI	FSFI
Adjuvant Chemotherapy (Yes/No)	P = 0,18	P = 1,00	P = 0,86
Adjuvant Chemotherapy regimen type	P = 0,11	P = 0,39	P = 0,54
Adjuvant Chemotherapy duration	P = 0,62	P = 0,93	P = 0,59
Adjuvant Trastuzumab (Yes/No)	P = 0,61	P = 0,60	P = 0,80
Adjuvant RT (Yes/No)	P = 0,92	P = 0,75	P = 0,84
Adjuvant Endocrine Treatment type	P = 0,74	P = 0,34	P = 0,09
Adjuvan Endocrine Treatment duration	P = 0,56	P = 0,78	P = 0,15
Adjuvant LHRH (Yes/No)	P = 0,33	P = 0,51	P = 0,39

RT: Radiotherapy, LHRH: Luteinizing hormone releasing hormone

Table 6. Correlation relationship

		FSFI score	BDI score
PSQI score	r	-0,04	0,57
	p	0,71	<0,001
FSFI score	r		-0,36
	p		<0,001
r: correlation coefficient			

BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index,
FSFI: Female Sexual Function Index

study were in the early stage, the reason for the higher prevalence of depression compared to this study may be that the number of patients who received chemotherapy in our study was higher. On the other hand, the prevalence in our study was significantly lower than a study conducted in Iran which reported the prevalence of depression among cancer patients to be 95.9% [17] Different living environments and medical conditions may explain such a large difference.

In a recent meta-analysis of 16,298 women from 17 countries between 2000 and 2019, the prevalence of anxiety in breast cancer patients was found to be 41.9%. The meta-analysis showed a high level of anxiety among breast cancer patients [18]. The different prevalence rates of depression or anxiety in different studies may be due to the type of cancer, the stage of cancer treatment, the severity of the disease, the status of family support, patient's economic level and cultural context and education level among the patients studied.

In our study, the depression status of the patients before endocrine treatment is not known, since the cases were analyzed in cross-section. However, in a retrospective analysis study examining the development of depression in patients in whom tamoxifen treatment was initiated, it was shown that no statistically significant relationship was found between the initiation of tamoxifen treatment and the subsequent development of depressive symptoms [19].

In the literature, it has been reported that the prevalence of depressive symptoms increases in breast cancer patients receiving chemotherapy and radiotherapy [20, 21]. In our study, no significant difference was found between BDI, PSQI and FSFI score values levels in the group that received adjuvant chemotherapy and radiotherapy and the group that did not. It was thought that the reason for the lack of a significant relationship between chemotherapy and depression in our study may be since most of the patients completed the chemotherapy period and at least 3 months had passed.

Sleep disorders, one of the most important cancer-related problems affecting the quality of life, are observed with a rate of 30-50% in cancer patients [22]. In our study, patients with breast cancer under endocrine treatment were evaluated with the Pittsburgh Sleep Quality Index, and 60.6% of patients had poor sleep quality, and sleep disorders were observed in the vast majority of patients.

In a meta-analysis evaluating the relationship between sleep disorders and other symptoms in cancer patients, especially fatigue and depression, it was shown that the connection of insomnia with depression was moderate [23]. In the study of Palesh et al., it was found that sleep problems were positively correlated

with depression and fatigue [24]. In our study, parallel to previous studies, there was a high correlation between BDI and PSQI scores, and a significant correlation was found between sleep disturbance and depression disposition in patients.

When the sexual function index results of our study were examined, a tendency to sexual dysfunction was observed in the majority of the patients (77.1%). Similar to the result obtained in our study Joanne et al. observed that women treated with tamoxifen may experience symptoms of sexual dysfunction [25]. However, the effect of tamoxifen on sexual function is uncertain, and conflicting publications are showing that endocrine treatment causes sexual dysfunction. In the study of McCaughan et al., it was found that women who received endocrine treatment did not experience a significantly different sexual dysfunction than women who did not receive endocrine treatment [26]. Similarly, Ganz et al. examined the relationship between tamoxifen use and sexual function in breast cancer patients and found that there was no difference in sexual functioning among women treated without tamoxifen [27].

When the effect of demographic characteristics of the patients on sexual function was examined, no significant relationship was found, except being married which was found as a negative effect on sexual functionality (P=0.04). There are not enough studies on this subject but this result suggested that the disease may have affected their sexual life worse in married patients than in single or divorced patients since they experienced the entire disease process and difficulties with their sexual partners.

In our study, when the effects of ER and PR positivity on sexual function were compared, patients with PR positivity showed a tendency to sexual dysfunction, and it was found to be statistically significant. However, its clinical significance is not clear. In a different study based on FSFI questionnaires similar to our study, no relationship was found between ER status and sexual function in breast cancer patients. However, only postmenopausal patients were included in the study [28].

In the literature, it is known that sexual dysfunction and depression are associated with both cause and effect in breast cancer patients [29, 30]. In our study supporting the literature, a moderate correlation was observed between depression and sexual dysfunction. In our study, we evaluated the cross-sectional status of breast cancer patients who were hormone receptor-positive and were receiving endocrine treatment, and we found sexual dysfunction in most of the patients. However, we found no difference in the effects of different endocrine treatment agents (tamoxifen, anastrozole, and letrozole) on sexual function. The limited number of patients and different follow-up intervals were the main limitations of our study. The other limitation was that we did not know the anxiety and depression scores of the patients before taking endocrine treatment. An additional limitation was that we could not accurately evaluate the menopausal status of patients using LHRH analogs.

Although endocrine treatment is not a risk factor, we found a tendency to depression, sleep disturbance, and sexual dysfunction in most patients. The high incidence of depression in breast cancer itself makes it particularly difficult to isolate and measure the psychological impact of endocrine treatments on patients. In our study, it was revealed that some sociodemographic features and hormone receptor status may affect sexual functionality. Future research may shed light on the size of these independent risk factors and as a result, it may guide treatment decisions for breast cancer patients in the coming years.

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REFERENCES

1. R. L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1): 7-30.
2. B. Kara, H. Fesci, Kanserde öz-bakım ve yaşam kalitesi. Hematoloji–Onkoloji. 2004; 6(3): 124–129.
3. A.E. Giuliano, J.L. Connolly, S.B Edge, E.A. Mittendorf, H.S. Rugo, L.J. Solin, Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67(4): 290–303.
4. U. Halbreich, N. Rojansky, S. Palter, H. Tworek, P. Hissin, K. Wang, Estrogen augments serotonergic activity in postmenopausal women. Biol Psychiatry. 1995; 37(7): 434–441.
5. B.E.H. Sumner, K.E. Grant, R. Rosie, C. Hegele-Hartung, K.H. Fritzemeier, G. Fink, Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites and mRNA levels in the brain of ovariectomized rats with or without acute estradiol replacement. Mol Brain Res. 1999; 73(1-2): 119–128.
6. T.C. Moynihan, T.M. Habermann, A.K. Gosh, Breast cancer. In: Mayo Clinic Internal Medicine: Concise Textbook; 2009. p. 661–665.
7. B.P.A. Ganz, K.A. Desmond, T.R. Belin, B.E. Meyerowitz, J.H. Rowland, Predictors of Sexual Health in Women After a Breast Cancer Diagnosis. J Clin Oncol. 1999; 17(8): 2371-2380.
8. R. Zhao, H. Liu, J. Gao, Side Effects of Endocrine Therapy Are Associated with Depression and Anxiety in Breast Cancer Patients Accepting Endocrine Therapy: A Cross-Sectional Study in China. Frontiers in Psychology. 2022, 13.
9. A.T. Beck, R.A. Steer, G. Brown,BD I-II, Beck depression inventory manual. Psychological Corp.San Antonio, TX. 1996; 3: 601-608
10. N. Hisli, Beck Depresyon Envanteri'nin Geçerliği Üzerine Bir Çalışma. Psikol Derg. 1988; 6: 118–122.
11. M.Y. Ağargün, H. Kara, Ö. Anlar, Pittsburgh Uyku Kalitesi İndeksi'nin Geçerliği ve Güvenirliği. Türk Psikiyatr Derg. 1996; 7(2): 107–115.
12. R. Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, R. D'Agostino, The female sexual function index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26(2): 191–208.
13. E. Öksüz, S. Malhan, Kadin cinsel fonksiyon indeksi. Sendrom Derg. 2005; 17: 54–60.
14. B.B. Keseroğlu, B.C. Özgür, A.K. Yıldız, E. Gülen, Kadin Cinsel İşlev Ölçeğine Etki Eden Faktörler. Kırıkkale Üniversitesi Tıp Fakültesi Derg. 2008; 20(3): 269–273.
15. M.A. Weitzner, C.A. Meyers, K.K. Stuebing, A.K. Saleeba, Relationship between quality of life and mood in long-term survivors of breast cancer treated with mastectomy. Support Care Cancer. 1997; 5(3): 241–248.
16. L.J. Fallowfield, A. Hall, G.P. Maguire, M. Baum, Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. Br Med J. 1990; 301(6752): 575–580.
17. J. Shakeri, S. Golshani, E. Jalilian, V. Farnia, R. Nooripour, M. Alikhani, K. Yaghoobi, Studying the amount of depression and its role in predicting the quality of life of women with breast cancer. Asian Pac. J. Cancer Prev. 2016;17: 643–646.
18. S.M. Hashemi, H. Rafiemanesh, T. Aghamohammadi, et al. Prevalence of anxiety among breast cancer patients: a systematic review and meta-analysis. Breast Cancer. 2020; 27: 166–178.
19. K.C. Lee, G.T. Ray, E.M. Hunkeler, P.R. Finley, Tamoxifen treatment and new-onset depression in breast cancer patients. Psychosomatics. 2007; 48(3): 205–210.
20. A.M. Schreier, S.A. Williams, Anxiety and quality of life of women who receive radiation or chemotherapy for breast cancer. Oncol Nurs Forum. 2004; 31(1): 127–130.
21. S.E. Ward, G. Viergutz, D. Tormey, J. deMuth, A. Paulen, Patients' reactions to completion of adjuvant breast cancer therapy. Nurs Res. 1992; 41(6): 362–366.
22. M.J. Sateia, K. Doghramji, P.J. Hauri, C.M. Morin, Evaluation of Chronic Insomnia. Sleep. 2000; 23(2): 243–308.
23. K.A. Donovan, P.B. Jacobsen, Fatigue, Depression, and Insomnia. Evidence for a Symptom Cluster in Cancer. Semin Oncol Nurs. 2008; 23(2): 127–135.
24. O.G. Palesh, J.A. Roscoe, K.M. Mustian, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-community clinical oncology program. J Clin Oncol. 2010; 28(2): 292–298.
25. J.E. Mortimer, L. Boucher, J. Baty, D.L. Knapp, E. Ryan, J.H. Rowland, Effect of tamoxifen on sexual functioning in patients with breast cancer. J Clin Oncol. 1999; 17(5): 1488–1492.
26. S. Young-McCaughan, Sexual functioning in women with breast cancer after treatment with adjuvant therapy. Cancer Nurs. 1996; 19(4): 308–319.
27. P.A. Ganz, J.H. Rowland, K. Desmond, B.E. Meyerowitz, G.E. Wyatt, Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. J Clin Oncol. 1998; 16(2): 501–504.
28. J.A.C. Cavalheiro, A. Bittelbrunn, C.H. Menke, Jet al. Sexual function and chemotherapy in postmenopausal

women with breast cancer. BMC Womens Health. 2012; 12(1): 28.
29. E.N. Boswell, D.S. Dizon, Breast cancer and sexual function. Transl Androl Urol. 2015; 4(2): 160–168.
30. D. Buković, J. Fajdić, Z. Hrgović, M. Kaufmann, I. Hojsak, T. Stančerić, Sexual dysfunction in breast cancer survivors. Onkologie. 2005; 28(1): 29–34.

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Doi: 10.5505/aot.2023.24654

Original Article

Evaluation of Anesthesia Applications and Postoperative Care Results in Patients Who Underwent Reconstruction Surgery with Tumor Resection Prosthesis in Primary and Metastatic Bone Tumors

Primer ve Metastatik Kemik Tümörlerinde Tümör Rezeksiyon Protezi ile Rekonstrüksiyon Cerrahisi Yapılan Hastalarda Anestezi Uygulamaları ve Postoperatif Bakım Sonuçlarının Değerlendirilmesi

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ABSTRACT

Introduction: Patients scheduled for orthopedic oncological surgery often receive various treatments, such as chemotherapy or radiotherapy, before the operation. The treatments applied and related side effects, accompanying co-morbidities and the characteristics of the surgery to be performed affect the choice of anesthesia and require specificity. In this study, it was planned to retrospectively evaluate the patients who underwent tumor resection prosthesis with the diagnosis of primary or metastatic bone tumor in our hospital.
Materials and methods: 72 patients between the ages of 6-84 who underwent tumor resection prosthesis operation with the diagnosis of primary or metastatic bone tumor and who are in American Society of Anesthesiologists (ASA) I-III group were included in the present study. Demographic characteristics of patients, accompanying diseases, malignity diagnoses, ASA scores, surgical intervention carried out and anesthesia method, duration of anesthesia and operation, pre and postoperative hemoglobin values, amount of intraoperative bleeding, intraoperative fluid management and need for blood transfusion, need for and duration of postoperative intensive care and/or mechanic ventilation were recorded.
Results: The most frequently diagnosed primary bone tumor was osteosarcoma, and the most common operation was wide tumor resection and femoral proximal tumor resection prosthesis. Parameters such as duration of anesthesia, amount of bleeding, age, ASA, and comorbidity were shown to be associated with the need for postoperative mechanical ventilation or intensive care. In the postoperative analgesia methods applied to the patients, it was seen that the most frequently preferred method was intravenous analgesia.
Discussion: In orthopedic oncologic surgeries, anesthesia management should encompass evaluating the patient with a holistic approach starting from the preoperative period, and considering the need for postoperative analgesia and/or for intensive care in addition to intraoperative anesthesia. Communication between members of anesthesia and surgery teams is important for providing optimal surgical care.

Keywords: Bone neoplazms, reconstructıon surgery. anaesthesia. postoperatıve care, tumor resectıon, prosthesıs

ÖZET

Giriş: Ortopedik onkolojik cerrahi planlanan hastalar sıklıkla operasyondan önce kemoterapi veya radyoterapi gibi çeşitli tedaviler almaktadır. Uygulanan tedaviler ve bunlara bağlı yan etkiler, eşlik eden ko-morbiditeler ve yapılacak olan cerrahinin özellikleri anestezi seçimini etkileyerek spesifikleşmeyi

First Received: 04.02.2023, Accepted: 16.05.2023 doi: 10.5505/aot.2023.67689

gerektirir. Bu çalışmada, hastanemizde primer veya metastatik kemik tümörü tanısı ile tümör rezeksiyon protezi uygulanan hastaların retrospektif olarak değerlendirilmesi planlandı.
Gereç ve yöntemler: Çalışmaya hastanemiz Ortopedi ve Travmatoloji Kliniği tarafından Ocak 2015 ve Aralık 2016 tarihleri arasında Primer veya metastatik kemik tümörü tanısı ile tümör rezeksiyonu protez operasyonu uygulanan, American Society of Anesthesiologists (ASA) I-III grubunda yer alan 6-84 yaş arası 72 hasta bu çalışmaya dahil edildi. Hastaların demografik özellikleri, eşlik eden hastalıkları, malignite tanıları, ASA skorları, yapılan cerrahi girişim ve anestezi yöntemi, anestezi ve operasyon süresi, ameliyat öncesi ve sonrası hemoglobin değerleri, intraoperatif kanama miktarı, intraoperatif sıvı yönetimi ve kan transfüzyon ihtiyacı, ve postoperatif yoğun bakım ve/veya mekanik ventilasyon süreleri kaydedildi.
Bulgular: En sık tanı alan primer kemik tümörü osteosarkom, en çok yapılan ameliyat ise geniş tümör rezeksiyonu ve femur proksimal tümör rezeksiyon protezi olarak bulundu. Anestezi süresi, kanama miktarı, yaş, ASA ve ek hastalık gibi parametrelerin postoperatif mekanik ventilasyon veya yoğun bakım ihtiyacıyla ilişkili olduğu gösterildi. Hastalarda uygulanan postoperatif analjezi yöntemlerinde ise en sık olarak intravenöz analjezi yöntemi tercih edildiği görüldü.
Tartışma: Ortopedik onkolojik cerrahilerde anestezi yönetimi, preoperatif dönemden başlayarak hastayı bütüncül bir yaklaşımla değerlendirmeyi, intraoperatif anesteziyle birlikte postoperatif analjezi ve / veya yoğun bakım gereksinimini belirlemeyi kapsamalıdır. Anestezi ve cerrahi ekip üyeleri arasında iletişim optimal onkolojik cerrahi bakımın sağlanması açısından önemlidir.

Anahtar kelimeler: Kemik tümörleri, rekonstrüksiyon cerrahisi, anestezi, ameliyat sonrası bakım, tümör rezeksiyonu, protez

Introduction

In 2009, approximately 2600 new cases of primary bone malignancies and a more significant number of metastatic bone tumors were reported in the USA [1]. Osteosarcoma, Ewing sarcoma, and chondrosarcoma are the three most common types of sarcoma. The recent employment of new chemotherapy treatment agents and radiological imaging methods, treatment options conserving extremity have become more popular [2].

Patients planned to undergo orthopedical oncological surgery commonly receive treatments such as chemotherapy or radiotherapy before the operation. The treatment administered and associated side effects and the characteristics of the surgery influence choice of anesthesia, making it necessary to be more specific. In operations of tumors with rich vascular structure, fluid resuscitation, and adequate intravenous intervention for probable blood transfusion, invasive monitorization or preoperative tumor embolization may be required [3]. It is known that sufficient postoperative analgesic efficacy enables early mobilization and rehabilitation, decreasing morbidity [1].

In the present study, retrospective analysis of the patients who underwent tumor resection prosthesis between January 2015- December 2016 with the diagnosis of the primary or metastatic bone tumor was planned. It was aimed to evaluate demographic characteristics of patients, malignity diagnoses, surgical operation and anesthesia method used, amount of intraoperative bleeding and fluid management, need for blood transfusion, methods used for postoperative analgesia, duration of stay in postoperative ICU, complications developing and need for mechanic ventilation. In addition, the relation between duration of stay in intensive care and mechanic ventilation with other parameters were investigated.

Material and Method

The present study was carried out at University of Health Sciences Ankara Abdurrahman Yurtarslan Oncology Education and Research Hospital Anesthesiology and Reanimation Clinic after ethical approval numbered 2017-05/01 was obtained on 10/5/2017. The study was planned as a retrospective descriptive.72 patients between the ages of 6-84 who underwent tumor resection prosthesis operation with the

diagnosis of primary or metastatic bone tumor between January 2015 and December 2016 and who are in American Society of Anesthesiologists (ASA) I-III group were included in the present study. Cases who were planned to undergo tumor resection prosthesis but who turned out to have benign masses after biopsy were excluded from the study. The study was planned as a retrospective evaluation.

The files of patients who underwent tumor resection between the dates mentioned above were retrieved from hospıtal archive and preoperative anesthesia examination forms, anesthesia monitorization forms, post-operative anesthetic care unit monitorization forms and records of patients who needed monitorization in intensive care unit and/or mechanical ventilation were investigated.

Demographic characteristics of patients, accompanying diseases, malignity diagnoses, ASA scores, surgical intervention carried out and anesthesia method, duration of anesthesia and operation, pre and postoperative hemoglobin values, amount of intraoperative bleeding, intraoperative fluid management and need for blood transfusion, need for and duration of postoperative intensive care and/or mechanic ventilation duratıon were recorded. The relation between evaluated parameters and the need for postoperative intensive care duratıon and/or mechanical ventilation duratıon was investigated.

The number of patients administered regional or general anesthesia was determined and demographic characteristics and differences in the need for postoperative intensive care and/or mechanic ventilation between regional and general anesthesia groups were investigated (Group R, n:28, regional anesthesia - Group G, n:44, general anesthesia). Postoperative analgesia methods and drugs used and their doses were recorded

Statistical analysis

Statistical evaluation was made with SPSS 20.0 program using the tests listed below. $P<0.05$ was considered statistically significant. Statistical analysis was presented as follows: [mean ±standard deviation, minimum- maximum), median (minimum-maximum), n (%)]. Inter groups differences in age, hemoglobin levels, duration of anesthesia and surgical intervention, blood products and fluids used were evaluated with Student's t-test. Data on duration of stay in intensive care and mechanic ventilation, which were not normallly distributed, were evaluated with Mann Whitney U test. Data on ASA class, and additional disease, and the number of patients requiring intensive care and mechanic ventilation were evaluated with Chi-square or Fisher's exact tests.Correlation between data of patients that need intensive care and mechanic ventilation and duration of operation, ASA class, products used, and other parameters were evaluated with Spearman or Pearson correlation test.

Results

Demographic characteristics and accompanying diseases were as follows. 5.6% of the patients were in ASA I, 62.5% in ASA II and 31.9% in ASA III risk group. The most common accompanying disease was hypertension (13.9%) and 62.5% of patients had no additional disease (Table 1). Cancer diagnoses of the patients are shown in (Table 2).The most commonly diagnosed primary bone tumor was established to be osteosarcoma (21%) and the type of operation carried out most commonly wide tumor resection + Femur proximal tumor resection prosthesis with 32 (44%) patients. Upper extremity operation was performed in only one patient out of 72 patients. In 71 patients, the operation was in the lower extremities.

Postoperative analgesia methods used in patients. It was established that epidural PCA (Patient controlled analgesia) method was used in 33% of the patients. The most commonly used intravenous anesthesia method was tramadol bolus administration and PCA prepared with tramadol. (n=14, 19%). It was also determined that two patients underwent femoral plexus, and one patient brachial plexus block and two patients were administered i.v. NSAII (Non steroidal antiinflamatuar drug).

Table1.Demographic characteristics of patients and accompanying diseases [mean ± SD, n (%)]

		(n=72)
Age(year)		47.22±19.12
Weight(kg)		72.35±18.61
ASA(I/II/III)		4 (5.6)/45 (62.5)/23(31.9)
Additional diseases	Acute renal failure	1 (1.4)
	Asthma	1 (1.4)
	Asthma + Goitre	1 (1.4)
	Diabetes Mellitus	3 (4.2)
	Diabetes Mellitus + Hypertension	3 (4.2)
	Hepatitis B	1 (1.4)
	Hypertension	10 (13.9)
	Hypertension + Coronary Artery Disease	4(5.6)
	Hypertension + Chronic Obstructive Pulmonary Disease	1 (1.4)
	Obesity	1 (1.4)
	Pulmonary Hypertension	1 (1.4)
	No additional disease	45 (62.5)

Correlation between the need for duratıon of intensive care and evaluated parameters is shown in table 3. A positive correlation was found between the need for intensive care and duration of anesthesia, amount of bleeding and the amount of erythrocyte suspension used (p=0.025, p=0.003, p<0.0001, respectively). A negative correlation was found, however, between preoperative hemoglobin amount and need for duratıon of intensive care (p<0.0001). No correlation was found between the need for duratıon of intensive care and other parameters evaluated (Table 3).

The correlation between the need for duratıon of mechanic ventilation and the investigated parameters is demonstrated in (Table 4). A positive correlation was found between need for mechanic ventilation and age, ASA, additional disease, duration of anesthesia and amount of erythrocyte suspension used (p=0.005, p=0.012, p=0.041, p<0.0001, respectively). A negative correlation was found between the amount of preoperative hemoglobin and need for duration of mechanic ventilation (p<0.0001). No correlation was found between other parameters and the need for duratıon of mechanic ventilation (Table 4).

In the present study, the number of patients administered regional anesthesia was 28 (39%) (Group R), while the number of patients administered general anesthesia was 44 (61%) (Group G). Combined spinal epidural anesthesia was applied to 28 patients in the regional anesthesia group. Our rate of application of regional anesthesia was similar to the literatüre [1].

Table2.Cancer diagnoses of patients [n (%)]

Cancer diagnoses (n=72)	n (%)
Metastatic adenocarcinoma with unknown primary	4 (%5)
Lung Ca +Bone metastasis	4 (% 5)
Stage 4 Lung Ca+Primary bone malignant mesenchymal tumor	1 (% 1.4)
Giant cell tumor in Femur distal	1 (% 1.4)
Chondrosarcoma	10 (% 14)
Malignant melanoma bone metastasis+ Lung metastasis	1 (% 1.4)
Breast Ca +Bone metastasis	11 (% 15)
Bladder Ca+ left femur metastasis	2 (% 2.8)
Metastatic larynx Ca+ Right femur metastasis	1 (% 1.4)
Multiple myeloma+Humerus proximal carcinoma metastasis	3 (% 4.2)
Nasopharynx Ca +Right humerus proximal and left femur subtrochanteric fracture	1 (% 1.4)
Osteosarcoma	15 (% 21)
Prostat Ca + Bone metastasis	3 (% 4.2)
RCC +Bone metastasis	2 (% 2.8)
Right femur proximal fibrous dysplasia	1 (% 1.4)
Right tibia proximal Ewing sarcoma	1 (% 1.4)
Right tibia proximal giant cell tumor	1 (% 1.4)
Pleomorphic sarcoma in thigh	2 (% 2.8)
Femur malignant mesenchimal tumor	3 (% 4.2)
Left femur distal desmoid tumor	1 (% 1.4)
Left femur proximal pleomorphic rhabdomyosarcoma	1 (% 1.4)
Left thigh posterior mixoid liposarcoma	1 (% 1.4)
Tibia proximal malignant mesenchimal tumor	1 (% 1.4)
Thyroid carcinoma metastasis lytic lesion in proximal of left femur	1 (% 1.4)

Table 3. Correlation between the need for intensive care and other parameters

	R	*P*
Age(year)	0.139	*0.244*
Weight (kg)	0.108	*0.367*
ASA(I/II/III)	0.137	*0.251*
Additional disease	0.085	*0.489*
Duration of anesthesia (min)	0.265	*0.025**
Duration of operation (min)	0.211	*0.075*
Preoperative hemoglobin(g/dl)	-0.403	*<0.0001**
Postoperative hemoglobin(g/dl)	-0.163	*0.173*
Amount of bleeding (ml)	0.340	*0.003**
Erithrocyte suspension (unit)	0.490	*<0.0001**
Cristalloid (ml)	0.185	*0.119*
Colloid (ml)	0.191	*0.331*

Table 4. Correlation between the need for mechanic ventilation and other parameters

	R	*P*
Age(year)	0.330	*0.005**
Weight (kg)	0.058	*0.627*
ASA(1/2/3)	0.259	*0.012**
Additional disease	0.283	*0.018**
Duration of anesthesia(min)	0.242	*0.041**
Duration ofsurgery(min)	0.183	*0.123*
Preoperative hemoglobin (g/dl)	-0.400	*0.001**
Postoperative hemoglobin (g/dl)	-0.184	*0.122*
Amount of bleeding (ml)	0.162	*0.309*
Erithrocyte suspension (unit)	0.613	*<0.0001**
Crystalloid(ml)	0.155	*0.194*
Colloid (ml)	0.206	*0.294*

The comparison of the amount of crystalloid, colloid fluids, erythrocyte suspension, pre and postoperative hemoglobin, and duration of surgical intervention and anesthesia between groups were similar between groups.The amount of preoperative hemoglobin was found to be significantly higher in Group R (p=0.015).

The need for duration of mechanical ventilation was found to be significantly higher in Group R than Group G (p=0.031). Mechanic ventilation was required in eight patients (28.8%) in Group R, and four patients (9.1%) in Group G. Other findings were found to be similar between groups. Death did not occur within 24 hours, preoperatively or postoperatively in any patient.

Discussion

The most commonly diagnosed primary bone tumor was established to be osteosarcoma, and the operation carried out most commonly was found to be wide tumor resection and femur proximal tumor resection prosthesis. Metastatic bone tumors occur more commonly than primary tumors. As many primary cancers metastasize to bone, it is difficult to determine the exact incidence of metastatic bone cancer. Breast and prostate cancers are those that metastasize most commonly to the bone and do so at the rate of 70% in advanced stages [4]. In the present study, metastatic bone cancer was detected in 46% of patients. Of these patients, 11 had breast cancer metastasis, which is similar to the incidence reported in other studies [4]. The increase in developed countries in the prevalence of cancer with the increasing elderly population necessitates more care to be given for cancer patients in the routine practice of health professionals. Anesthetists work with cancer patients not only in operating theaters but also in supportive treatment processes such as pain, nutrition, and intensive care. Although various surgical guidelines have been developed in oncology patients according to cancer types, there are not adequate studies on anesthesia management in these patients [5]. Patients planned to undergo an operation for bone tumors experience an intensive treatment process before surgery. Cancer patients are immune-suppressed due to their disease inducing apoptosis of immune cells,

chemotherapy, and radiotherapy they undergo, malnutrition and psychological stress [6]. Along with immunosuppressive factors, surgical inflammation, pain, hypoxia, hypothermia, hyperglycemia, and immuno-modulation triggered with blood transfusion markedly influence the function of T lymphocytes and natural killer cells (NK) which are active in antitumor activity [7,8]. Recognition of these immune factors and selection of suitable methods in anesthesia management will decrease perioperative risks leading to tumor progression in cancer patients. Volatile anesthetics, morphine and blood transfusion promote immune suppression directly, while propofol, regional anesthesia, and cyclooxygenase inhibitors have been reported to exert positive effects on the immune system [5]. In patients undergoing chemotherapy or radiotherapy, anemia and thrombocytopenia occur frequently. Tumors are generally of vascular structure and tend to bleed at intraoperative period. It has been reported that perioperative tumor embolization may be useful if abundant bleeding is expected associated with a highly vascular tumor [3]. Adequate intravenous access for fluid resuscitation and probable transfusions and preparations for invasive monitorization should be incorporated into preoperative planning. Accompanying co-morbidities such as hypertension, diabetes mellitus, and chronic obstructive lung disease, may make anesthesia management more difficult. Communication with the surgical team is important in that characteristics of the operation can be learned, and anesthesia preparations can be made appropriately [3]. In the present study, the highest amount of bleeding occurred in the case who underwent wide resection, femur and humerus proximal tumor prosthesis operation due to metastasis of the renal cell tumor. As there was about 3000 ml loss of blood in the patient, intensive fluid and blood transfusion was required.

As primary bone tumors and metastases may arise at different sites in the body, anesthesia techniques specialized for certain anatomic localizations provide postoperative analgesia in addition to intraoperative analgesia. In upper extremity tumor resections, regional anesthesia methods may be used as in other surgical operations. If there are a large surgical area and excessive blood loss, difficulty in positioning or long duration of the operation is expected, general anesthesia may be used. In operations carried out under general anesthesia, postoperative analgesia may be given by local anesthetic infiltration via placement of perineural, subfascial or subcutaneous catheters in wound region. In lower extremity tumor resections, regional anesthesia methods may be used on their own or along with general anesthesia[1]. In the present study, 39% of the patients (n=28) were administered regional anesthesia and the remaining patients 61% (n=44) were administered general anesthesia.

Among metastatic tumor resection operations, the most difficult ones are surgeries involving femur. It may be difficult to position patients and use regional anesthesia methods due to primary lesion and other present metastases [1,9]. In cases with excessive bleeding together with sympathetic block associated with neuraxial anesthesia, it may not be easy to control intraoperative blood pressure. In the present study, no significant difference was found between regional and general anesthesia groups in terms of bleeding and the amount of blood transfusion.

It is known that sufficient postoperative analgesia after surgery decreases morbidity by enabling early mobilization and rehabilitation and shortens the duration of hospitalization [10,11]. In oncological surgical operations, postoperative analgesia may be carried out with multimodal analgesia approach, in which drugs and methods exerting effect on different regions in pain pathway such as central or peripheric nerve blocks, local anesthetic infusion via catheters placed in nerve sheath, local infiltration and PCA are used in combination [1]. In the present study, it was established that 33% of the patients used epidural PCA method. Operating theaters with the heavy workload, lack of a separate room for the administration of peripheric blocks in advance, lack of time for the anesthetist and

surgeon, difficulties in the supply of material may be the reasons why peripheric nerve blocks are not used commonly. Orthopedic oncology patients usually use strong opioids due to their pain in the preoperative period. This should be considered when planning postoperative opioid doses and opioid need and tolerance characteristics should be adjusted according to patients. In the study of Chung et al in which pain patterns in recovery unit were investigated, it was reported that the highest pain was described by orthopedics patients in ambulatory surgery [12]. In the study of Barbosa et al, similar results were obtained and 65.6% of patients complained of pain. It was also suggested that physicians and nurses do not adequately evaluate the pain of patients [13]. The efficacy of adjuvant drugs in postoperative pain management has been demonstrated in various studies [14-16]. There are publications reporting the efficacy of alpha 2 agonists such as Dextro-methorphan, NMDA antagonists, gaba-pentinoids, and clonidine[15-17] . NSAII drugs are commonly added to treatment in order to enhance the analgesic efficacy of opioids. The multimodal analgesic approach will decrease the need for intravenous opioids and hence the incidence of probable opioid side effects such as nausea-vomiting, somnolence, ileus and urine retention will also decline.

Orthopedic tumors are quite vascular and may lead to massive intraoperative bleeding[18] . For control and management of intraoperative bleeding, many methods such as preoperative embolization, acute normovolemic hemo-dilution, preoperative blood transfusion, controlled hypotension and antifibrinolytic treatment have been tried and each has its own characteristics [1]. Blood transfusion is an important risk factor in-hospital morbidity[19]. Bower et al investigated the effect of blood transfusion in non-cardiac patients on hospitalization, recovery, and cost and demonstrated that in patients undergoing blood transfusion, duration of hospitalization and frequency of complications was higher [20]. They also reported that in such patients the risk of surgical wound infection increased two-fold and hospital mortality increased 1.4 fold for every unit of blood transfused. Ogura et al in their study on 5716 patients, reported that female sex, age over 80, Charlson Comorbidity Index score of 4 or over, duration of anesthesia longer than 240 minutes, and blood transfusion increased morbidity and mortality [21]. In the present study, a positive correlation was found between duration of anesthesia, amount of bleeding, and amount of erythrocyte suspension used and the need for duration intensive care ($p=0.025$, $p=0.003$, $p<0.0001$, respectively). However, a negative correlation was found between the amount of perioperative hemoglobin and need for intensive care ($p<0.0001$). In patients with high intraoperative bleeding and transfusion need, duration of admission to intensive care was longer. A positive correlation was also found between age, ASA class, additional disease, duration of anesthesia, and the amount of erythrocyte suspension used and the need for duratıon of mechanic ventilation. Similar to other studies, increasing age, comorbidity, high ASA values, prolonged duration of anesthesia and bleeding, and complications increase the need for intensive care [21-27]. In the present study, it was established that the need for duration of mechanic ventilation was higher in the regional anesthesia group (28.6%) than in the general anesthesia group. We believe that this is because ASA class and mean age was higher in the regional anesthesia group and that anesthetists prefer regional methods in patients considered risky.

Bone cancers are usually metastatic tumors rich in vascular structure and localized in various regions of the body. Intense medical treatment patients receive before operation, radiotherapy and accompanying diseases, malnutrition and immune suppression render the operation that will be carried out more critical, necessitating more care to be taken. Bleeding, transfusion and intraoperative complications such as hemodynamic disturbances or embolus may lead to the need for intensive care and mechanic ventilation. The limited number of patients included in the

study and the fact that almost all of the patients were in the lower extremities are the limitations of the study. If larger patient series and patients with tumors in the upper extremity were included in the study, different results could be obtained.

Conclusion

In orthopedic oncological surgery, the need for intensive care may be greater in groups of patients who are older,have a higher ASA score,the duration of anesthesia is longer,the amount of bleeding and the amount of erythrocyte suspension used is excessive. In addition, the hemoglobin value should be optimized in terms of postoperative results before such major surgeries.

In orthopedic oncologic surgeries, anesthesia management should encompass evaluating the patient with a holistic approach starting from the preoperative period, and considering the need for postoperative analgesia and/or for intensive care in addition to intraoperative anesthesia. Communication between members of anesthesia and surgery teams is important for providing optimal surgical care.

REFERENCES

1. Anderson MR, Jeng CL, Wittig JC, Rosenblatt MA. Anesthesia for patients undergoing orthopedic oncologic surgeries. J Clin Anesth. 2010; 22(7): 565-572

2.Winkler K, Beron G, Kotz R et al. Adjuvant chemo-therapy in osteosarcoma- Effects of cisplatinum, BCD, and fibroblast interferon in sequential combination with HD-MTX and adriamycin. J Cancer Res Clin Oncol. 1983; 106 sup:1-7.

3. Zhang L, Gong Q, Xiao H, Tu C, Liu J. Control of blood loss during sacral surgery by aortic balloon occlusion. Anesth Analg. 2007; 105: 700–703

4. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004; 350: 1655–1664

5.Kurosawa S. Anesthesia in patients with cancer disorders. Curr Opin Anesthesiology. 2012; 25: 376-384

6.Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. J Environ Pathol Toxicol Oncol. 2003; 22: 139–146.

7. Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. J Anesth. 2008; 22: 263–277.

8. Homburger JA, Meiler SE. Anesthesia drugs, immunity, and long-term outcome. Curr Opin Anesthesiol. 2006; 19:423–428.

9.Kawai VFA, Cortez PJO, Valenti VE, Oliveira FR, Vitorino LM. Pre and postoperative analgesia for orthopedic surgeries. Rev Dor. São Paulo. 2015; 16(3): 166-170

10. Chester JG, Rudolph JL. Vital signs in older patients: age-related changes. J Am Med Dir Assoc. 2011; 12(5): 337-43

11. Sharma V, Morgan PM, Cheng EY. Factors influencing early rehabilitation after THA: a systematic review. Clin Orthop Relat Res. 2009; 467(7): 1400-1411.

12. Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. Anesth Analg. 1997; 85: 808-816.

13. Barbosa MH, Araujo NF, Silva JA, Corrêa BT, Moreira MT, Andrade VE. Pain assessment intensity and pain relief in patients post-operative orthopedic surgery. Esc Anna Nery. 2014; 18(1): 143-147.

14. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002; 96: 725-741.

15.Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. Anesth Analg. 2008; 107: 1380-1383.

16.Mercadante S, Fulfaro F. Management of painful bone metastases. Curr Opin Oncol. 2007; 19: 308-314

17. Pinkerton PH, Covens A. Autologous blood transfusion in radical hysterectomy. Transfus Med. 1996 ;6: 223-225.

18.Nakai S, Yoshizawa H, Kobayashi S, Naga K, Ichinose H. Role of autologous blood transfusion in sacral tumor resection: patient selection and recovery after surgery and blood donation. J Orthop Sci. 2000; 5: 321-327

19. Hormozi AK, Mahdavi N, Foroozanfar MM et al. Effect of Perioperative Management on Outcome of Patients after Craniosynostosis Surgery. World J Plast Surg. 2017; 6(1): 48–53.

20. Bower WF, Jin L, Underwood MJ, Lam YH, Lai PB. Peri-operative blood transfusion increases length of hospital stay and number of postoperative complications in non-cardiac surgical patients. Hong Kong Med J. 2010; 16(2): 116-120.

21. Ogura K, Yasunaga H, Horiguchi H, Fushimi K, Kawano H. What Is the Effect of Advanced Age and Comorbidity on Postoperative Morbidity and Mortality After Musculoskeletal Tumor Surgery? Clin Orthop Relat Res. 2014; 472: 3971–3978

22. Lupei MI, Chipman JG, Beilman GJ, Oancea SC, Konia MR. The association between ASA status and other risk stratification models on postoperative intensive care unit outcomes. Anesth Analg. 2014; 118(5): 989-994.

23. Lahat G, Dhuka AR, Lahat S et al. Complete soft tissue sarcoma resection is a viable treatment option for select elderly patients. Ann Surg Oncol. 2009; 16: 2579–2586.

24. Al-Refaie WB, Habermann EB, Dudeja V et al. Extremity soft tissue sarcoma care in the elderly: insights into the generalizability of NCI Cancer Trials. Ann Surg Oncol. 2010; 17: 1732–1738.
25. Boden RA, Clark MA, Neuhaus SJ, A'Hern JR, Thomas JM, Hayes AJ. Surgical management of soft tissue sarcoma in patients over 80 years. Eur J Surg Oncol. 2006; 32: 1154–1158.
26. Buchner M, Bernd L, Zahlten-Hinguranage A, Sabo D. Primary malignant tumours of bone and soft tissue in the elderly. Eur J Surg Oncol. 2004; 30: 877–883.
27. Osaka S, Sugita H, Osaka E, Yoshida Y, Ryu J. Surgical management of malignant soft tissue tumours in patients aged 65 years or older. J Orthop Surg. 2003; 11: 28–33.

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Doi: 10.5505/aot.2023.67689

Original Article

Prognostic Role of Pan Immune Inflammation Value and Systemic Inflammation Response Index in Small Cell Lung Cancer

Küçük Hücreli Akciğer Kanserinde Pan İmmün Enflamasyon Değeri ve Sistemik Enflamasyon Yanıt İndeksinin Prognostik Rolü

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) is a highly lethal form of lung cancer with very poor prognosis. Systemic inflammation is an important risk factor for cancer development. Circulating immune cells play an important role in fighting against cancer. This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers as components of circulating immune cells in small cell lung cancer.

Materials and methods: A total of 81 SCLC patients followed up at Dokuz Eylül University Hospital Department of Medical Oncology between 2012 and 2021 were included in this study. Demographic characteristics and clinic-pathological features of each patient were recorded. Peripheral blood tests of patients were recorded at the time of diagnosis. Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count × platelet count × monocyte count)/lymphocyte count. The optimal cut-off values were determined according to the receiver operating characteristic (ROC) curve. These values were 2.8 and 585 in limited stage SCLC, and 1.33 and 497 in all-stage SCLC for SIRI and PIV, respectively. Overall survival (OS) was calculated by Kaplan-Meier method and compared by log rank test. Multivariate analysis was calculated using the Cox regression model.

Results: Among 81 SCLC patients,28 (34.6%) patients had LS-SCLC while 53 (65.4%) patients had extensive stage disease. In whole group, median SIRI was 2.37 (IQR, 0.34–18.59), while median PIV was 634.80 (IQR, 61.57–8320). Although there was a numerical difference between survival in analysis performed in the patient group including all stages, statistical significance could not be achieved for both markers (p=0.20 for SIRI; p=0.058 for PIV). While statistical significance was found for OS and ECOG; SIRI, and PIV status in univariate analysis ofpatients with limited stage SCLC, no significant difference was found between the variables with multivariate analysis..

Discussion: Our findings show that SIRI and PIV may be promising predictors for prognosis in SCLC.

Keywords: Small cell lung cancer; inflammation index; inflammation value

ÖZET

Giriş: Küçük hücreli akciğer kanseri (KHAK), çok kötü prognozlu, oldukça ölümcül bir akciğer kanseri türüdür. Sistemik inflamasyon, kanser gelişimi için önemli bir risk faktörüdür. Dolaşan bağışıklık hücreleri, kansere karşı mücadelede önemli bir rol oynar. Bu çalışma, küçük hücreli akciğer kanserinde dolaşımdaki bağışıklık hücrelerinin bileşenleri olarak farklı periferik kan lökosit biyobelirteçlerinin prognostik değerini araştırmak için tasarlanmıştır.

Gereç ve yöntemler: Bu çalışmaya 2012-2021 yılları arasında Dokuz Eylül Üniversitesi Hastanesi Tıbbi Onkoloji Anabilim Dalı'nda izlenen toplam 81 KHAK hastası dahil edildi. Her hastanın demografik özellikleri ve klinikopatolojik özellikleri kaydedildi. Hastaların tanı anında periferik kan testleri kaydedildi. Sistemik immün-inflamasyon indeksi (SIRI) (nötrofilsayısı×monosit sayısı)/lenfosit sayısı olarak tanımlandı. Pan-immüninflamasyon değeri (PIV) şu şekilde hesaplandı: (nötrofil

First Received: 22.03.2023, Accepted: 01.06.2023 doi: 10.5505/aot.2023.02703

sayısıxtrombosit sayısıxmonosit sayısı)/lenfosit sayısı. Optimal cut-off değerleri, ROC eğrisine göre belirlendi. Bu değerler SIRI ve PIV için sınırlı evreli KHAK'de sırasıyla 2,8 ve 585 ve yaygın evre KHAK'de 1,33 ve 497 idi. Genel sağkalım (GS), Kaplan-Meier yöntemiyle hesaplandı ve log rank testiyle karşılaştırıldı. Cox regresyon modeli kullanılarak çok değişkenli analiz tahmin edildi.
Bulgular: 81 KHAK'li hastanın 28'inde (%34,6) sınırlı evre KHAK, 53'ünde (%65,4) yaygın evre hastalık vardı. Tüm grupta medyan SIRI 2,37 (IQR, 0,34–18,59), medyan PIV ise 634,80'di (IQR, 61,57–8320). Tüm evreleri içeren hasta grubunda yapılan analizde sağkalım arasında nümerik fark olmasına rağmen her iki belirteç için istatistiksel anlamlılık elde edilememiştir (SIRI için p=0,20; PIV için p=0,058). Sınırlı evre KHAK'li hastaların GS, ECOG, SIRI ve PIV durumu için istatistiksel anlamlılık bulunurken, çok değişkenli analizde değişkenler arasında anlamlı bir fark bulunmadı.
Tartışma: Bulgularımız, SIRI ve PIV'in KHAK'de prognoz için umut verici belirleyiciler olabileceğini göstermektedir.

Anahtar kelimeler: Küçük hücreli akciğer kanseri; inflamasyon indeksi; inflamasyon değer

Introduction

Lung cancer is a subset of tumours with poor prognosis among various solid tumours due to its high morbidity and mortality rate and is divided into two main groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)[1]. SCLC represents the most aggressive form of lung cancer. Although it is characterized by a rapid response to chemotherapy and sensitivity to radiotherapy (RT), the 5-year survival rate is less than 10%[2]. The incidence of SCLC has decreased in the last decade, with a prevalence of 1-5/10,000 people in the European population, and is therefore considered an orphan disease[3,4]. According to a lung study group, SCLC is classified in two stages: limited stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC)[5]. Despite the advances in diagnosis and treatment, the prognosis remains poor and overall survival is short as the doubling tumor time is rapid, the growth fraction is high and development of metastasis is early [6].

The essential component of treatment for SCLC is systemic therapy.The primary treatment is chemo-radiotherapy for limited stage disease, whereas palliative chemo-therapy remains at the forefront for extensive stage disease[7]. Although SCLC is highly sensitive to chemotherapy, most patients relapse within 6 months. The response rate to second-line therapy depends on the treatment-free time following first-line therapy and response to first-line platinum-based induction therapy. The response rate to second-line therapy is usually around 20% to 30% in platinum-sensitive patients and 15% in platinum-resistant patients [8].

In terms of prognosis, the relationship between systemic immunity and cancer-related inflammation is important. Several blood and biochemical parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), cytokines and lactate dehydrogenase (LDH), have been studied as potential biomarkers associated with inflammation to predict drug efficacy and prognosis [9,10]. High lymphocyte and low neutrophil counts were associated with better prognosis in various tumor models[11]. Recently two immune biomarker models were developed: the systemic inflammation response index (SIRI) and the pan-immune-inflammation-value (PIV). SIRI, which integrates different inflammatory parameters (neutrophils, monocytes and lymphocytes), has proved to be a promising prognostic marker in different cancers[12,13], while PIVis derived from neutrophil, platelet, monocyte and lymphocyte counts. PIV, which has the potential to comprehensively reveal the state of systemic immune and cancer-related inflammation, has been recognised as a reliable marker for clinical outcomes in patients with advanced cancer[14]. In SCLC, some prognostic parameters such as poor performance score, extensive stage, higher lactate dehydrogenase (LDH), and weight loss

were recognized as major poor prognostic factors in retrospective studies.

This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers, as components of circulating immune cells, in small cell lung cancer. We analyzed the prognostic role of SIRI and PIV in patients with SCLC.

Materıals and Method

Study Population:

The study population included 81 SCLC patients (n=120), who applied to Medical Oncology Outpatient Clinic of Dokuz Eylül University Hospital between 2012 and 2021 for diagnosis and treatment. Medical information was retrieved retrospectively from patient files. Gender, age, comorbidities, albumin, hemoglobin, lymphocyte, monocyte, neutrophil and platelet levels at the time ofdiagnosis, disease stage, site of metastasis, treatments received and responses of patients were recorded. Tumor staging was evaluated according to the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines[15]. SCLC was defined in two stages: (a) limited stage: patients with Stage I-III disease that can be reliably treated with precise radiation doses (T any, N any, M0), and (b) extensive stage: patients with Stage IV disease (T any, N any, M 1a/b/c) or T3-4 tumor due to multiple lung nodules that are too extensive or have higher tumor/nodal volume. It includes tumors that are too large to be encompassed in a tolerable radiation plan. The end point of our study was overall survival (OS), whichwas defined as the time from diagnosis to date of death or last check-up visit.

The inclusion criteria were as follows: (1) pathologically diagnosed small cell lung adenocarcinoma; (2) suffering relapsed or metastasized disease; (3) suffering limited stage patients; (4) complete record of blood test results and follow-up data prior to initiation of therapy. The exclusion criteria were as follows: (1) history of other malignant tumors; (3) clinical evidence of recent acute infection or inflammation.

This study was approved byDokuz Eylül University Clinical Research Ethics Committee (dated: 28/09/2022, with decision number: 2022/31-05).

SIRI and PIV:

Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count×platelet count×monocyte count)/lymphocyte count. The optimal cut-off value was determined according to the receiver operating characteristic curve (ROC) and these values were 2.8 and 585 for SIRI and PIV in limited stage SCLC (LS-SCLC), while values were 1.33 and 497 for SIRI and PIV in all-stage SCLC, respectively.

Statistical Analysis:

Descriptive statistical analyses were performed for demographic, clinic-pathological and treatment modalities of patients. Analysis of study data was performed using IBM SPSS software version 24.0. Descriptive statistics of participants were shown as percentages and (n) for categorical variables, and as mean±SD for continuous variables. Before performing the hypothesis tests, the Kolmogorov Smirnov test was used to determine whether the data were normally distributed. The sensitivity and specificity of SIRI and PIV for prognosis prediction were evaluated using a time-dependent receiver operating characteristic (ROC) curve in R software. Multivariate Cox hazard regression analysis was performed on the factors that were found to be significant in the univariate analysis. Overall Survival was defined as the time from randomization to death. OS was estimated using the Kaplan-Meier method, and the results were compared using the log-rank test.The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

Table 1. Clinicopathological characteristics and inflammatory markers of patients

Variable	No of patients(%)/median(range)
Age(years)	
≤60	29(35.8)
>60	52(64.2)
Sex	
Male	67(82.7)
Female	14(17.3)
TNM stage	
LS-SCLC	28(34.6)
ES-SCLC	53(65.4)
ECOG performance score	
0	25(30.9)
1	28(34.6)
2	23(28.4)
3	5(6.2)
Death	
No	10(12.3)
Yes	71(87.7)
Neutrophils, $\times 10^9$/L	6.5(1-23.9)
Monocytes, $\times 10^9$/L	0.7(0.2-1.5)
Lymphocytes, $\times 10^9$/L	1.85(0.2-15)
Platelets, $\times 10^9$/L	274(105-687)
SIRI	2.37(0.34-18.59)
PIV	634.8(61.57-8320)
SIRI in LS-SCLC	
≤2.80	16(57.1)
>2.80	12(42.9)
PIV in LS-SCLC	
≤585	13(46.4)
>585	15(53.6)

Results

Patient Characteristics:

The characteristics of 81 patients included in this retrospective analysis aresummarized in Table 1. Among these 81 patients, 67(82.7%) were male, and 14 (17.3%) were female. The mean age was 63.38±8.7 years. Twenty eight (34.56%) patients had limited stage disease while53 (65.43%) patients had extensive stage disease.

Systemic Treatment:

In all patients, 32.1% received cisplatin+ etoposide and 38.3% received carboplatin+ etoposide chemotherapy regimens. For first-line treatment, platinum-based chemotherapy could be applied to 95.9% of all patients. Prophylactic cranial radiotherapy was applied to 3.8% of the patients and definitive radiotherapy was applied to 23.1%. In the LS-SCLC group, 9% of patients received concurrent radiotherapy with chemotherapy. After first-line chemotherapy, radiological complete response was obtained in 10 (15.3%) patients, partial response in 23 (28.4%) patients,

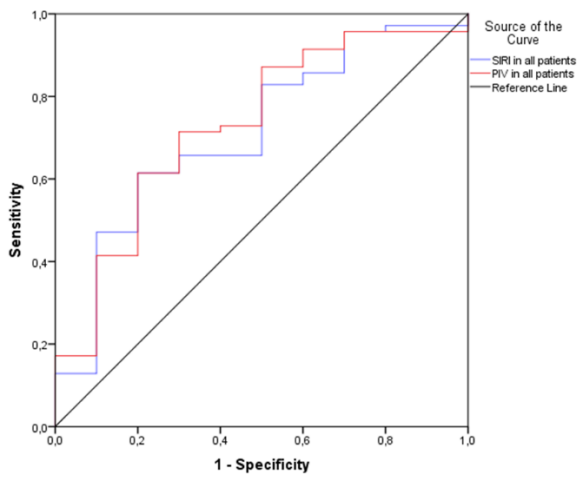


Figure 1. Receiver operating characteristic curve analysis of the optimal cut-off value for systemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 81patients with small cell lung cancer. Areas under the curve for overall survival were 0.711and 0.730 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

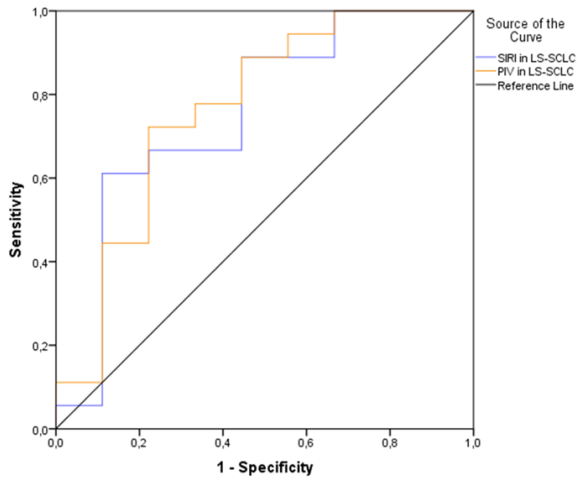


Figure 2. Receiver operating characteristic curve analysis of the optimal cut-off value forsystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 28 patients with limited stage small cell lung cancer. Areas under the curve for overall survival were 0.753and 0.765 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

progression in 20 (24.7%) patients, and stable response in the remaining patients.

Analysis of SIRI and PIV:

The median PIV of patients was 634.80 (IQR, 61.57–8320), while median SIRI was 2.37 (IQR, 0.34–18.59). For all stages, cut-off values were determined as ≥497 and ≥1.33 to establish the prediction of PIV and SIRI biomarkers and estimate prognosis for OS using the time-dependent ROC curves, respectively. In the limited stage group comprising 28 patients, the SIRI and PIV cut-off values were ≥2.80 and ≥585, respectively. Median follow-up was 29.73 (3-131) months. AUC for SIRI and PIV were 0.711(95%CI: 0.541-0.881, P=0.031) and 0.730 (95%CI:0.562-0.898, P=0.019), respectively, for all stages (Figure 1).

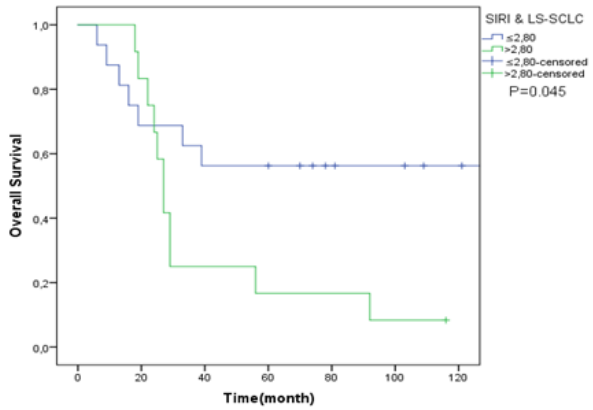
Survival Analyses:

At the end of follow-up, 87.7% of patients had died, and 12.3%were alive. For survival analysis, patients were stratified according to their optimal threshold values for SIRI and PIV. No statistically significant difference was found forsurvival between genders (p=0.67). Survival graphs for patients stratified for SIRI and PIV according to different cut-off values are shown in Figure 2. While the mOS for all patients were 17 months, the mOS were 31 months in the LS-SCLC group and 11 months in the ES-SCLC group.

Survival Analyses according to SIRI and PIV:

The mOS was 45.05 months for patients with SIRI value below 1.33, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 27.76 months for those with a value above 1.33. The mOS was 48.85 months for patients with a PIV value below 497, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 25.44 months for patients with PIV value above 497. The mOSwas 65 months in the patient group with

A



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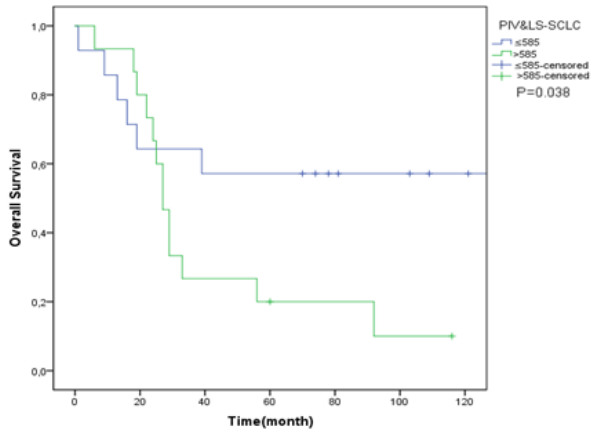

Figure 3. Kaplan-Meier curves for overall survival (OS) according tosystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV)in 28 patients with limited stage small cell lung cancer. (A) and (B).

a SIRI value below 2.80, the cut-off value determined for limited stage patients, while it was 31 for the patient group with SIRIvalue above 2.80 (p=0.045, Figure 3). Similarly, themOSwas 74 months in the patient group with a PIV value below 585, the cut-off value determined for limited stage patients, while it was 27 months for the patient group with a PIV value above 585 (p=0.038, Figure 3).

In this analysis, although there was a numerical difference between the survival rates for the patient group including all stages, statistical significance could not be obtained for both biomarkers (p=0.20 for SIRI; p=0.058 for PIV). However, when SIRI and PIV were evaluated individually in the limited and extensive stage patient groups, survival analysis showed no statistical significance in the patient group with extensive stage, whereas both biomarkers had statistically significant prediction power for prognosis in patients with limited stage disease. Univariate analysis showed statistically significant differences between OS and ECOG, SIRI and PIV status in patients with limited stage SCLC, while multivariate analysis showed no difference between the variables (Table 2).

Discussion

The markers with prognostic value in predicting the survival of the patients are lacking. Therefore, it is important to find reliable tumor markers of prognosis and facilitate treatment adjusting and patient stratification. In the present study, we evaluated prognostic effect of blood-based immune-inflammation indices, including SIRI and PIV, in small cell lung cancer. We think that SIRI and PIV may play a prognostic role especially in patients with limited stage SCLC. There is no study has examined the prognostic impact of the SIRI and PIV in SCLC patients. Consistent with these previously published data for other types of cancers, we found that a high SIRI and PIV was independently associated with worse patient OS.

Through recent advances in molecular biology, remarkable improvement has been achievedfor non-small-cell lung cancer with the use of targeted therapy and immuno-therapy. However, survival still remains short in SCLC due to the lack of effective new therapies and prognostic markers. The mean survival is 2 to 4 months in untreated patients, while it is prolonged with the use of platinum/etoposide or platinum/ irinotecan regimens to 10 months in extensive stage disease and up to 3 years in limited stage disease[16,17]. There is a lack of prognostic markers to predict survival of patients. As it is important to identify tumor markers to predict prognosis and facilitate treatment planning and patient classification, we investigated the prognostic power of two immune inflam-mation indices, SIRI and PIV, based on

Table 2.Univariate and multivariate Cox regression analyses for overall survival in LS-SCLC

Variables		Univariate analysis		Multivariate analysis	
	N(%)	HR (95% CI)	P value	HR (95% CI)	P value
Sex					
Male	26(92.9)	0.52(0.07-3.9)	0.53		
Female	2(7.1)				
Age					
≤60	11(39.3)	1.59(0.59-4.24)	0.35		
>60	17(60.7)				
ECOG PS					
0-1	19(67.9)	4.45(1.63-12.1)	**0.003**	0.22(0.04-1.02)	0.05
2-3	9(32.1)				
Hemoglobin					
≤12	8(28.6)	1.87(0.60-5.75)	0.27		
>12	20(71.4)				
SIRI					
≤2.80	16(57.1)	2.5(0.9-6.6)	**0.045**	1.90(028-12.5)	0.50
>2.80	12(42.9)				
PIV					
≤585	13(46.4)	2.8(1-8.1)	**0.04**	0.44(0.83-2.33)	0.33
>585	15(53.6)				

SIRI: systemic inflammation response index; HR: hazard ratio; CIL confidence interval; PIV: Pan-immune-inflammation value; ECOG PS: ECOG performance status scale

peripheral blood samples for SCLC. SIRI and PIV were found to be prognostic factors for OS in patients with limited stage SCLC. Inflammation is a hallmark of cancer[18]. Recent studies have shownthat prognosis is associated with patient-related factors such as inflammation, immune deficiency and nutrition in several types of cancer and the correlation between nutritional status and prognosis of cancer is particularly striking. Local and systemic inflammation is a significant promoter of tumorigenesis, tumor cell proliferation, invasion and metastasis, and it also plays a role in the response to therapeutic agents[19]. Based on this working principle of the immune system, a model consisting of peripheral blood inflammatory cells has been established. Grivennikov et al.suggest that tumor-induced inflammation results in peripheral hematological changes, including in neutrophils, lymphocytes, monocytes and platelets via release of various cytokines[20]. Therefore, blood cell count is an easy to obtain and cost-effective index to represent the host immune inflammation status. Li et al reported that SIRI is an independent prognostic factor in lung cancer patients after thoracoscopic surgery. However, the prognostic role of SIRI in advanced stage lung cancer patient remains unclear[21]. In our study, we found that SIRI can be a prognostic marker in limited-stage small cell lung cancer, both easily and cost-effectively. PIV is a biomarker that was recently developed based on neutrophils, monocytes, platelets and lymphocytes, and its relationship with OS has been well established[14]. High PIV was a strong predictor of poor PFS and OS in colorectal cancer, breast cancer, renal cancer, melanoma and NSCLC treated with immunotherapy [14,22,23]. Ligorio et al. reported that the PIV was a useful predictor of OS in HER2+ advanced breast cancer patients treated with first-line trastuzumab-pertuzumab containing biochemotherapy[24]. Our results demonstrate that there is a significant relation-ship between inflammatory markers and cancer. Our findings with SIRI and PIV reflecting the systemic immunological status

demonstrated that it is possible to predict prognosis. In the present study, we found a statistically insignificant difference in OS across all patient groups when patients with low SIRI and low PIV were compared to those with high SIRI and PIV. However, for limited stage SCLC patients, our results showed that patients in the low SIRI and PIV group (SIRI≤2.80; PIV≤585) had longer OS compared to those in the high SIRI and PIV group (p=0.045; p=0.038). We of course acknowledge that future studies are needed to confirm our findings, and also to examine other potential mechanism(s) by which SIRI and PIV affects clinical outcome in cancer patients. Besides SIRI and PIV, ECOG performance score (PS) and disease stage have also been shown to be independent prognostic factors. In our patients with extensive stage disease and poor ECOG PS, higher SIRI and PIV levels may reflect impairment in the overall status of systemic inflammation. While there was a statistical significance between OS and ECOG, SIRI and PIV status in univariate analysis, no significance was found between the variables with multivariate analysis. This may be associated with our restricted number of patients. Although our study included patients with all stages of SCLC, we suggest that SIRI and PIV may play prognostic roles, particularly in patients with limited stage SCLC.Considering that prognostic markers such as SIRI and PIV have been studied relatively lessin SCLC compared to other cancers in previous studies, we believe that our study will contribute to increasing knowledge in this field.

Although our study, together with previous researches, demonstrated that SIRI and PIV are promising tools for predicting prognosis in SCLCpatients, the results of our research should be interpreted with caution due to the obvious limitation of the research.The mainlimitations include its retrospective design and restricted patient population. To the best of our knowledge, the number of studies ofpatients with SCLC is low in this field.

Conclusion

In conclusion, SIRI and PIV may be suitable, cost-effective and reliable markers of immune inflammation, especially for predicting prognosis in patients with limited-stage SCLC. They may help therapeutic planning and patient classification. However, well-designed prospective studies are required.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin 2021; 71(3):209–49.
2. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society. 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed October 20, 2020.
3. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006; 24(28): 4539-4544.
4. Breitling LP, Rinke A, Gress TM. Recent survival trends in high-grad neuroendocrine neoplasms and lung cancer. Neuroendocrinology 2020; 110(3-4): 225-233.
5. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and Classification of SCLC. Cancers 2021: 13(4): 820.
6. World Health Organization. International Agency for Research on Cancer, Section of Cancer Information. Cancer Incidence and Mortality Worldwide, 2008.
7. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. Oncologist 2010; 15: 187-195.
8. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small cell lung cancer. J Thorac Oncol 2012; 7(5): 866-872.
9. Hardy-Werbin M, Rocha P, Arpi O, et al. Serum Cytokine Levels as Predictive Biomarkers of Benefit From

Ipilimumabin Small Cell Lung Cancer. Oncoimmunology 2019; 8(6): e1593810.
10. Russo A, Franchina T, Ricciardi GRR, et al. Baseline Neutrophilia, Derived Neutrophil-to-Lymphocyte Ratio (dNLR), Platelet-to-Lymphocyte Ratio (PLR), and Outcome in nonSmall Cell Lung Cancer (NSCLC) Treated with Nivolumab or Docetaxel. J CellPhysiol 2018; 233(10): 6337–43.
11. Deng M, Ma X, Liang X, et al. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? Oncotarget 2017; 8: 37200-7.
12. Geng Y, Zhu D, Wu C, et al. A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. Int Immunopharmacol 2018; 65: 503-10.
13. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 2016; 122: 2158-67.
14. Corti F, Lonardi S, Intini R, et al. The pan-immune-inflammation value in microsatellite instability-high metastatic colorectal cancer patients treated with immune checkpoint inhibitors. Eur J Cancer 2021; 150:155–67.
15. Rami-Porta R, Asamura H, Travis WD, et al. Lung cancer- major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer JClin 2017; 67: 138-55.
16. Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007; 12(1): 20–37
17. Kubota K, Hida T, Ishikura S, et al. Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with oposide and cisplatin plusc on current accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomized phase 3 study. Lancet Oncol. 2014; 15(1): 106–13.
18. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674.
19. Chen L, Kong X, Wang Z, et al. Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med. 2020; 24(5): 2993–3021
20. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140(6): 883–899.
21. Li S, Yang Z, Du H, Zhang W, Che G, Liu L. Novel systemic inflammation response index to predict prognosis after thoracoscopic lung cancer surgery: a propensity score-matching study. ANZ J Surg. 2019; 89(11): E507–E513.
22. Fucà G, Guarini V, Antoniotti C, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE First-Line Trials. Br J Cancer 2020; 123(3):403–9.
23. Prelaj A, Ferrara R, Rebuzzi SE, et al. EPSILoN: a prognostic score for immunotherapy in advanced non-small-cell lung cancer: a validation cohort. Cancers 2019, 11(12): 1954.
24. Ligorio F, Fucà G, Zattarin E, et al. The pan-immune-inflammation-value predicts the survival of patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive advanced breast cancer treated with first-line taxane-trastuzumab-pertuzumab. Cancers (Basel). 2021; 13: 1964.

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Doi: 10.5505/aot.2023.02703

Original Article

Prognostıc Factors and Changing Paradigms in Febrile Neutropenia Episodes

Febril Nötropeni Ataklarında Prognostik Faktörler ve Değişen Paradigmalar

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ABSTRACT

Introduction: The epidemiology of pathogens responsible for febrile neutropenia (FEN) has changed and so did the diagnostic tools in the field of infectious diseases. This study examined the changing paradigms and prognostic factors in FEN episodes.

Materials and methods: This was a prospective and observational study of 145 adult patients aged 18 and older with solid tumor and hematological malignancies and who received FEN treatment at our cancer center between April 2020 and April 2021; 176 FEN episodes developed in patients and were examined.

Results: Hematological malignancy was present in 70.3% (n=102) of the 145 patients. Microbiologically-confirmed infections were seen in 46% of FEN episodes. The most common focus of infection was lower respiratory tract infections with 27.1%. In 66.2% (n=45) of FEN episodes, only gram-negative microorganisms grew while only gram-positive microorganisms grew in 19.1% (n=13). Bacteremia was significantly higher in patients with hematological malignancies versus patients with solid organ tumors (p<0.001). Deep neutropenia on day zero was associated with bacteremia (p<0.001), but the relationship between prolonged neutropenia and bacteremia could not be demonstrated (p=0.34). FEN-related mortality was 9.7% (n=17). The risk of mortality in FEN was 10.25-fold higher in patients with pneumonia and 6.05-fold higher in patients with prolonged neutropenia.

Discussion: We determined that the frequency of pneumonia increased in the FEN clinic due to the effects of newly introduced chemotherapeutics. Gram-negative microorganisms were more common in the causative profile unlike the previous decade. Pneumonia and prolonged neutropenia increase mortality. Comprehensive multicenter studies will allow for the development of new management algorithms for changing paradigms.

Keywords: Febrile neutropenia, Hematological Malignancies, Mortality, Solid Tumor

ÖZET

Giriş: Enfeksiyon hastalıklarının klinik ve laboratuvar tanısındaki gelişmeler ve yıllar içinde değişen etken spektrumu kanser tedavisi süresince Febril nötropeni (FEN) ataklarının güncel takibini gerekli hale getirmiştir. Bu çalışmada FEN ataklarında değişen paradigmaların ve prognostik faktörlerin araştırılması amaçlanmıştır

Gereç ve yöntemler: Prospektif, gözlemsel yürütülen bu çalışmaya, Nisan 2020-Nisan 2021 tarihleri arasında kanser merkezimizde FEN nedeniyle yatarak tedavi gören 18 yaş ve üzeri solid tümörü ve hematolojik malignitesi olan 145 erişkin hasta alındı ve hastalarda gelişen 176 FEN atağı incelendi.

Bulgular: Çalışmaya dâhil edilen 145 hastanın %70.3'ünde (n=102) hematolojik malignite mevcuttu FEN ataklarının %46'sında mikrobiyolojik olarak kanıtlanmış enfeksiyon saptandı ve en sık enfeksiyon odağının %27.1 ile alt solunum yolu enfeksiyonları olduğu görüldü. FEN ataklarının %66.2'sinde (n=45) sadece gram negatif, %19.1'inde (n=13) sadece gram pozitif mikroorganizma üredi. Hematolojik maligniteli hastalarda solid organ tümörlü hastalara göre bakteriyemi istatistiksel olarak anlamlı olacak şekilde daha yüksekti (p<0.001). Sıfırıncı günde derin nötropeni olması bakteriyemi ile ilişkili

First Received: 01.04.2023, Accepted: 07.06.2023 doi: 10.5505/aot.2023.79990

bulunurken (p<0.001), uzamış nötropeninin bakteriyemi ile ilişkisi gösterilemedi (p=0.34). FEN'e bağlı mortalite %9.7 (n=17) oranında görüldü. FEN'de mortalite riski, pnömonisi bulunan hastalarda 10.25 kat ve uzamış nötropenisi olan hastalarda 6.05 kat daha fazlaydı.
Tartışma: FEN ataklarının klinik ve laboratuvar bulgularının araştırıldığı bu çalışmada yeni kullanıma giren kemoterapötiklerin etkisiyle FEN kliniğinde pnömoni sıklığının arttığı ve etken profilinde geçtiğimiz dekattan farklı olarak gram negatif mikroorganizmaların daha çok olduğu saptanmıştır. Ayrıca pnomoni ve uzamış nötropeni varlığının mortaliyeti arttırdığı görülmüştür. Kapsamlı multicenter çalışmalar, değişen paradigmalara yönelik yeni yönetim algoritmalarının oluşturulmasına olanak sağlayacaktır.

Anahtar kelimeler: Febril Nötropeni, Hematolojik maligniteler, Mortalite, solid tümör

Introduction

The development of multi-drug chemotherapy protocols and the use of higher doses in cancer treatment has increased treatment success, the resulting immunosuppression (especially neutropenia) predispose patients to severe infections. Infections occurring in the neutropenic period can cause rapid mortality due to the insufficiency of defense cells. Infection signs that are vague in the neutropenic patient group cause clinical complexity in the FEN period and delay the start of treatment. The most important approach reduces mortality in these patients and initiates empirical antibiotic therapy as soon as possible after taking the necessary samples for culture [1,2]. Therefore, it has become a priority to quickly interpret clinical and laboratory findings and proceed to the treatment phase without losing time.

The patient's primary disease, the chemotherapy protocol, the factors detected in the previous FEN attack, and the level and duration of neutropenia should all be considered during the empirical treatment decision. In addition, each clinic's causative profile is a crucial factor that should be considered when choosing an empirical antibiotic [3,4]. Therefore, surveillance data that includes causative microorganisms and antibiotic susceptibility play an important role in developing an effective empirical treatment protocol [5,6].

This study aimed to determine the clinical characteristics of FEN episodes, laboratory parameters, agents growing in culture, and growth rates to identify the causes of infection and review compatible treatment plans. We further aimed to determine the factors impacting mortality and prognosis in patients with solid tumor and hematological malignancies who were followed up prospectively for one year at the our cancer center.

Material and Methods

Patients

This study included 145 adult inpatients with solid tumors and hematological malignancies aged 18 and older and treated for FEN between April 2020 and April 2021 at the our cancer center; 176 FEN episodes developed in these patients and were examined prospectively. No intervention was made in the follow-up and treatment of the patients enrolled here. Permission was obtained from the Clinical Research Ethics Committee prior to the study (Decision no:2020-03/581).

In accordance with the Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) clinical guidelines, the episodes of patients who had a fever of ≥38.3°C determined with one oral measurement or a fever of ≥38.0°C for more than one hour, those who had an absolute neutrophile count of ≤500 cells/mm^3 or 500-1000 cells/mm^3 and expected to decrease to below 500 cells/mm^3 within 24-48 hours were included as FEN. People with more than one isolate during the same episodes were not included in the study. The study's criterion was that each FEN patient included in the study recovered completely from the previous neutropenia attack. If there was a period longer than four weeks between the two episodes in the same patient, then the

second attack was also considered a new neutropenic attack.

Data collection

All patients eligible for the study were followed up in the wards with daily visits, and their data were recorded in the patient data form after obtaining signed informed consent form. Laboratory data and microbiological data were recorded daily from the hospital automation system. Peripheral blood cultures, urine cultures, and catheter blood cultures, if any, were taken simultaneously from all patients included in the study prior to treatment. Peripheral blood culture was obtained as two blood samples from peripheral veins in patients without a catheter. There was at least half an hour between the two blood samples. Other cultures such as sputum and stool cultures were taken from the sites considered to be the focus of infection based on the clinical symptoms and findings. The samples taken for culture were examined using traditional microbiological methods. Isolated agents were identified using conventional methods and the automated VITEK 2 (bioMerieux, France) system. If a known pathogenic microorganism grew in at least one blood culture, then the blood culture was deemed positive. Two or more growths in the blood culture of coagulase-negative staphylococci were considered positive. According to the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the disc diffusion method or an automated system were used to determine the antibiotic susceptibility of these grown agents.

In the hematology and medical oncology clinics of our center, empirical antibiotic therapy was started by the doctor in charge of the ward or an infectious diseases specialist after considering the microorganism profile from the previous year and their antibiotic susceptibility. The patients were evaluated with clinical findings, physical examination findings, laboratory results, and micro-biological results at daily visits; daily changes were also recorded. Infectious diseases in FEN patients who were followed up were defined as primary bloodstream infection, catheter-related bloodstream infection, urinary tract infection, pneumonia, soft tissue infection, and gastrointestinal tract infection in accordance with the Centers for Disease Control and Prevention (CDC) definitions. Other patients in whom no focus could be detected with clinical, laboratory, microbiological, and radiological findings were evaluated as fever of unknown origin (FUO).

Statistical Method

Data were analyzed with the SPSS software (version 22.0. Armonk, NY: IBM Corp.). The conformity to normal distribution of the data was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrorov-Smirnov/Shapiro-Wilk tests). The arithmetic mean, standard deviation, median, minimum and maximum values were used for evaluation of numerical data while frequency distributions and percentages were used to summarize categorical data. A Chi-squared ($\chi 2$) test was used to compare categorical data. The relationship between non-normally distributed numerical data and categorical data was evaluated with the Mann-Whitney U test. The Kruskal-Wallis test was used to evaluate three or more groups with numerical data. A posthoc Mann-Whitney U-test and Bonferroni correction were performed for pairwise comparisons between groups with significant Kruskal-Wallis test results. Logistic regression analysis was used to examine potential risk factors and independent predictors of treatment outcomes in FEN patients. The Hosmer-Lemeshow test was used to determine the goodness of fit of the model. A p-value of <0.05 was considered statistically significant.

Results

Sociodemographic Characteristics of Patients

We found 176 FEN episodes in 145 adult inpatients. Of the 145 patients included in the study, 52.4% (n=76) were female. The mean age of the patients was 47.16±15.50 years ranging from 18 to 80 years old; 70.3% (n=102) of the patients had hematological

Table 1: Baseline Characteristics of Patients

	n	%
Mean age	47.16 (±15.50)	
Gender		
Female	76	52.4
Male	69	47.6
Malignancy Type		
Solid Organ Tumor	43	29.7
Hematological Malignancy	102	70.3
Comorbidities		
Diabetes Mellitus (DM)	16	11.0
Hypertension	28	19.3
Coronary Artery Disease	5	3.4
Other (Chronic kidney disease, COPD)	25	17.2

malignancies, while 29.7% (n=43) had a solid organ tumor. The characteristics and comorbidities of the patients are presented in Table 1.

Characteristics of the FEN Episodes

Of the 176 FEN episodes, 112(63.6%) were developed during hospitalization, while 64 (36.4%) began outside the hospital. Among the nosocomial FEN episodes, 108 (96%) occurred in patients with haematological malignancies and 84 (75%) were associated with prolonged neutropenia. Bacteremia was significantly more frequent in patients who had FEN episodes during hospital stay ($p<0.001$). The most common focus of infection in FEN episodes was pneumonia. This was followed by catheter infection (22.6%) and primary bloodstream infection (20.3%) (Table 2). The total mucositis rate was 17.0% (n=30). Diarrhea was seen in 19.9% (n=35) of the FEN episodes.

Considering neutropenic fever syndromes both clinically and microbiologically, 46% (n=81) of the FEN episodes were micro-biologically-proven infections (44.8% diagnosed with culture, 1.2% with PCR test); 29.5% (n=52) had clinically identified focus of infection. The FEN focus could not be detected in 24.5% (n=43) of the patients, and thus they were evaluated as FUO. The median duration of treatment in FEN episodes was 14 days (min: 2.00-max: 47.00) and 13 days (min:2.00 - max: 50.00) days, respectively, for microbiological and clinically-documented infections. This was significantly longer than

Table 2. Distribution of Infection Foci

Focus	n	%
Lung Infection	36	27.1
Catheter Infection	30	22.6
Primary Bloodstream Infection	27	20.3
Gastrointestinal System Infection	18	13.5
Soft Tissue Infection	17	12.8
Urinary Tract Infection	5	3.8

the treatment duration of patients with unexplained fever. The total FEN time and total neutropenia times were shorter in the group of patients with unexplained fever ($p<0.001$). The mean duration of FEN was 7 (min:1-max:141) days in patients with hematological malignancies, and 2 days (min:1-max:14) in patients with solid organ malignancies ($p<0.01$). Additionally, 96.2% (n=51) of patients with prolonged neutropenia (neutropenia lasting longer than 10 days) (n=53) had hematological malignancies.

Laboratory and Radiological Characteristics of Patients

The mean leukocyte count at the onset of FEN attack was 595.7 $x10^3$ cells/uL, the mean neutrophil count was 129.6 $x10^3$ cells/uL, and the mean CRP was 121.21 mg/L. The effects of leukocyte count, CRP, and procalcitonin level at the time of diagnosis on mortality and duration of neutropenia was not shown ($p>0.05$). Here, 64.8% (n=114) of the patients had deep neutropenia on day zero, and the mean duration of deep neutropenia in these patients was 8.15±13.34 days (min: 1.00 - max: 112.00). The laboratory findings of the patients during FEN are presented in Table 3. Computed tomography (CT) was performed in 64.8% (n=114) of the patients. The CT of 53.5% (n=61) of the patient did not reveal any findings of infection, while pneumonia findings were detected in 46.5% (n=53) of the patients.

Microbiological Characteristics of FEN Episodes

Culture samples were positive in 53.4% (n=94) of FEN episodes. Growth was observed in peripheral blood culture in 38.6% (n=68), catheter culture in 36.4% (n=64), urine culture in 9.1% (n=16), and sputum culture in 5.1% (n=9). Simultaneous growth

Table 3. Laboratory Values of Patients in the Neutropenic Fever Period

Value	Mean±SD	Median (Min-Max)
WBC (n=176)	595.79±771.53	340.00 (00.00-6180.00)
Neutrophil (n=176)	129.60±160.95	70.00 (0.00-500.00)
Lymphocyte (n=176)	476.16±2154.44	160.00 (00.00-27900.00)
Platelet (n=176)	57,256.00±74,344.96	26,000.00 (9.60-523,000.00)
Hemoglobin (n=176)	8.70±1.84	8.30 (5.00-14.30)
MPV (n=176)	9.98±2.35	10.00 (0.00-14.30)
AST (n=159)	29.14±35.99	17.80 (5.70-221.00)
ALT (n=161)	33.47±47.53	19.20 (3.00-412.00)
Creatinine (n=165)	0.85±0.90	0.66 (0.19-6.80)
CRP (n=164)	121.21±89.14	106.01 (0.24-517.00)
Procalcitonin (n=132)	6.34±21.99	0.39 (0.01-75.00)
Glucose (n = 131)	126.99±76.53	111.00 (67.00-888.00)

Abbreviations: WBC= White Blood Cell, MPV=Mean Platelet Volume, AST=Aspartate Aminotransferase, ALT=Alanine Transaminase, CRP=C-Reactive Protein

Table 4. Microorganisms in Blood Culture

Microorganism	**n**	**%**
Gram Negative Bacteria		
E. coli	28	41.2
K. pneumoniae	8	11.8
P. aeruginosa	7	10.3
Enterobacter cloacae	3	4.4
Achromobacter xylosoxidans	1	1.5
Aeromonas sobria	1	1.5
Gram Positive Bacteria		
Coagulase negative staphylococci	12	17.6
Enterococcus spp.	2	2.9
Streptococcus gordonii	2	2.9
Staphylococcus aureus	1	1.5
Other		
Candida spp.	3	4.4

Table 5: Comparison of Treatment Results and Characteristics of Patients

	Recovered		Ex			
	n	%	n	%	χ^2	*p*
Combined Treatment	115	72.8	16	94.1**	3.711	0.041
Comorbidities	46	29.1	4	23.5	0.235*	0.433
Hematological Malignancy	115	72.8	15	88.2	1.918*	0.135
Attack Developed at the Hospital	99	62.7	12	70.6	0.416	0.519
G-CSF prophylaxis	52	32.9	3	17.6	1.659	0.198
Antibiotic prophylaxis	112	70.9	15	88.2	2.321*	0.103
Mucositis Presence	27	17.1	3	17.6	0.003*	0.587
Pneumonia	30	19.0	13	76.5	27.364*	<0.001
Antifungal Therapy	27	17.1	10	58.8	16.035*	<0.001
Second Line Treatment	13	8.2	14	82.4	64.632*	<0.001
Final Focus Detected	116	73.4	16	94.1**	3.548*	0.046
Culture Positivity	81	51.3	13	76.5**	3.922	0.048
Prolonged Neutropenia	41	25.9	12	66.7	12.730	<0.001

Fisher's exact chi-square test was used.** Represents the group from which the difference originates

Table 6. Logistic regression model developed to predict treatment outcomes

Variables		B	Standard error	*p*	Exp (β)
Pneumonia presence	Yes (Ref)	2.328	0.638	0.000	10.25
Prolonged Neutropenia	Yes (Ref)	1.800	0.643	0.005	6.05
Hematological Malignancy	Yes (Ref)	1.363	1.352	0.313	3.910
G-CSF Prophylaxis	Yes (Ref)	0.143	0.928	0.878	1.154
Antifungal Therapy	Yes (Ref)	0.197	0.936	0.834	1.217
Final Focus Detected	Yes (Ref)	0.401	1.315	0.760	1.493
Blood Culture Positivity	Yes (Ref)	1.067	0.846	0.207	2.908

Ref= Reference Assessed by binary logistic regression analysis. Hosmer-Lemeshow test: 0.590 Nagelkerke R Square: 0.425

was observed in peripheral blood and catheter blood cultures in 27.27% (n=48) of the episodes. The most frequently isolated micro-organisms in blood cultures were E. coli and coagulase-negative staphylococci. Of fatal cases, 50% had P. aeruginose and 33% had Klebsiella pneumoniae (K. pneumoniae) (Table 4) in blood culture.

Bacteremia was detected in 47.7% (n=84) of the episodes. Bacteremia was significantly higher in patients with hematological malignancies compared to patients with solid organ tumors ($p<0.001$). While deep neutropenia on day zero was found to be associated with bacteremia ($p<0.001$), the relationship between prolonged neutropenia and bacteremia could not be demonstrated ($p=0.34$). A model was developed with the type of malignancy, the initial antibiotic treatment regimen (monotherapy or combination therapy), and the presence of deep neutropenia on the first day to predict the development of bacteremia in patients with FEN. The logistic regression model explained 28.9% of the bacteremia risk (Nagelkerke R Square= 0.289). According to the model, the risk of developing bacteremia in patients with hematological malignancies was 8.33-fold higher than the risk of developing bacteremia in patients with solid organ tumors. The risk of developing bacteremia was 2.77-fold higher in patients receiving combined therapy than in patients receiving monotherapy. Patients with deep neutropenia on the first day were 2.45-fold more likely to develop bacteremia than those without.

Treatment Characteristics

Monotherapy was started as an initial treatment in 68.7% (n=121) of 176 FEN episodes. Cefaperazone- sulbactam was used most frequently. Here, 76.3% of the patients who were started on combination therapy were given β-lactam/β-lactamase inhibitors. It was determined that 51.1% (n=90) of the patients who received the initial treatment had a treatment change. Growth in blood culture was detected in 61.8% of the patients whose treatment was changed, and patients with a growth in their blood culture required more treatment changes after isolation ($p<0.05$). Due to clinical course and/or culture results treatment success was achieved in 75.5% of the patients who underwent a treatment change but 24.4% of them underwent another treatment change

Factors Affecting Survival Outcomes and Mortality

It was observed that 18.2% (n=32) of the patients developed hypoxia during the given treatments, and 9.7% (n=17) of the patients were intubated. Another 12.5% (n=22) of the patients were treated in the intensive care unit for an average of 3.77±2.28 days (min: 1.00 - max: 10.00). It was determined that 89.8% (n=158) of the patients were discharged with full recovery, 9.7% (n=17) of the patients died due to infection, and 0.6% (n=1) died due to other causes. Table 5 compares the patient characteristics associated with mortality.

A model including pneumonia and prolonged neutropenia was developed to predict treatment success in FEN patients (Table 6). The logistic regression model can predict 42.5% of treatment success (death or discharge with cure) (Nagelkerke R Square= 0.425). Table 6 shows that the mortality risk of patients with pneumonia in the FEN period was 10.25-fold higher than that of those

without pneumonia. Patients with prolonged neutropenia during the FEN period had a 6.05-fold higher risk of dying after treatment than those without prolonged neutropenia.

Discussion

Our study prospectively examined FEN patients in our hematology, oncology, and bone marrow transplant (BMT) centers: 9.7% (n=17) of the patients died due to FEN. The mortality rates related to FEN vary according to the literature. Ghosh et al. studied hematological patients and found that mortality due to FEN was 19.5% [7]. Another study's mortality rate was 11.2% in 232 patients—56.6% of whom had hematological malignancies [8]. Hatamabadi et al. examined FEN episodes in patients with mostly solid organ tumors (97.8%), and the mortality rate was 5.3% [9]. These differences may be due to several factors such as malignancy types, chemotherapy regimens given, accompanying comorbid diseases, different microorganisms grown in the culture depending on flora of centers and demographic characteristics of the population.

The mean age of the patients in the study was 57, and 52.4% were female. Most patients had hematological malignancies, and one-third of them had comorbidities such as DM, hypertension, and coronary artery disease. Gender, type of malignancy and presence of additional diseases were not associated with mortality. The absence of differences between gender and mortality in the study by Hatamabadi et al. supports our study [9]. However, unlike our study, there are also publications in the literature suggesting that additional diseases affect mortality negatively [10,11]. While the rate of patients over 65 years of age in our study was 15%, it was 28.5% in the studies of Kuderer et al [10]. The entire population of Hosmer et al.'s study consists of elderly people [11]. Therefore, the reason for this difference with the literature can be because comorbidities are more common in the elderly population, and the elderly population in these studies is higher than in our study.

The use of granulocyte colony stimulating factor (G-CSF) in patients receiving chemotherapy leads to a decrease in the normalization of neutrophil counts and the duration of hospitalization but has no effect on mortality [12,13]. Renner et al. found evidence for the decrease of all-cause mortality during chemotherapy with prophylactic G-CSF administration, but this relationship was less reliable. In this study, there was no relationship between the use of G-CSF and the mortality associated with infection after the development of FEN [13]. We found that 31.8% of the patients were receiving primary G-CSF prophylaxis: No relationship between the use of primary G-CSF and mortality could be demonstrated, which is consistent with the literature.

The long duration of neutropenia during episodes not only facilitates the development of complications due to the long-term insufficiency of the immune system, but also leads to a dose reduction in subsequent chemotherapy and thus to the disruption of effective cancer treatment. The mean duration of neutropenia was 12 days in the study of Demirel et al., and 15 days in Mert et al [14,15]. The mean duration of neutropenia was shorter than in those studies. Özden et al. observed a short duration of neutropenia (mean 3.3 days) in their study similar to our study [16]. While no statistically significant difference was found in this study in the mean neutropenia duration between patients with hematological malignancies and patients with solid organ tumors, the neutropenia duration was significantly longer in patients with hematological malignancies in our study. Neutropenia duration is one of the factors that is directly associated with mortality [17,18]. We found that a prolonged neutropenia duration (longer than 10 days of neutropenia) was significantly associated with mortality ($p<0.001$). Ceken et al. reported that the duration of neutropenia was also a risk factor for mortality [19].

Leukocyte count, CRP, and procalcitonin had no effect on mortality or duration of neutropenia. On the other hand, there are

many publications in the literature reporting that CRP and procalcitonin are effective in predicting the course of FEN and mortality. A Turkish study by Sahin et al. showed that CRP was an important prognostic parameter in FEN episodes [20]. Another study conducted in hematological malignancies revealed that the procalcitonin measured on hour 24 and the CRP measured on hour 48 were helpful in detecting fungal infections. On the other hand a study found that CRP could be a better marker than procalcitonin in determining disease-related fever [21].

The focus of infection could not be detected by clinical, microbiological, and radiological methods in 24.5% of the episodes. Demirel et al. reported that the rate of clinically-proven infection was 36% [15]. Maybe the main reason why more clinically and microbiologically proven fever foci and fewer unknown fevers were seen in our study is that we have finest diagnostic tools now like procalcitonin, quicker CT scan, ultrasound, cultures etc.

The most common infection focus detected was pneumonia at 27.1%. In studies conducted on hematological and oncological patients, the rate of pneumonia was 12.3% and 18.6% [9,22]. Our study was conducted during the COVID-19 pandemic, and imaging studies were performed more frequently during episodes. Thorax CT was performed in 64.8% of the patients, and pneumonia was found in 46.5% of the images. Therefore, patients in our series may have been diagnosed with pneumonia more frequently.

An uprising of gram-positive infections was reported after the 2000s [23,24,25]. Gram negative infections are much more commonly reported lately [26,27]. This is consistent with our findings. It is known that the presence of mucositis is an important risk factor for the predominance of gram-positive micro-organisms [28,29]. Safia et al. found that the incidence of mucositis was 50% [30]. Similarly, the rate of mucositis was 36% in a multicenter Spanish study conducted by Aguilar-Guisada [31]. In our study, mucositis was present in 17% of FEN episodes. Reducing the incidence of mucositis with appropriate oral care in our center may have reduced the incidence of FEN episodes caused by gram-positive bacteria.

Bacteremia was significantly more frequent in patients with hematological malignancies than in patients with solid organ tumors. Patients with hematological malignancies are usually treated with high-dose cytotoxic chemo-therapy regimens: Thus, the length of hospitalization is longer, and immuno-suppression is deeper, which causes a high risk of bacteremia [32]. In support of this, the rate of bacteremia in our study was higher in patients with deep neutropenia at day zero versus those without. A Turkish study examined 164 FEN cases, and found that the rate of bacteremia was higher in the group with deep neutropenia at the beginning33. Although it is known that prolonged neutropenia increases the risk of bacteremia, no relationship between prolonged neutropenia and bacteremia was found in our study [34].

One of the most important factors reducing mortality in FEN is the rapid initiation of empirical antibiotic therapy [35]. Mono-therapy was started as the initial treatment in 68.7% of the episodes. A review of the literature identified studies showing that monotherapy has similar efficacy to combination therapy and is even more advantageous because it has fewer side effects [36,37,38]. We found that the mortality rate in the group in which combination therapy was initiated was higher than that in the monotherapy group. The need for glycopeptide group antibiotics in the clinical evaluation at the beginning of the treatment suggests that the clinical situation in these patients is severe. The cause of mortality depends on the severity of the patient's FEN attack rather than the inadequacy of the combination therapy.

Invasive fungal infections (IFI) are important causes of morbidity and mortality in febrile neutropenic patients and other immuno-compromised populations after intensive chemotherapy [39]. Candidemia was

observed in three FEN episodes (1.7%) in our study. Goldberg et al. showed in a systematic review that empirical treatment did not significantly reduce mortality but reduced IFIs [40]. In our study, antifungal treatment was started in 21% (n=37) of the patients. Mortality was statistically higher in the group that received antifungal therapy than in those who did not. This proves that the mortality of invasive fungal infection is high even with appropriate treatment protocols.

Limitations

Our study has several limitations. First, the empirical treatment change rates were high in episodes. The reasons for these treatment changes in patients could not be investigated. Second, we could not reported data regarding susceptibility patterns and colonization. Third, we could not report etiological data for pneumonia which was the major cause of death in the study. Furthermore, the single-center limited the study population. Multicenter studies can offer more detailed results.

Conclusion

We prospectively examined the clinical and laboratory findings of FEN episodes in patients with hematological and solid malignancies and found that the frequency of pneumonia increased in FEN. The mortality associated with pneumonia was high, and gram-negative microorganisms were more common in the causative profile. The increasing rates of resistance in gram-negative microorganisms worldwide have brought this agent profile change to an alarming level. For better management of the process in FEN episodes, centers should know their own causative pathogen profiles and antibiotic susceptibilities and develop treatment algorithms accordingly.

REFERENCES

1. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis 2005; 40: 246-252.
2. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580-637.
3. Demiraslan H, Yıldız O, Kaynar L, Altuntaş F, Eser B, Aygen B. Febril nötropenik hastalardan izole edilen mikroorganizmalar ve antimikrobiyal duyarlılıkları: 2005 yılı verileri. Erciyes Tıp Dergisi. 2007; 29: 376–380.
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52: 427-431.
5. Sigurdardottir K, Digranes A, Harthug S, et al. A multi-centre prospective study of febrile neutropenia in Norway: microbiological findings and antimicrobial susceptibility. Scand J Infect Dis 2005; 37: 455-464.
6. Deniz Yayla B, Azak E, Mutlu B, Dündar D. Febril nötropenik hastalardan izole edilen mikroorganizmaların dağılımı ve antimikrobiyal duyarlılıkları: Altı yıllık bir gözlemin sonuçları. Klimik Dergisi. 2019; 32: 71–77.
7. Ghosh S, Chakraborty M, Samanta S, et al. Analysis of blood stream infections, antibiograms and clinical outcomes in haematological patients with febrile neutropenia: data from a tertiary care haematology institute in India. Ann Hematol 2021; 100: 395-403.
8. Al-Tawfiq JA, Hinedi K, Khairallah H, et al. Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. J Infect Public Health. 2019; 12: 364-366.
9. Hatamabadi H, Arhami Dolatabadi A, Akhavan A, Safari S. Clinical Characteristics and Associated Factors of Mortality in Febrile Neutropenia Patients; a Cross Sectional Study. Arch Acad Emerg Med 2019; 7: 39.
10. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006; 106: 2258-2266.
11. Hosmer W, Malin J, Wong M. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer. 2011; 19: 333-341.
12. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Version 3.2021: Hematopoietic Growth Factors. http://www.nccn. org. 2021.

13. Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database Syst Rev 2012; 10: CD007913.
14. Mert D, Ceken S, Iskender G, et al Epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies. J Infect Dev Ctries 2019; 13: 727-735.
15. Demirel A, Tabak F, Ar MC, et al. Secondary Infections in Febrile Neutropenia in Hematological Malignancies: More Than Another Febrile Neutropenic Episode. Turk J Haematol 2015; 32: 243-50.
16. Özden M, Denk A, Demirağ K, Elkıran T. Febril Nötropenik Olgular ve Risk Faktörlerinin Değerlendirilmesi. Mediterr J Infect Microb Antimicrob 2013; 2: 1–7.
17. Bulut N, Kiki I, Sincan G, Yıldırım R, Polat M, Bilen Y, Gündogdu M. Akut myeloid lösemili hastalarda indüksiyon kemoterapisi sonrası gelişen nötropeni süresini etkileyen faktörler. Abant Tıp Dergisi. 2015; 4: 371–377.
18. Dale DC. Advances in the treatment of neutropenia. Curr Opin Support Palliat Care. 2009; 3: 207-212.
19. Ceken S, Gedik H, Iskender G, et al Evaluation of Risk Factors for Mortality in Febrile Neutropenia. J Infect Dev Ctries 2020; 14: 886-892.
20. Şahin S, Gençer S, Doğan M, Demirhan G, Özer S. Febril nötropenik olgularımızda C-reaktif proteinin infeksiyon ve mortalite göstergesi olarak incelenmesi. Flora. 2009; 14: 72–80.
21. Halder R, Seth T, Chaturvedi PK, et al. Comparison of CRP and procalcitonin for etiological diagnosis of fever during febrile neutropenia in hematology patients- an experience from a tertiary care center in Northern India. Blood Cells Mol Dis 2020; 84: 102445.
22. Parodi RL, Lagrutta M, Tortolo M, et al A multicenter prospective study of 515 febrile neutropenia episodes in Argentina during a 5-year period. PLoS One. 2019; 14: e0224299.
23. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. Virulence. 2016; 7: 280–297.
24. Eslami Nejad Z, Ghafouri E, Farahmandi-Nia Z, Kalantari B, Saffari, F. Isolation, Identification, and Profile of Antibiotic Resistance of Bacteria in Patients with Cancer. Iranian Journal of Medical Sciences. 2010; 35: 109-115.
25. Meidani M, Bagheri A, Khorvash F. A population-based study of bacterial spectrum in febrile neutropenic patients. Jundishapur J Microbiol 2013; 6:150–156.
26. Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile Neutropenia in Hematological Malignancies: Clinical and Microbiological Profile and Outcome in High Risk Patients. J Lab Physicians. 2015; 7:116-120.
27. Babu KG, Lokanatha D, Lakshmaiah KC, et al. Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. Indian J Med Paediatr Oncol 2016; 37: 174-182.
28. Hansen BA, Wendelbo Ø, Bruserud Ø, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. Mediterr J Hematol Infect Dis 2020; 12: e2020009.
29. van der Velden WJ, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol 2014; 167: 441-452.
30. Safia M, Khanfir A, Maalej-mezghani S, Hammami A, Frikha M. Chemotherapy-induced febrile neutropenia: About 186 episodes. Clinical, microbiological and therapeutic characteristics. La Tunisie Medicale. 2015; 93: 217–222.
31. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematology 2017; 4: e573-e583.
32. Rasmy A, al Mashiakhi M, Ameen A. Chemotherapy-induced febrile neutropenia in solid tumours. Gulf J Oncolog 2017; 1: 77–84.
33. Calik S, Ari A, Bilgir O, Cetintepe T, Yis R, Sonmez U, Tosun S. The relationship between mortality and microbiological parameters in febrile neutropenic patients with hematological malignancies. Saudi Med J 2018; 39: 878-885.
34. Menichetti F. Infectious complications in neutropenic cancer patients. Intern Emerg Med 2010; 5: 21–25.
35. Clarke RT, Warnick J, Stretton K, Littlewood TJ. Improving the immediate management of neutropenic sepsis in the UK: lessons from a national audit. Br J Haematol 2011; 153: 773-779.
36. Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, Tanimoto M, Masaoka T; Japan Febrile Neutropenia Study Group. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. Clin Infect Dis 2004; 39: 15-24.
37. Castagnola E, Mikulska M, Viscoli C. Prophylaxis and Empirical Therapy of Infection in Cancer Patients. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015: 3395–3413.e2.
38. Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta- lactam versus beta-lactam-aminoglycoside combination therapy

in cancer patients with neutropenia. Cochrane Database Syst Rev 2013; 2013: CD003038
39. Slobbe L, Polinder S, Doorduijn JK, Lugtenburg PJ, el Barzouhi A, Steyerberg EW, Rijnders BJ. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia- myelodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin Infect Dis 2008; 47: 1507-1512.
40. Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. European Journal of Cancer. 2008; 44: 2192–2203.

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Doi: 10.5505/aot.2023.79990

Original Article

Naples Score May Predict Overall Survival in Metastatic Gastric Cancer and is Superior to CONUT

Naples Skoru Metastatik Mide Kanserinde Genel Sağkalımı Öngörebilir ve CONUT'a Üstündür

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ABSTRACT

Introduction: Gastric adenocarcinoma (GC) is a common malignancy with a poor prognosis. There is a need for prognostic markers to assist treatment decisions in GC. Naples prognostic score (NPS) and controlling nutritional status (CONUT) score are immune-nutritional scores that predict outcomes in different early-stage tumours. Data on the performance of these in metastatic GC are scarce. We evaluated the relationship of CONUT and NPS with prognosis in patients with metastatic GC.
Materials and methods: We retrospectively analysed 201 patients who received first-line platinum-based chemotherapy for metastatic GC between 2017-2021. NPS and CONUT were calculated depending on the pre-treatment laboratory. Overall survival (OS) analyses were performed regarding NPS and CONUT.
Results: Median survival negatively correlated with NPS and CONUT. Clinical parameters that may be associated with OS were evaluated. Liver metastases were associated with shorter survival, while peritoneal involvement did not. Tumour differentiation was not associated with OS. In the univariate analysis, the number of metastatic foci, the presence of hepatic metastases, increased Ca19-9, decreased albumin levels, extraperitoneal metastatic disease, NPS, and CONUT were associated with lower OS. Age, gender, tumour differentiation ECOG, and CEA levels did not affect survival. In multivariate analyses, lower albumin, higher Ca19-9, hepatic metastases, and NPS (OR:2.9) were independently associated with shorter survival. CONUT did not have an effect on OS in multivariate analysis.
Discussion: Among immuno-nutritional scores, CONUT and NPS, predict poor prognosis in metastatic GC patients. The NPS seems superior to the CONUT.

Keywords: Metastatic Gastric Cancer; Naples; CONUT; overall survival

ÖZET

Giriş: Gastrik adenokarsinom (GK), sık görülen ve kötü prognoza sahip bir malignitedir. GK'de tedavi kararlarına yardımcı olmak için prognostik belirteçlere ihtiyaç vardır. Naples prognostik skoru (NPS) ve beslenme durumunun kontrol edilmesi (CONUT) skoru, farklı tümörlerde prognoz ile ilişkili immün-beslenme skorlarıdır. Bunların metastatik GK'deki performansına ilişkin veriler ise azdır. Metastatik GK'li hastalarda CONUT ve NPS'nin prognoz ile ilişkisini değerlendirdik.
Gereç ve yöntemler: 2017-2021 yılları arasında metastatik GC için birinci basamak platin bazlı kemoterapi alan 201 hastayı geriye dönük olarak analiz ettik. Tedavi öncesi laboratuvar sonuçları değerlendirilerek NPS ve CONUT skorları hesaplandı. NPS ve CONUT ile ilgili genel sağkalım (OS) analizleri yapıldı.
Bulgular: Medyan sağkalım, NPS ve CONUT ile negatif korelasyona sahipti. OS ile ilişkili olabilecek klinik parametreler değerlendirildi. Karaciğer metastazları daha kısa sağkalım ile ilişkiliyken, peritoneal

First Received: 29.05.2023, Accepted: 16.06.2023 doi: 10.5505/aot.2023.80269

tutulum bunu göstermedi. Tümör farklılaşması OS ile ilişkili değildi. Tek değişkenli analizde, metastatik odakların sayısı, hepatik metastazların varlığı, artmış Ca19-9, azalmış albümin seviyeleri, ekstraperitoneal metastatik hastalık, NPS ve CONUT, daha düşük OS ile ilişkiliydi. Yaş, cinsiyet, tümör farklılaşması ECOG ve CEA seviyeleri sağkalımla ilişkili değildi. Çok değişkenli analizlerde, daha düşük albümin, daha yüksek Ca19-9, hepatik metastazlar ve NPS (OR:2.9) bağımsız olarak daha kısa sağkalım ile ilişkilendirildi. CONUT, çok değişkenli analizde OS üzerinde bir etkiye sahip değildi.
Tartışma: İmmüno-beslenme skorları arasında CONUT ve NPS, metastatik GK hastalarında kötü prognozu öngörür. Bu açıdan NPS, CONUT'tan üstün görünmektedir.

Anahtar kelimeler: Metastatik Gastrik Kanser; Naples; CONUT; Genel sağkalım

Introduction

Gastric adenocarcinoma (GC) is one of the most common malignancies with a poor prognosis. Although the incidence of GC has decreased compared to previous decades, it is among the leading causes of cancer-related deaths worldwide [1]. 5-year survival is below 30% due to high case fatality rates [2, 3]. There are regional differences in the prevalence and mortality of GC. Turkey is among the countries with high GC-related mortality [4]. Surgical resection is the curative treatment modality in patients with early-stage disease. However, patients with metastases at the time of diagnosis are unsuitable for surgery, and the expected survival is less than one year [5]. In parallel with the introduction of new biomarkers and treatment options, significant advances have been made in treating metastatic malignancies in the last decade. On the other hand, the treatment of GC needs further progress in this regard, given the poor prognosis of metastatic disease. There is also a need for better prognostic and/or predictive biomarkers to assist in making appropriate treatment decisions in GC.

The immune response, and thus associated systemic inflammatory markers, are associated with survival in different types of cancer. The prognostic significance of scores based on systemic inflammation has been investigated in cancers of different origins, such as lung, oesophagus, colorectal, and kidney, in recent years [6-8]. Also, in addition to inflammatory scores, some scores consider the negative effects of malnutrition on survival. Some of these inflammation or malnutrition-based scores can be listed as Glasgow Prognostic Score, CRP-based prognostic index, neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio, and controlling nutritional status (CONUT) score [9, 10]. We recently demonstrated the association of the Naples prognostic score (NPS) with survival in metastatic pancreatic carcinoma [11].

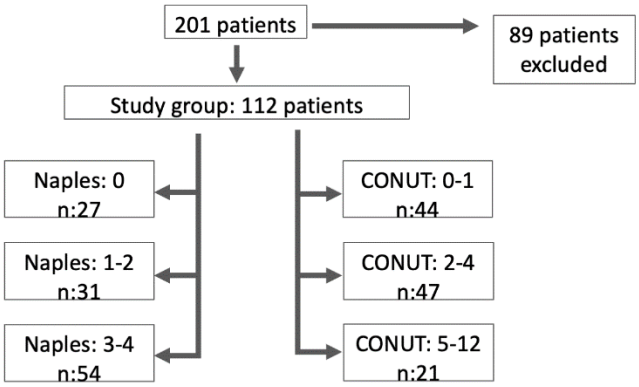
NPS was developed as a scoring system that assesses systemic inflammatory burden and malnutrition based on serum albumin, total cholesterol, lymphocyte-monocyte ratio (LMR), and NLR. NPS calculated before surgical treatment is associated with surgical outcomes in GC [12]. On the other hand, data on the prognostic, predictive power of immuno-nutritional scores in patients with metastatic disease are still scarce. Therefore, we aimed to evaluate the relationship of immuno-nutritional scores CONUT and NPS with prognosis in patients with metastatic GC who received first-line chemotherapy and the power of these scores to predict overall survival.

Material and methods

Patient group

The study was conducted in a tertiary referral centre in Turkey's largest city. We retrospectively analysed 201 consecutive patients who received first-line platinum-based chemotherapy for newly diagnosed metastatic GC between 2017 and 2021. Regarding treatment-related effects, only patients receiving FOLFOX chemotherapy were included in the study to ensure the homogeneity of study results.

Exclusion criteria for the study can be listed as follows: concomitant infectious processes,



Naples Score Factor Points		
Serum albumin, mg/dL	≥4	0
	<4	1
Total cholesterol, mg/dL	>180	0
	≤180	1
Neutrophil:lymphocyte ratio	>2.96	0
	≤2.96	1
Lymphocyte:monocyte ratio	>4.44	0
	≤4.44	1

CONUT Score Factor Points		
Serum albumin, mg/dL	≥3.5	0
	3-3.4.9	2
	2.5-2.9	4
	<2.5	6
Total cholesterol, mg/dL	≥180	0
	140-180	1
	100-139	2
	<100	3
Total lymphocyte (count/mm3)	≥1600	0
	1200-1599	1
	800-1199	2
	<800	3

Figure 1. Study design and patients according to Naples and CONUT groups. Factor points for Naples and CONUT scores

absence of laboratory parameters (complete blood count, serum albumin or total cholesterol levels) in the last two weeks before first-line chemotherapy, GC treatment other than the specified chemotherapy regimen, patients with insufficient follow-up data, and patients continuing their treatment in different centres. Eighty-nine patients who did not meet these criteria were excluded from the study. Accordingly, 112 patients were included in the final analysis (Figure 1). The local ethics committee approved the study protocol and was in accordance with the Declaration of Helsinki.

Data collecting

Values from the last 2 weeks before the start of chemotherapy were used as laboratory data. The parameters evaluated were: CA19-9 and CEA levels, serum albumin, total cholesterol, absolute neutrophil count, lymphocyte count, and monocyte count; NLR and LMR were calculated using these. To determine sub-scores of NPS parameters: Albumin concentration ≥4.0 g/dL was scored as 0, <4.0 g/dL as 1; total cholesterol >180 mg/dL as 0, ≤180 mg/dL as 1; NLR >2.96 as 0, NLR ≤2.96 as 1; LMR >4.44 was scored as 0 and LMR ≤4.44 as 1 (Figure -1). NPS was then calculated as the sum of the above-mentioned scores ranging from 0 to 4. Finally, the patients were divided into three groups based on their NPS scores: 0 points - group 1, 1 or 2 points - group 2, 3 or 4 points - group 3.

The CONUT score was calculated as the sum of albumin, cholesterol, and lymphocyte scores; albumin score (≥ 3.5 g/dL as 0; 3.0–3.49 g/dL as 2; 2.50–2.99 g/dL as 4; <2.50 g/dL as 6), total cholesterol score (≥180 mg/dL as 0; 140–179 mg/dL as 1; 100–139 mg/dL as 2; <100 mg/dL as 3), and lymphocyte score (≥1.6 103 /mm3 as 0; 1.20–1.59 103 /mm3 as 1; 0.80–1.19 as 2 g/L; <0.8 103 /mm3 as 3) (Figure 1)[13]. Patients were grouped according to their CONUT scores; scores 0-1: 1st group; scores 2-4: group 2 and 5-12: group 3[9]. In addition, the total number of metastatic sites, liver metastases, or peritoneal involvement of the patients was

Table 1. Demographic characteristics, laboratory parameters, and prognostic factors of the study groups

	Whole Group (n:112)	Naples 0 (n:27)	Naples 1-2 (n:31)	Naples 3-4 (n:54)	*p*	CONUT 0-1(n:44)	CONUT 2-4 (n:47)	CONUT 5-12(n:21)	p
Demography									
Sex (F%(n))	22.3 (25)	25.9	19.4	22.2	0.83	18.2	29.8	14.3	0.25
Age	60.1 (±10)	60.5(±9.4)	61(±10.3)	56.9 (±9.6)	0.22	61.3(±9.7)	59.4(11.3)	56.7(±6.9)	0.29
Age >65	34.8(39)	18.5	35.5	42.6	0.10	36.4	27.7	47.6	0.27
Ecog performance status									
0	10.7(12)	14.8	6.5	11.1		15.9	4.3	14.3	
1	71.4(80)	55.6	77.4	75.9	0.27	68.2	72.3	76.2	0.28
2-3	17.9 (20)	29.6	16.1	13		15.9	23.4	9.5	
Differentiation									
Poor	75.9	70.4	74.2	79.6	0.22	70.5	87.2	61.9	0.04
Metastasis									
Focus n	2(1)	1(2)	2(1)	2(1)	0.38	2(2)	2(2)	2(2)	0.44
Liver	43.8(49)	29.6	54.8	44.4	0.15	43.2	40.4	52.4	0.65
Peritoneal	54.5 (61)	85.2	48.4	42.6	<0.001	54.5	59.6	42.9	0.44
Laboratory									
Hgb	11.2 (±2.1)	12.3(±1.8)	11.3(±2.6)	10.7(±2)	0.08	11.7(±2)	11.1(±2.7)	10.8(±1.1)	0.13
Albumin	3.9(0.6)	4.1(0.3)	4 (0.5)	3.7(0.5)	<0.001	4.1(0.4)	3.9(0.7)	3.5 (1)	<0.001
C19-9	16.8(55.8)	44(83)	20 (127)	16.3(65)	0.137	16.6(49)	19.5(82)	15(80)	0.55
CEA	3.7 (21.2)	2.2(6)	2.8(5)	4.1(18.3)	0.03	3.1(21)	3.8(12)	5.8 (31)	0.81
OS	15 (19)	32(11)	16(6)	9(7)	<0.001	18(13)	11(16)	10 (7)	<0.001

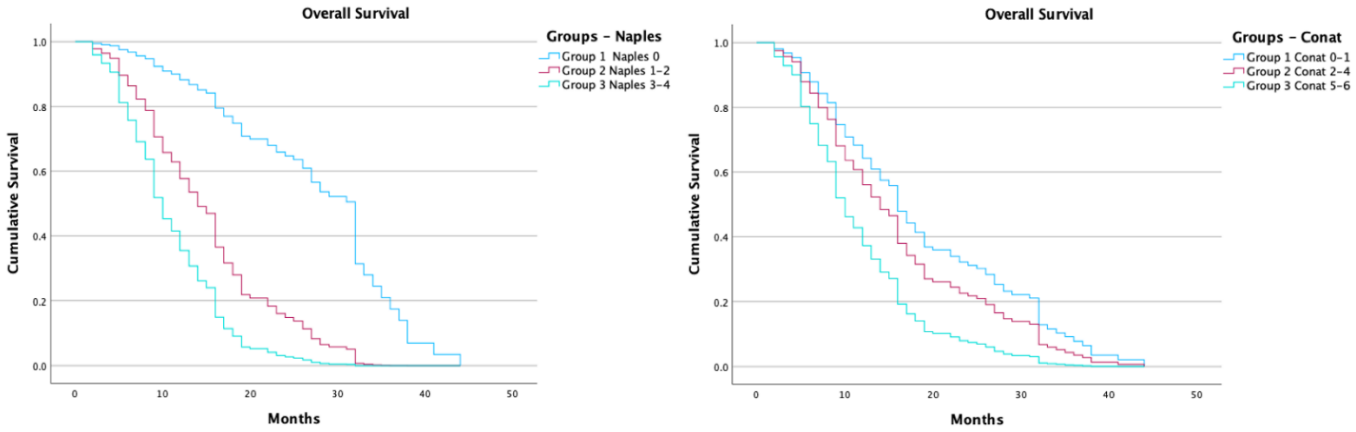


Figure 2. Overall survival of patients according to Naples (0; 1-2; 3-4) and CONUT (0-1; 2-4; 5-12) groups (Naples: Log Rank p<0.001; CONUT: Log Rank p:0.007)

noted. The overall survival (OS) was defined as the time from initiation of first-line chemotherapy to death (if happened) for each patient.

Statistical analysis

Parametric data were expressed as mean (standard deviation), and non-parametric data as median (distribution range). Non-parametric data comparisons between groups were made using independent sample tests, Kruskal-Wallis, and Mann-Whitney U tests. Survival analysis was performed by the Kaplan-Meier method using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Prognostic variables identified by univariate analysis with a $p < 0.1$ value were also evaluated by multivariate analysis. A $p<0.05$ value was accepted for statistical significance. IBM-SPSS v.29 program was used for statistical analysis.

Results:

Our study examined the overall survival and associated prognostic markers of 112 metastatic gastric adenocarcinoma patients who received first-line chemotherapy. 22.3% of the patient group was female, and we found the mean age to be 60.1. The median survival in the whole group was 15 months. Table- I summarises the demographic characteristics, laboratory parameters, and prognostic factors of the study group. The median number of metastasis foci of the patients in the study group was 2. Liver metastasis was observed in 43.8% of the patients, and peritoneal involvement was observed in 54.5% of the patients. Three-quarters of the patients had tumours showing poor differentiation.

Our study examined Naples and CONUT scores in terms of immuno-nutritional prognostic scores. We created three groups for each score. NPS 0 was defined as group 1 (n:27), NPS 1-2 group 2 (n:31), and NPS 3-4 group 3 (n:54). Similarly, CONUT 0-1 (n:44), CONUT 2-4 (n:47), CONUT 5-12 (n:21) were evaluated as three separate groups. Demo--graphic, laboratory, and clinical charac-teristics according to prognostic groups are summarised in Table - I. There was no difference between the NPS and CONUT groups in terms of demographic charac-teristics and ECOG performances of the patients (Table -1). Tumours with poor differentiation were significantly more common in the CONUT 2-4 group (87.2% vs 70.5-61.9; p: 0.04). Peritoneal involvement was found more frequently among the groups in the NPS 0 group (85.2% vs 48.4-42.6; p:<0.001). There was no difference between the groups regarding liver metastasis and the number of metastasis foci. Within the laboratory parameters, albumin decreased proportionately to the increasing scores for both (p<0.001). There was a significant difference in CEA levels between NPS groups (2.2 ng/mL - 2.8 - 4.1; p:0.03). Although haemoglobin values showed a decreasing

trend in parallel with increasing prognostic scores, the difference did not reach statistical significance (NPS p: 0.08; CONUT p: 0.13)

Median survival was negatively correlated with increasing scores in both NPS and CONUT groups (both p<0.001). The median survival was found to be 32-16-9 months in the NPS groups and 18-11-10 months in the CONUT groups, respectively. Clinical parameters that may be associated with patients' overall survival were evaluated by Kaplan-Meier analysis. There was no difference between ECOG performance scores and overall survival (Log Rank p:0.08). A significant relation was found between NPS groups and overall survival (Log Rank p<0.001); similarly, CONUT groups were also associated with survival (Log Rank p:0.007) (Figure 2). Liver metastases were associated with shorter survival (Log Rank p:0.004). Peritoneal involvement of metastatic disease showed a better prognosis than extraperitoneal metastatic disease (Log Rank p:0.008) (Figure 3). Tumour differentiation was not associated with overall survival (Log Rank p: 0.564).

We also analysed the parameters that may be related to overall survival by multivariate Cox regression analysis (Table –2). In the univariate analysis, the number of metastatic foci, the presence of hepatic metastases, increased Ca19-9 levels, decreased albumin levels, extraperitoneal metastatic disease, and both NPS (3-4) and CONUT (5-12) prognostic scores were associated with lower overall survival. Age, gender, tumour differentiation ECOG performance status, and CEA levels did not affect survival. In multivariate analyses, lower albumin, higher Ca19-9 levels, presence of hepatic metastases, and NPS (3-4) (OR:2.9) were found to be independently associated with shorter survival. CONUT (5-12) did not have a significant effect on overall survival in multivariate analysis (p:0.373)

Discussion:

Our study showed that scores evaluating the immuno-nutrition status before first-line chemotherapy can predict prognosis in patients with metastatic GC. The NPS score seems superior to the CONUT score in this respect. This association of NPS score with prognosis in patients with metastatic GC unsuitable for surgery is a novel contribution to the literature.

Many studies show that immune response and nutritional state are associated with malignancy. This has led to the research and development of new biomarkers or immune and nutrition-based prognostic scoring systems [14]. GC ranks among the top in cancer-related deaths worldwide [4]. The prognosis in metastatic patients is quite poor. The nutritional status of these patients is generally poor due to gastrointestinal involvement and cachexia of malignancy. This and the impaired immune response may be among the reasons for the shorter survival we encounter in these patients [15].

The inflammatory response in the tumour microenvironment may exert a role in the destruction of tumour cells, and angiogenesis. Thus, they may modify the response of tumours to radiotherapy and chemotherapy. Lymphocytes play a major role in this immune response. Lymphopenia is associated with adverse reactions and poor prognosis in many tumours, including GC [16, 17]. On the other hand, increased tumoural neutrophil infiltration generally has poor clinical outcomes. Neutrophils may participate actively in tumorigenesis by some cytokines, inducing tumor cell proliferation and even metastasis [18, 19]. Therefore, NLR and LMR have been evaluated in many studies, and increasing NLR and decreasing LMR are generally associated with worse outcomes [20].

Malnutrition is closely associated with angiogenesis and tumour growth, thus with disease progression. The serum albumin concentration is one of the important markers of nutritional status and inflammatory load as a negative acute phase reactant. Hypoalbuminemia is often associated with worse outcomes in various tumors[21]. Similarly, our study showed that hypoalbuminemia is related to poor prognosis

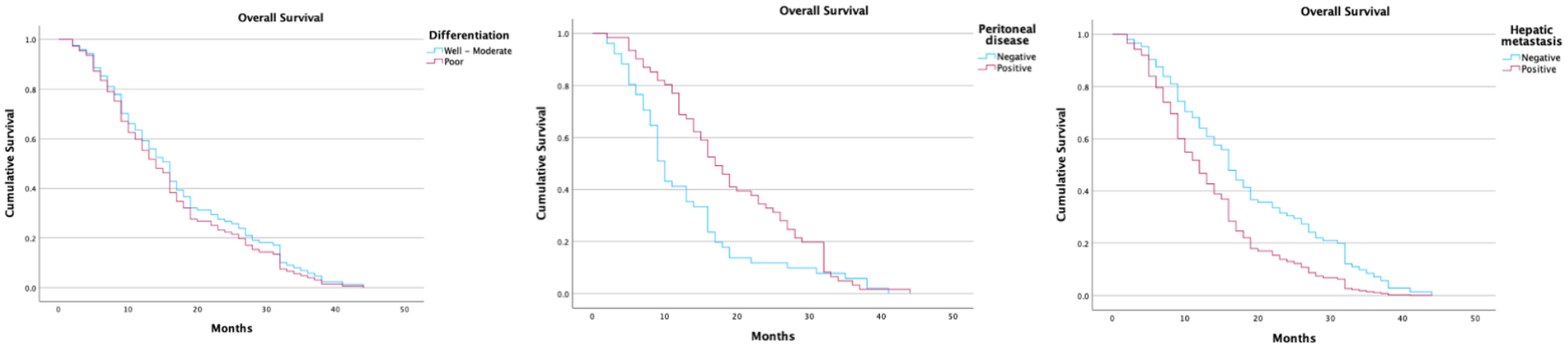


Figure 3. Overall survival of patients according to peritoneal and hepatic metastasis status (Log Rank p:0.008, p:0.004 respectively)

Table 2. Univariate and multivariate factors associated with overall survival

	Univariate	*p*	Multivariate	*p*
Age	1.007 (0.988-1.026)	0.488		
Age>65	1.301(0.876-1.933)	0.192		
Sex (M)	1.109 (0.706-1.742)	0.652		
Differentiation (poor)	1.133 (0.727-1.767)	0.577		
Number of Metastatic foci	1.272 (1.024-1.582)	0.03	1.292 (0.947-1.762)	0.106
Hepatic metastasis	1.714 (1.161-2.532)	0.007	1.744 (1.025-2.968)	0.04
Peritoneal disease	0.613 (0.418-0.897)	0.012	0.701 (0.454-1.089)	0.111
Ca19-9	1.0002 (1-1)	0.02	1 (1-1)	0.022
CEA	1 (1-1)	0.329		
Albumin (-)	2.272 (1.461-3.533)	<0.001	2.331 (1.230-4.424)	0.010
Ecog (2-3)	1.410 (0.861-2.309)	0.172		
CONUT (5-12)	1.967 (1.204-3.212)	0.007	1.328 (0.711-2.475)	0.373
Naples (3-4)	3.784 (2.501-5.726)	<0.001	2.983 (1.849-4.812)	<0.001

in metastatic GC [22]. In addition to albumin, cholesterol level also provides information about nutritional status, and low cholesterol levels are associated with a poor prognosis[23]. For these reasons, the nutritional status scores include albumin and cholesterol levels.

The right treatment options can be selected by accurately demonstrating the patient's immune and nutritional status. Studies have pointed out that laboratory parameters like low lymphocyte count and low serum albumin level are associated with poor prognosis of various tumours. Thus, integrating multiple parameters into a compound model has the potential to significantly improve the prognostic value [24, 25]. The scoring system, formed by combining nutritional and immune indicators, can effectively reflect patients' condition and estimate the prognosis with better accuracy. CONUT and NPS scores can be listed among these scores. The CONUT score is calculated using lymphocyte count, albumin and total cholesterol concentration. A high CONUT score represents a weak immune-nutritional state. 26147805. NPS is an index of serum albumin concentration, total cholesterol concentration, LMR, and NLR, and has proven to be an indicator of OS in various tumours [11, 26]. NPS and CONUT are among the most used scoring systems.

There are studies evaluating immune-nutritional scores such as NPS-CONUT scores for surgical success and long-term survival in patients with respectable tumours. However, there is scarce literature on the relationship between immune-nutritional scores with survival and which score is better in metastatic GC. NPS and CONUT are practical scores that can be easily calculated in outpatient conditions. In many ways, they represent the overall inflammatory burden and nutritional status of patients with metastatic GC. In our study, we showed that both NPS and CONUT can predict survival before first-line chemotherapy in metastatic GC patients when we evaluated them separately. Although both scores can be used in this sense, we have shown that NPS is superior in predicting prognosis in patients with metastatic GC. In our patient group, the presence of liver metastases and the number of metastatic foci were the other parameters related to survival. The relatively good prognosis of patients with peritoneal metastases may be because they are considered metastatic but do not have solid organ-liver metastases. On the other hand, among tumor markers, CA 19-9 also seem to be associated with prognosis per the literature. In multivariate regression analyses, CA19-9, serum albumin level, presence of liver metastases, and NPS score were found to be independently associated with prognosis, suggesting that this score is superior to CONUT in metastatic GC patients.

The contribution of immuno-nutritional scores in predicting the prognosis of metastatic GC and the superiority of NPS score over CONUT in this regard can be listed as the contribution of our study to the literature. Among its shortcomings, retrospective design and our inability to examine the prognostic importance of nutritional support can be listed. Another point is that our study group consisted of patients who received conventional first-line chemotherapy. This design prevents us from evaluating the prognostic significance of these scores in metastatic GC patients receiving immunotherapy.

In conclusion, CONUT and NPS, which evaluate the immuno-nutritional status calculated before first-line chemotherapy, predict poor prognosis in metastatic GC patients. The NPS seems superior to the CONUT in this respect.

REFERENCES

1. Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clin Gastroenterol Hepatol. 2020; 18(3): 534-542.
2. Asplund J, Kauppila JH, Mattsson F, Lagergren J. Survival Trends in Gastric Adenocarcinoma: A Population-Based Study in Sweden. Ann Surg Oncol. 2018; 25(9): 2693-2702.
3. Dassen AE, Lemmens VE, Van De Poll-Franse LV, Creemers GJ, Brenninkmeijer SJ, Lips DJ, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer. 2010; 46(6): 1101-1110.
4. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019; 14(1): 26-38.
5. Digklia A, Wagner AD. Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol. 2016; 22(8): 2403-2414.
6. Ramsey S, Lamb GW, Aitchison M, Graham J, Mcmillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer. 2007; 109(2): 205-212.
7. Forrest LM, Mcmillan DC, Mcardle CS, Angerson WJ, Dagg K, Scott HR. A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2005; 92(10): 1834-1836.
8. Mcmillan DC, Canna K, Mcardle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg. 2003; 90(2): 215-219.
9. Daitoku N, Miyamoto Y, Tokunaga R, Sakamoto Y, Hiyoshi Y, Iwatsuki M, et al. Controlling Nutritional Status (CONUT) Score Is a Prognostic Marker in Metastatic Colorectal Cancer Patients Receiving First-line Chemotherapy. Anticancer Res. 2018; 38(8): 4883-4888.
10. Dolan RD, Mcsorley ST, Horgan PG, Laird B, Mcmillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017; 116: 134-146.
11. Gulturk I, Yilmaz M, Tacar SY, Bakkaloglu OK, Sonmezoz GB, Erdal GS, et al. Naples prognostic score may predict overall survival in metastatic pancreatic cancer. Journal of Cancer Research and Therapeutics. 9000.
12. Galizia G, Auricchio A, De Vita F, Cardella F, Mabilia A, Basile N, et al. Inflammatory and nutritional status is a predictor of long-term outcome in patients undergoing surgery for gastric cancer. Validation of the Naples prognostic score. Ann Ital Chir. 2019; 90: 404-416.
13. Ignacio De Ulibarri J, Gonzalez-Madrono A, De Villar NG, Gonzalez P, Gonzalez B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp. 2005;20(1):38-45.
14. Zheng X, Li L, Yu C, Yang J, Zhao Y, Su C, et al. Establishment of a tumor immune microenvironment-based molecular classification system of breast cancer for immunotherapy. Aging (Albany NY). 2021;13(21):24313-24338.
15. Ramos M, Pereira MA, De Castria TB, Ribeiro RRE, Cardili L, De Mello ES, et al. Remnant gastric cancer: a neglected group with high potential for immunotherapy. J Cancer Res Clin Oncol. 2020; 146(12): 3373-3383.
16. Eberst G, Vernerey D, Laheurte C, Meurisse A, Kaulek V, Cuche L, et al. Prognostic value of CD4+ T lymphopenia in non-small cell lung Cancer. BMC Cancer. 2022; 22(1): 529.
17. Tatara T, Suzuki S, Kanaji S, Yamamoto M, Matsuda Y, Hasegawa H, et al. Lymphopenia predicts poor prognosis in older gastric cancer patients after curative gastrectomy. Geriatr Gerontol Int. 2019; 19(12): 1215-1219.
18. Xia X, Zhang Z, Zhu C, Ni B, Wang S, Yang S, et al. Neutrophil extracellular traps promote metastasis in gastric cancer patients with postoperative abdominal infectious complications. Nat Commun. 2022; 13(1): 1017.
19. Guan X, Lu Y, Zhu H, Yu S, Zhao W, Chi X, et al. The Crosstalk Between Cancer Cells and Neutrophils Enhances Hepatocellular Carcinoma Metastasis via Neutrophil Extracellular Traps-Associated Cathepsin G Component: A Potential Therapeutic Target. J Hepatocell Carcinoma. 2021; 8: 451-465.
20. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg. 2011; 35(4): 868-872.
21. Hardt J, Pilz L, Magdeburg J, Kienle P, Post S, Magdeburg R. Preoperative hypoalbuminemia is an independent risk factor for increased high-grade morbidity after elective rectal cancer resection. Int J Colorectal Dis. 2017; 32(10): 1439-1446.
22. Ma LX, Taylor K, Espin-Garcia O, Anconina R, Suzuki C, Allen MJ, et al. Prognostic significance of nutritional markers in metastatic gastric and esophageal adenocarcinoma. Cancer Med. 2021; 10(1): 199-207.
23. Hirano H, Ide H, Lu Y, Inoue Y, Okada H, Horie S. Impact of Pretreatment Total Cholesterol Level Is Associated With Metastasis of Prostate Cancer. Am J Mens Health. 2020; 14(2): 1557988320918788.
24. Schueneman AJ, Sugar EA, Uram J, Bigelow E, Herman JM, Edil BH, et al. Low total lymphocyte count is associated with poor survival in patients with resected pancreatic adenocarcinoma receiving a GM-CSF secreting pancreatic tumor vaccine. Ann Surg Oncol. 2013; 20 Suppl 3(0 3): S725-730.

25. Lien YC, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, et al. Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. J Gastrointest Surg. 2004; 8(8): 1041-1048.

26. Nakagawa N, Yamada S, Sonohara F, Takami H, Hayashi M, Kanda M, et al. Clinical Implications of Naples Prognostic Score in Patients with Resected Pancreatic Cancer. Ann Surg Oncol. 2020; 27(3): 887-895.

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Doi: 10.5505/aot.2023.80269

Original Article

Clinical Importance of the Hemoglobin, Albumin, Lymphocyte, Platelet Score in Metastatic Pancreatic Cancer

Metastatik Pankreas Kanserinde Hemoglobin, Albümin, Lenfosit, Trombosit Skorunun Klinik Önemi

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ABSTRACT

Introduction: Pancreatic adenocarcinoma is one of the deadliest cancers. Effective, simple and practical methods that can be used in daily life are still lacking to predict the prognosis of patients with advanced pancreatic cancer and a promising biomarker is needed to predict prognosis. Our study's objective was to demonstrate the correlation between the HALP score and prognosis in patients with metastatic pancreatic cancer.

Methods: Patients diagnosed with metastatic pancreatic cancer from 4 centers in Turkey between 2016 and 2022 were included. Demographic data, hemogram parameters, biochemistry values, as well as the treatments received were recorded. Survivals were also recorded

Results: There were 280 patients in our study. The median PFS was 7.53 months, while the median OS was 11.53 months for the whole population. Median PFS was 7.1 months for the HALP-Low group and 14.8 months for the HALP-High group. The HALP-Low group exhibited a significantly shorter median progression-free survival (PFS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$). Median OS was 10.57 months for the HALP-Low group and 18 months for the HALP-High group. The HALP-Low group demonstrated a significantly shorter median overall survival (OS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$)

Discussion and Conclusion: In conclusion, the HALP score is an inexpensive, practical, literature-contributing marker and, if validated by prospective studies, can be used in routine clinical practice to predict the prognosis of patients with metastatic pancreatic cancer.

Keywords: HALP score, Overall survival, Metastatic Pancreatic cancer, Progression-free survival

ÖZET

Giriş ve Amaç: Pankreas adenokarsinomu en ölümcül kanserlerden biridir. Metastatik pankreas kanserli hastaların prognozunu tahmin etmek için günlük hayatta kullanılabilecek etkili, basit ve pratik yöntemler halen eksiktir ve prognozu tahmin etmek için umut verici bir biyobelirteç gerekmektedir. Çalışmamızda metastatik pankreas kanserinde HALP skorunun prognoz ile ilişkisini göstermeyi amaçladık.

First Received: 25.07.2023, Accepted: 28.08.2023 doi: 10.5505/aot.2023.26779

Yöntem ve Gereçler: 2016-2022 yılları arasında Türkiye'de 4 merkezden metastatik pankreas kanseri tanısı alan hastalar dahil edildi. Demografik veriler, hemogram parametreleri, biyokimya değerleri ve alınan tedaviler kaydedildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) da kaydedildi.
Bulgular: Çalışmamızda 280 hasta vardı. Tüm popülasyon için medyan PFS 7,53 aydı, medyan OS ise 11,53 aydı. Medyan PFS, HALP-Düşük grup için 7,1 ay ve HALP-Yüksek grup için 14,8 aydı. HALP-Düşük grubun median PFS'si HALP-Yüksek gruba göre daha kısaydı ve gruplar arasında istatistiksel olarak anlamlı bir fark vardı (p: <0,001).
Tartışma ve Sonuç: Sonuç olarak, HALP skoru ucuz, pratik, literatüre katkıda bulunan bir belirteçtir ve prospektif çalışmalarla doğrulanırsa, metastatik pankreas kanseri olan hastaların prognozunu tahmin etmek için rutin klinik uygulamada kullanılabilir.

Anahtar Kelimeler: HALP skoru, Genel sağkalım, Metastatik Pankreas kanseri, Progresyonsuz sağkalım

Introduction

Pancreatic ductal adenocarcinoma (PC) is a highly lethal cancer, responsible for 496,000 new cases and 466,000 deaths in the United States in 2018. It ranks as the 7th leading cause of cancer-related deaths. PC is increasing in both sexes and the median age at diagnosis is around 40 years [1]. Although surgery is a curative treatment option, 80% of patients are metastatic or locally advanced at the time of diagnosis [2]. Although chemo-therapy, immunotherapies and targeted therapies are being developed, 5-year survival is around 5% [3,4]. There is currently a lack of effective, straightforward, and feasible methods for predicting the prognosis of individuals with advanced pancreatic cancer, despite the existence of proto-oncogenes like BRCA and PALB2, as well as some molecular tests such as tumor mutation burden and a promising biomarker is needed to predict prognosis. Developments in the field of cancer and inflammation and the lack of biomarkers in patients with PC have led to the need for many studies.

The link between nutritional status and inflammation and cancer progression has been known for many years. Chronic inflammation accelerates the neovascularization process by increasing cytokines and this contributes to tumor growth [5,6]. Nutritional status contributes to prognosis by affecting the immune system through cytokines [7,8]. Cancer-related anemia is highly prevalent. In the presence of anemia, hypoxia occurs at the cellular level. This leads to genomic and proteomic changes (e.g. increased growth factors for example vascular endothelial growth factor). Thus, it increases tumor growth and metastasis potential [9]. Platelets are involved in inflammation-mediated cancer development through growth factors, chemokines and proinflammatory cytokines. It is known that thrombocytosis increases the metastasis potential and plays a poor prognostic role in many malignancies [10,11].

Recent research has demonstrated that hemoglobin, albumin, lymphocyte, platelet score (HALP score) has significant relevance in forecasting the development of renal cancer, non-small cell lung cancer (NSCLCL), gastric cancer, and small cell lung cancer. (SCLC) [12,15]. As far as we know, there have been no studies demonstrating the correlation between HALP score and prognosis in metastatic PC.

Our study aims to establish the association between HALP score and prognosis in metastatic PC.

Materials and Methods

Patients diagnosed with metastatic pancreatic cancer at Mardin Training and Research Hospital, Aydın Adnan Menderes University Hospital, Manisa Celal Bayar University, and Aydın Atatürk State Hospital between 2016 and 2022 were included. Patient records and hospital databases were examined for this

study. The patients' age, ECOG performance status, gender, comorbidities, hemoglobin at the time of metastasis, thrombocyte, lymphocyte, albumin and the treatments they received were recorded.

Patients with another malignancy, younger than 18 years of age, known hematologic disease, autoimmune disease, inflammatory bowel disease, history of steroid or anticoagulant use, non-metastatic patients whose data could not be securely accessed were excluded. HALP score had been calculated as × lymphocyte (/L) x albumin (g/L) x hemoglobin (g/L) / platelet count (/L). The cut-off for HALP score was determined as 0.6 with the X-tile program.

Statistical analyses were conducted using R version 2.15.3 (R Core Team, 2013). The study data were summarized using various descriptive statistics, including the minimum, maximum, first quartile, third quartile, median, mean, standard deviation, frequency, and percentage. These measures were utilized to provide a comprehensive overview and description of the study data. The normality of the quantitative data was assessed through the Shapiro-Wilk test and graphical analysis to determine if it followed a normal distribution. These methods were used to examine the distributional characteristics of the data and assess its adherence to the assumptions of a normal distribution. The Dunn-Bonferroni test and Kruskal-Wallis test were employed to compare quantitative variables among more than two groups when the data did not exhibit a normal distribution. These statistical tests were used to examine potential differences or relationships between the groups, considering the non-normal distribution of the data. Qualitative data were compared using Fisher's exact test, Pearson chi-square test, and Fisher-Freeman-Halton exact test. These statistical tests were employed to assess potential associations or differences among categorical variables. For evaluating progression-free survival (PFS) and overall survival (OS), univariable and multivariable Cox regression analyses were performed. A significance level of $p<0.05$ was considered to determine statistical significance in the results.

This study was conducted and designed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. It received approval from the ethics committee of Diyarbakır Gazi Yaşargil Training and Research Hospital (Approval Date-No: 25.11.2022-2022/242). Informed consent was obtained from all patients Results

There were 280 patients in our study. The median age was 64.5 years (58, 72). 165 (58.9%) of our patients were male. ECOG performance scale was 0 or 1 in 182 (65%) of our patients. Most of our patients 230 (82.1%) were de-novo metastatic. Liver was the site of metastasis in 202 (72.1%) of our patients. The primary site of origin was the head of the pancreas in 184 (65.7%) of our patients. In metastatic 1st line chemotherapy, 59 (21.1%) patients received cisplatin + gemcitabine, 59 (21.1%) patients received single agent gemcitabine and 47 (16.8%) patients received FOLFIRINOX regimen. In our study, 254 (90.7%) patients were exited. No statistically significant differences were found concerning gender, ECOG performance status, and tumor localization.

Percentages between the group with a HALP score ≤ 0.6 (HALP-Low) and the group with a HALP score > 0.6 (HALP-High) ($p>0.05$). We observed a statistically significant difference between the HALP-Low group and the HALP-High group in terms of the proportion of patients receiving the 1st step chemotherapy ($p=0.002$).

The HALP-Low group had a higher percentage of patients receiving capecitabine. Detailed information on the general characteristics and demographics of the patients is provided in Table 1.

Table 1. Demographic and clinicopathological characteristics of the patients

	Total (n=280)	Low HALP score (≤0.6) (n=234)	High HALP score (>0.6) (n=46)	p
Age, year	64.5 (58, 72)	65 (59, 72)	63 (56, 71)	0.253
Gender				0.972
Female	115 (41.1)	96 (41)	19 (41.3)	
Male	165 (58.9)	138 (59)	27 (58.7)	
ECOG				0.761
0-1	182 (65)	153 (65.4)	29 (63)	
2-3	98 (35)	81 (34.6)	17 (37)	
Smoking (%)				0.788
No	151 (53.9)	126 (53.8)	25 (54.3)	
Active	121 (43.2)	102 (43.6)	19 (41.3)	
Former	8 (2.9)	6 (2.6)	2 (4.3)	
BMI				0.919
<20	44 (15.7)	37 (15.8)	7 (15.2)	
>20	236 (84.3)	197 (84.2)	39 (84.8)	
De-novo metastasis, n (%)				0.741
Yes	230 (82.1)	193 (82.5)	37 (80.4)	
No	50 (17.9)	41 (17.5)	9 (19.6)	
Liver metastasis				0.770
No	78 (27.9)	66 (28.2)	12 (26.1)	
Yes	202 (72.1)	168 (71.8)	34 (73.9)	
Lung metastasis				0.324
No	196 (70)	161 (68.8)	35 (76.1)	
Yes	84 (30)	73 (31.2)	11 (23.9)	
Periton metastasis				0.263
No	168 (60)	137 (58.5)	31 (67.4)	
Yes	112 (40)	97 (41.5)	15 (32.6)	
Others				0.543
No	222 (79.3)	184 (78.6)	38 (82.6)	
Yes	58 (20.7)	50 (21.4)	8 (17.4)	
First Line				0.002
FOLFOX	16 (5.7)	12 (5.1)	4 (8.7)	
FOLFIRINOX	47 (16.8)	39 (16.7)	8 (17.4)	
KAPOX	15 (5.4)	9 (3.8)	6 (13)	
Gemcitabine	59 (21.1)	49 (20.9)	10 (21.7)	
Gemcitabin+Capesitabin	25 (8.9)	24 (10.3)	1 (2.2)	
Gemcitabin+ Nab-paclitaxel	22 (7.9)	19 (8.1)	3 (6.5)	
Cisplatin+Gemcitabine	59 (21.1)	45 (19.2)	14 (30.4)	
Capesitabin	37 (13.2)	37 (15.8)	0 (0)	
Tumor location, n (%)				0.178
Head	184 (65.7)	159 (67.9)	25 (54.3)	
Body	55 (19.6)	42 (17.9)	13 (28.3)	
Tail	41 (14.6)	33 (14.1)	8 (17.4)	
Survival				0.401
Live	26 (9.3)	20 (8.5)	6 (13)	
Exitus	254 (90.7)	214 (91.5)	40 (87)	

HALP: Hemoglobin-Albumin-Lymphocyte-Platelet-Ratio

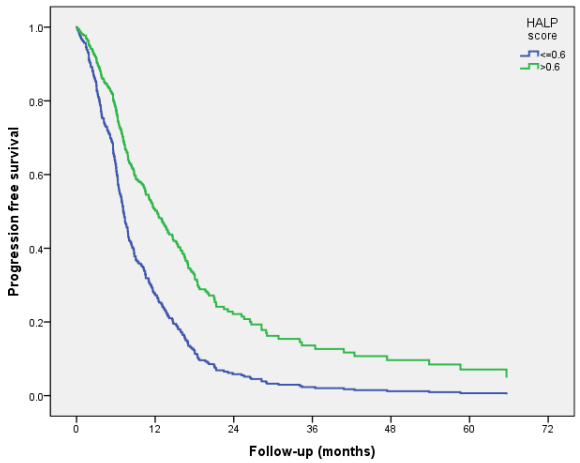

Figure-1: Progression free survival analysis functions

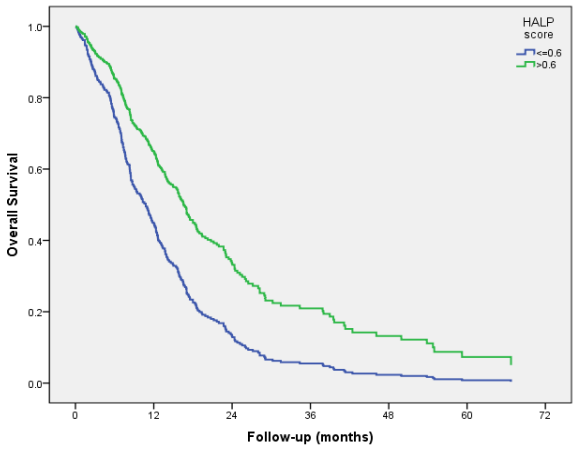

Figure-2: Overall survival analysis functions

For the whole population, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. Median PFS was 7.1 (95% CI: 6.37-7.83) months for the HALP-Low group and 14.8 (95% CI: 12.36-17.24) months for the HALP-High group. The HALP-High group exhibited a significantly longer median PFS compared to the HALP-Low group, with a p-value of less than 0.001 indicating statistical significance (Figure 1).

The HALP-Low group had a median overall survival (OS) of 10.57 months (95% CI: 8.66-12.47), while the HALP-High group had a median OS of 18 months (95% CI: 14.51-21.49). The HALP-Low group exhibited a shorter median OS compared to the HALP-High group, and this difference was statistically significant (p<0.001). (Figure 2).

There were no statistically significant differences observed between the HALP-Low group and the HALP-High group in terms of gender, ECOG performance status, and tumor localization percentages respectively (p-values: 0.972, 0.761, 0.178,). Median PFS was higher and statistically significant in patients with an ECOG performance score of 0-1 compared to those with an ECOG performance score of 2-3, 8.33 (95% CI: 7.16-9.51) and 6.77 (95% CI 5.68-7.85), respectively (p<0.001).

Furthermore, the median OS was higher and statistically significant in patients with ECOG performance score 0-1 compared to those with ECOG performance score 2-3, 13.3 (95% CI: 11.43- 15.17) and 7.9 (95% CI: 6.26, 9.54), respectively (p:0.001).

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). Univariate analyses of PFS and OS are shown in detail in Table 2.

Multivariate analysis was conducted to identify independent prognostic factors for progression-free survival (PFS) and overall survival (OS). The HALP-Low group had a lower PFS compared to the HALP-High group [HR (95% CI)=2.288 (1.587, 3.301), p<0.001]. Additionally, individuals with de-novo disease status had a lower PFS compared

Table 2: Univariate analysis of PFS and OS

	mOS (95%CI)	p-value	mPFS (95% CI)	p-value
Age, year	-	0.132	-	0.715
Gender				
Female	10.97 (9.01 – 12.93)	0.823	7.8 (6.52- 9.08)	0.863
Male	12.33 (10.32 -14.34)		7.3 (6.47- 8.13)	
ECOG-PS				
0-1	13.3 (11.39 - 15.21)		8.33 (7.16- 9.51)	
2-3	7.9 (6.34 - 9.46)	<0.001	6.77 (5.68- 7.85)	0.001
Smoking		0.989		0.679
Never	10.77 (9- 12.93)		7.63 (6.64- 8.62)	
Active	12.67 (10.64-14.83)	0.995	7.53 (6.26- 8.8)	0.406
Former	14.17 (0-28.81)	0.883	5.87 (0 - 19.73)	0.679
BMI				
<20	11.77 (6,04- 17.49)		7.3 (5.86- 8.74)	
>20	11.5 (9.92- 13.08)	0.362	7.63 (6.8 -8.47)	0.362
De-novo metastasis, n (%)				
Yes	10 (8.4 - 11.6)	<0.001	6.77 (6.12- 7.41)	<0.001
No	21.67 (15.41- 27.93)		16.43 (10.52-22.34)	
Liver metastasis				
No	11.53 (8.73- 14.34)		7.8 (6.18- 9.42)	
Yes	11.77 (10,02- 13.38)	0.215	7.4 (6.54- 8.26)	0.085
Lung metastasis				
No	11.53 (10,01- 13.06)		7.63 (6.68- 8.59)	
Yes	12.4 (7.51-17.29)	0.302	7.4 (5.65- 9.15)	0.592
Periton metastasis				
No	11.13 (8.9-13.33)		7.9 (6.41- 9.16)	
Yes	12 (10.2-13.8)	0.893	7.2 (6.44-7.96)	0.244
Others				
No	11.77 (10.16- 13.24)		7.4 (6.69- 8.11)	
Yes	11.3 (7.32-15.28)	0.942	8.5 (6.67- 10.33)	0.248
Tumor location, n (%)		0.446		0.144
Head	12 (10.97 – 13.03)		7.87 (6.78- 8.95)	
Body	10.1 (7.14- 13.06)	0.237	6.33 (5.26- 7.41)	0.057
Tail	10.3 (5.72- 14.88)	0.914	8.67 (5.05- 12.28)	0.820
HALP score				
Low (≤0.6)	10.57 (8.66-12.47)	<0.001	7.1 (6.37-7.83)	<0.001
High (>0.6)	18 (14.51- 21.49)		14.8 (12.36- 17.24)	

PFS: Progression-free survival , OS: Overall Survival, CI: Confidence interval, PS: performance status, BMI: Body mass index, n: number, HALP: Hemoglobin-Albumin-Lymphocyte-Platelet Ratio

to those with relapse [HR (95% CI) = 3.942 (2.747-5.656), p<0.001].

Multivariate analysis showed that OS was lower in the HALP-Low group than in the HALP-High group [HR (95% CI) = 2.076 (1.437, 2.998), p<0.001]. OS was lower in those with de-novo disease status than in those with relapse [HR (95% CI) = 3.205 (2.243-4.579), p<0.001].

Discussion

Many studies have been conducted to predict the prognosis of patients with metastatic PC and prognostic factors have been identified. Unfortunately, no markers have been found to be used in daily clinical practice. Many studies have shown that hemoglobin levels affect survival in patients with malignancy [16]. Albumin is a negative acute phase reactant synthesized in the liver. Hypo-

albuminemia may be caused by malnutrition, hypercatobolism caused by cancer cells and increased inflammation due to cytokine release and this plays a role in the survival of cancer patients. Lymphocytes inhibit apoptosis by secreting TNF alpha and interferon gamma and contribute to prolonged survival by preventing tumor migration and invasion [17,18]. Platelets increase angiogenesis, migration and vascular permeability through growth factors and therefore play an important role in cancer formation and prognosis. The Halp score, in which these parameters are used together, is one of the indices that is thought to play a prognostic role in the evaluation of nutrition and immune system. We decided to do this study, which we thought would play a prognostic role in metastatic cancer. To the best of our knowledge, this study represents the first investigation to assess the prognostic significance of the HALP score in metastatic PC.

In all our patients, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. The general characteristics and median survival times of the patient population in our study were found to be compatible with the literature [19]. The HALP-Low group had a shorter median PFS compared to the HALP-High group, and this difference was statistically significant ($p<0.001$) In this study, high HALP score was found to be a good prognostic indicator and our study is compatible with the literature [12,14,15].

The literature contains numerous studies highlighting the prognostic significance of the HALP score. For instance, a study involving 582 patients with resectable pançreatic cancer demonstrated that a high HALP score prior to surgery was identified as a prognostic factor for survival [20]. According to a study involving 355 patients diagnosed with esophageal squamous cell carcinoma, a high HALP score before surgery was identified as an independent and favorable prognostic indicator [21]. In a separate study conducted by Topal et al., which included 110 colorectal cancer patients who underwent surgical procedures, it was observed that the prognostic significance of a low HALP score was diminished in the presence of tumor budding [22]. Again, in a study in which 591 patients with locally limited gastrointestinal stromal tumors were followed up post-operatively, low HALP score predicted short PFS [23].

Numerous publications also exist on this topic concerning locally advanced or metastatic stages. For instance, in a study conducted by Ekinci et al. involving 123 patients diagnosed with metastatic renal cell carcinoma, a low HALP score was associated with a poor prognosis [14]. A study in gastric cancer showed that a low HALP score numerically indicates a poor prognosis. The reason for the lack of statistical significance was thought to be the fact that the number of metastatic patients was 58 (12). Similarly, in a study conducted by Güç et al. involving 401 patients with NSCLC, it was noted that a low HALP score was associated with unfavorable survival outcomes [13]. Again, in a study including patients with limited and diffuse stage SCLC, low HALP score was found to be poor prognostic [15].

Patients with an ECOG performance score of 0-1 demonstrated a significantly higher median PFS compared to those with an ECOG performance score of 2-3, with durations of 8.33 months and 6.77 months, respectively ($p<0.001$). Additionally, patients with an ECOG performance score of 0-1 exhibited a significantly higher median OS compared to those with an ECOG performance score of 2-3, with durations of 13.3 months and 7.9 months, respectively (p: 0.001). Our study findings align with the existing literature, confirming the association between ECOG performance score and survival outcomes [24].

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). In a study by Miotke et al. survival of recurrent patients was 10.8 months and OS of recurrent patients was 7.3 months and our study was found to be favorable with the literature [25].

The retrospective design of our study and the relatively limited sample size of the HALP-low group are acknowledged limitations. While we adopted a HALP score cut-off value of 0.6 based on previous literature, the optimal threshold is still undetermined. Another issue that should be mentioned at the same time was that our patient groups were heterogeneous. It included Denovo and metachronous metastatic patients. Therefore, more specific, prospective, well-designed studies with a larger patient population are needed to investigate this issue in more detail.

A high HALP score represents a cost-effective and practical marker that contributes to the existing literature. If validated by prospective studies, it could be utilized in clinical practice to prognosticate patients with metastatic prostate cancer. Furthermore, a high HALP score was identified as an independent predictor of unfavorable prognosis in patients with metastatic pancreatic cancer

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REFERENCES

1 - Sung, H., Ferlay, J., Siegel, R. L., et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.

2 - Siegel, R. L., Miller, K. D., & Jemal, A. et al. Cancer statistics, 2019. CA: a cancer journal for clinicians, 2019: 69(1), 7-34.

3- Shimizu, T., Taniguchi, K., Asakuma, et al. Lymphocyte–to–monocyte ratio and prognostic nutritional index predict poor prognosis in patients on chemotherapy for unresectable pancreatic cancer. Anticancer Research, 2019: 39(4), 2169-2176.

4- Medina-Jiménez, A. K., & Monroy-Torres, R. Repurposing Individualized Nutritional Intervention as a Therapeutic Component to Prevent the Adverse Effects of Radiotherapy in Patients with Cervical Cancer. Frontiers in Oncology, 2020: 10, 595351.

5- Wilde, L., Roche, M., Domingo-Vidal, M., et al. Metabolic coupling and the Reverse Warburg Effect in cancer: Implications for novel biomarker and anticancer agent development. Seminars in Oncology 2017: 44; 198-203

6- Chen, W., Wei, T., Li, Z., et al. Association of the preoperative inflammation-based scores with TNM stage and recurrence in patients with papillary thyroid carcinoma: a retrospective, multicenter analysis. Cancer Management and Research, 2020: 12, 1809.

7- Ravasco, P, Nutrition in cancer patients. Journal of Clinical Medicine, 2019: 8(8), 1211.

8- Ekinci, F., Sarı, D., Çelik, C., Dirican, A., Erdoğan, A. P., Gökse, G. Can Albumin Bilirubin Ratio and Inflammatory Prognostic Index Be A New Marker Determining Survival in Metastatic Pancreatic Cancer?. The Gulf Journal of Oncology, 2021: 1(36), 45-52.

9- Sounni, N. E., & Noel, A. Targeting the tumor microenvironment for cancer therapy. Clinical Chemistry, 2013:.59(1), 85-93.

10-Baldane, S., Ipekci, S. H., Sozen, M., & Kebapcilar, L. Mean platelet volume could be a possible biomarker for papillary thyroid carcinomas. Asian Pacific Journal of Cancer Prevention, 2015: 16(7), 2671-2674.

11- Franco, A. T., Corken, A., Ware, J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood, 2015: 126(5), 582-588.

12- Sargin, Z. G., Dusunceli, I. The Effect of HALP Score on the Prognosis of Gastric Adenocarcinoma. J Coll Physicians Surg Pak 2022: 64(104), 51.

13- Güç, Z. G., Alacacıoğlu, A., Kalender, M. E., et al. HALP score and GNRI: Simple and easily accessible indexes for predicting prognosis in advanced stage NSCLC patients. The İzmir oncology group (IZOG) study. Frontiers in Nutrition, 2022: 9; 905292

14- Ekinci, F., Balcik, O. Y., Oktay, E., & Erdogan, A. P. HALP Score as a New Prognostic Index in Metastatic Renal Cell

Cancer. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2022: 32(3), 313-318.
15- Shen, X. B., Zhang, Y. X., Wang, W., & Pan, Y. Y. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with small cell lung cancer before first-line treatment with etoposide and progression-free survival. Medical science monitor: international medical Journal of Experimental and Clinical Research 2019:. 25, 5630
16- Belcher, D. A., Ju, J. A., Baek, J. H., et al. The quaternary state of polymerized human hemoglobin regulates oxygenation of breast cancer solid tumors: A theoretical and experimental study. PLoS One, .2018: 13(2), e0191275
17 - Lucijanic, M., Veletic, I., Rahelic, D., et al. Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. Wiener klinische Wochenschrift, 2018: 130(3), 126-133.
18- Greten, F. R., & Grivennikov, S. I. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity, 2019: 51(1), 27-41
19 -Ettrich, T. J., Seufferlein, T. Systemic therapy for metastatic pancreatic cancer. Current Treatment Options in Oncology, 2021: 22(11), 1-12.
20-. Xu, S. S., Li, S., Xu, H. X., Li, et al. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. World Journal of Gastroenterology, 2020: 26(8), 828
21- Feng, J. F., Wang, L., & Yang, X. et al. The preoperative hemoglobin, albumin, lymphocyte and platelet (HALP) score is a useful predictor in patients with resectable esophageal squamous cell carcinoma. Bosnian Journal of Basic Medical Sciences, 2021: 21(6), 773.
22 - Topal, U., Guler, S., Teke, Z., Karakose, E., Kurtulus, I., Bektas, H. Diagnostic Value of Preoperative Haemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score in Predicting Tumour Budding in Colorectal Cancer. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2022: 32(6), 751-757.
23- Zhao, Z., Yin, X. N., Wang, J., Chen, X., Cai, Z. L., & Zhang, B. Prognostic significance of hemoglobin, albumin, lymphocyte, platelet in gastrointestinal stromal tumors: A propensity matched retrospective cohort study. World Journal of Gastroenterology, 2022. 28(27), 3476-3487.
24 - Ekinci, F., Erdogan, A. P., Yildirim, S., Ozveren, A. Options in First Line Management of Metastatic Pancreatic Cancer and the Determinative Role of ECOG Performance Status. Eurasian Journal of Medical Investigation. 2021: 5; 500-507.
25 - Miotke, L., Nevala-Plagemann, C., Ying, J., Florou, V., Haaland, B., & Garrido-Laguna, I. Treatment outcomes in recurrent versus de novo metastatic pancreatic adeno-carcinoma: a real world study. BMC Cancer, 2022: 22(1), 1-8..

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Doi: 10.5505/aot.2023.26779

Original Article

Systemic Immune-Inflammation Index and Hodgkin Lymphoma: An Underexplored Relationship

Sistemik İmmün-İnflamasyon İndeksi ve Hodgkin Lenfoma: Yeterince Keşfedilmemiş Bir İlişki

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ABSTRACT

Introduction: Tumor-associated inflammation is an important feature of tumor development and progression. We aimed to investigate whether the clinicopathological and prognostic characteristics of patients with classical Hodgkin lymphoma (cHL) were associated with systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).
Materials and methods: This was a retrospective cohort study conducted between January 2012 and December 2021. A total of 77 patients with newly diagnosed cHL were included in the study.
Results: The median age of the patients was 37 (24-49) years. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR. Female patients (p=0.005), those with B symptoms (p=0.014) and subjects with extranodal involvement (p=0.011) had significantly higher PLR. Also, the SII of patients with B symptoms was significantly higher compared to those without (p=0.009). There were significant but weak correlations between international prognostic score-7 and SII (r=0.271, p=0.017), PLR (r=0.294, p=0.010) and NLR (r=0.378, p=0.001).
Discussion: SII was associated with B symptoms, but was not prognostic for cHL. PLR and NLR were also unassociated with prognosis in patients with cHL. However, considering the exceedingly limited data on this topic, further studies to assess inflammation indices are necessary.

Keywords: Hodgkin lymphoma, prognosis, inflammation, biomarkers, neutrophil, lymphocyte, platelet

ÖZET

Giriş: Tümörle ilişkili inflamasyon, tümör gelişimi ve ilerlemesinin önemli bir özelliğidir. Klasik Hodgkin lenfoma (kHL) hastalarının klinikopatolojik ve prognostik özelliklerinin sistemik immün-inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranı (PLO) ile ilişkili olup olmadığını araştırmayı amaçladık.
Gereç ve yöntemler: Bu, Ocak 2012 ile Aralık 2021 tarihleri arasında yürütülen retrospektif bir kohort çalışmasıdır. Çalışmaya yeni tanı almış toplam 77 kHL hastası dahil edildi.
Bulgular: Hastaların ortanca yaşı 37 (24-49) idi. Evre IV hastalığı (p=0,036), B semptomları (p=0,005) ve ekstranodal tutulumu (p=0,012) olan hastalarda NLO anlamlı olarak daha yüksekti. Kadın hastalarda (p=0,005), B semptomu olanlarda (p=0,014) ve ekstranodal tutulumu olanlarda (p=0,011) PLR anlamlı olarak daha yüksekti. Ayrıca B semptomu olan hastaların olmayanlara göre SII değeri anlamlı olarak daha yüksekti (p=0,009). Uluslararası prognostik skor-7 ile SII (r=0,271, p=0,017), PLO (r=0,294, p=0,010) ve NLO (r=0,378, p=0,001) arasında anlamlı ancak zayıf düzeyde korelasyon vardı.
Tartışma: SII, B semptomları ile ilişkili bulundu, ancak kHL için prognostik değildi. Ayrıca PLO ve NLO da kHL'li hastalarda prognozla ilişkili değildi. Ancak bu konudaki verilerin son derece sınırlı olduğu düşünüldüğünde, inflamasyon indekslerinin değerlendirilmesi için daha fazla çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Hodgkin lenfoma, prognoz, inflamasyon, biyobelirteç, nötrofil, lenfosit trombosit

First Received: 09.05.2023, Accepted: 26.06.2023 doi: 10.5505/aot.2023.62582

Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas [1] and has an annual incidence of 2–3 cases per 100 000 people [2]. It is characterized by B lymphocyte-derived malignant cells and a general inflammatory microenvironment [3]. Although genetic and environmental factors and various viral infections contribute to pathophysiology [3, 4], it is still unclear what causes normal B lymphocytes to turn into malignant, biologically active tumor cells [3].

HL is histopathologically classified as classical HL (cHL) and nodular lymphocyte-predominant HL. Patients with cHL constitute 95% of all cases [3]. Today, up to 90% of patients with cHL can be cured [4]; however, 5-10% of cases develop primary resistant disease [1], and approximately 50% of patients with relapse or resistance die from progressive disease [1, 3]. Defined prognostic factors for early stage HL are high erythrocyte sedimentation rate (ESR), multiple nodular involvement, extra-nodal involvement, being aged >50 years, and presence of massive spleen disease, bulky disease, and B symptoms [5-7]. International prognostic scores (IPS-7 and IPS-3) are used to assess patients with advanced cHL [8]; however, many of the parameters required to obtain scores are generally difficult to clarify and require detailed investigation. As such, there is a lack of generally accepted, simple and inexpensive prognostic markers that may be applicable to cHL prognostication, including those with early stage cHL, and it is evident that such markers could facilitate individualized treatment for patients with poor prognosis.

Tumor-associated inflammation is an important feature of tumor development and progression [9, 10]. Several studies have reported that increased systemic inflammatory response may predict worse survival and prognosis for various neoplasms including lymphomas [11-13]. The literature on this topic has assessed the prognostic potential of various inflammatory markers in lymphoma, such as neutrophil-to-lymphocyte ratio (NLR) [12, 14], platelet-to-lymphocyte ratio (PLR) [12, 15] and systemic immune inflammation index (SII) [1, 11, 16]. The SII, which is based on peripheral blood neutrophil, platelet, and lymphocyte counts, has been shown to predict prognosis and/or severity in various cancer types including lymphomas [1, 16]. There have been many attempts to investigate the relationship between non-Hodgkin lymphoma (nHL) and SII [11, 16, 17]; however, to our knowledge, only one such study exists for HL [1].

Therefore, in this study, we aimed to investigate whether clinicopathological and/or prognostic parameters in patients with cHL were associated with SII, NLR and PLR values.

Material and Method

Study design and ethical considerations

This retrospective study was carried out in the Hematology department of our hospital. The protocol of this study was approved by the local ethics committee. It has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Study population

A total of 77 patients with new-onset cHL who were treated and followed up for cHL at our clinic, between January 2012 and December 2021, were included in the study. Patients younger than 18 years of age, those with known active infection, rheumatic or immunological disease at the time of blood sampling, patients with concomitant or previously treated malignancy, subjects with any known comorbid disease, patients with missing data, and those with no follow-up information were excluded from the study.

Data collection

All data about patients including age and sex information, performance status, pathology results, HL-related information, laboratory results, and follow-up data were retro-

spectively collected from hospital computer database.

Patient management and examinations

All steps of cHL management, including diagnosis, treatment and follow-up, were carried out in accordance with the current European Society for Medical Oncology Guidelines (www.esmo.org/ Guidelines/ Haematological-Malignancies) and the National Comprehensive Cancer Network, USA, Cinical Practice Guidelines (www.nccn.org /professionals/ physician_gls/ default.aspx).

The pretreatment information including B symptoms, performance score, pathological subtype, Ann Arbor stage, EBV positivity, bulky mass/mediastinal mass, diagnosis date and extranodal involvement positivity and IPS-7 score, treatment, and post-treatment data including refractory/recurrent disease and mortality were collected.

Performance status (PS) was determined in accordance with the Eastern Cooperative Oncology Group (ECOG) criteria [18]. The IPS-7 score was calculated as previously described [8]. Refractory disease was defined as a condition that either does not respond to treatment or achieves remission with treatment but relapses within six months. Relaps was defined as recurrent cHL after a documented complete remission that lasted at least six months after the first line treatment [19, 20].

Definitions for analyses

Patients with relapsed disease and/or death were defined as having a poor prognosis. However, disease (refractory/recurrent or death)-free-survival (DFS) was calculated using data from patients with poor prognosis (refractory/recurrent or death). When calculating DFS, the time between the diagnosis date and refractory/recurrent determining date or death date or data collection starting date was used. The follow-up time was calculated as the duration from the diagnosis date to data collection starting date or mortality.

Laboratory measurements and related tools

All laboratory analyses were performed in the Biochemistry department of our hospital using calibrated standard measuring devices and according to the manufacturer's recommendations. The results of the following laboratory findings, which were studied from blood samples obtained at the time of diagnosis and before any treatment, were included in the study: aspartate amino-transferase (AST), alanine amino-transferase (ALT), albumin, ESR, lactate dehydrogenase (LDH), C-reactive protein (CRP), and hemogram.

The NLR, PLR and SII were calculated using absolute neutrophil, lymphocyte, platelet counts. SII was calculated by using the following formula: SII ($\times 10^3$) = Absolute neutrophil count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [1].

Glomerular filtration rate (GFR) was calculated automatically using the short Modification of Diet in Renal Disease formula from the Turkish Society of Nephrology's internet application called “formula and calculations” (https://nefroloji.org.tr/tr/ formul-ve-hesaplamalar).

Statistical analysis

The classical $p<0.05$ threshold was accepted to show statistical significance. All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Between-group analyses were performed with the Mann-Whitney U test or Kruskal-Wallis test depending on normality of distribution. Pairwise comparisons were adjusted by the Bonferroni correction. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. DFS was calculated with the Kaplan-Meier method by using time between remission and recurrence or death. Cox regression analyses were performed to determine significant factors independently associated with poor prognosis.

Variables were analyzed with the univariable cox regression analysis and statistically significant variables were included into the multivariable cox regression model.

Results

The median age of the patients was 37 (24-49) years, and 62.34% (n=48) of them were males. Mean follow-up time was 48.74±26.46 (range 9-118) months. One patient died of ischemic heart disease 93 months after diagnosis. Patients' disease characteristics and laboratory measurements are depicted in Table 1 and Table 2.

The relationships between NLR, PLR and SII and the characteristics of patients with cHL are presented in Table 3. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR than patients without these characteristics. The PLR values of female patients (p=0.005), patients with B symptoms (p=0.014) and those with extra-nodal involvement (p=0.011) were significantly higher than comparative groups. The SII values of patients with B symptoms were significantly higher than those without (p=0.009).

Correlations between NLR, PLR, SII and other continuous variables are presented in Table 4. Significant correlations were found between NLR and age (r=-0.226, p=0.048), IPS-7 score (r=0.378, p=0.001), albumin (r=-0.280, p=0.014), ESR (r=0.416, p<0.001), CRP (r=0.452, p<0.001), hemoglobin (r=-0.387, p=0.001) and hematocrit (r=-0.387, p<0.001) levels. There were significant correlations between PLR and IPS-7 score (r=0.294, p =0.010), albumin (r=-0.264, p=0.020), ESR (r=0.446, p<0.001), CRP (r=0.541, p<0.001), hemoglobin (r=-0.519, p<0.001), hematocrit (r=-0.515, p<0.001) levels and mean corpuscular volume (MCV) (r=-0.367, p=0.001) values. Also, significant correlations were found between SII and age (r =-0.278, p=0.014), IPS-7 score (r=0.271, p=0.017), GFR (r=0.252, p=0.027), AST (r=-0.300, p=0.008), ALT (r=0.263, p=0.021), ESR (r=0.390, p<0.001), CRP (r=0.519, p<0.001), hemoglobin (r=-0.369, p=0.001),

Table 1. Summary of patients and disease characteristics

Age at diagnosis	37 (24 - 49)
Sex	
Male	48 (62.34%)
Female	29 (37.66%)
ECOG performance score	
0	60 (77.92%)
1	16 (20.78%)
2	1 (1.30%)
Histological subtype	
Nodular sclerosis	39 (50.65%)
Mixed cellularity	32 (41.56%)
Lymphocyte-depleted	1 (1.30%)
Lymphocyte-rich	5 (6.49%)
Other	0 (0.00%)
EBV	
Negative	21 (27.27%)
Positive	25 (32.47%)
Unknown	31 (40.26%)
Stage	
Stage I	3 (3.90%)
Stage II	29 (37.66%)
Stage III	25 (32.47%)
Stage IV	20 (25.97%)
Bulky disease	14 (18.18%)
B symptoms	35 (45.45%)
IPS-7	2 (2 - 3)
Mediastinal mass	35 (45.45%)
Extranodal involvement	16 (20.78%)
Chemotherapy	
ABVD	72 (93.51%)
BEACOPP	1 (1.30%)
GEMOX	0 (0.00%)
Brentuximab	4 (5.19%)
Nivolumab	0 (0.00%)
Radiotherapy	19 (24.68%)
Refractory/Recurrent disease	18 (23.38%)
Autologous stem cell transplantation	18 (23.38%)
Mortality	1 (1.30%)
Follow-up time, months	48.74 ± 26.46

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables
Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, IPS-7: International prognostic scores-7

Table 2. Summary of laboratory measurements

GFR (mL/min/1.73 m^2)	115.61 ± 18.21
AST (IU/L)	18 (16 - 28)
ALT(IU/L)	17 (12.6 - 33)
Albumin (g/dL)	3.96 ± 0.66
ESR (mm/h)	46 (11 - 67)
LDH (mg/dL)	207 (179 - 270)
CRP (mg/L)	12 (2.5 - 72)
Hemoglobin (g/dL)	11.74 ± 2.62
Hematocrit (%)	36.14 ± 6.74
MCV (fl)	81.13 ± 6.89
WBC ($x10^3$)	8.32 (4.96 - 15.47)
Neutrophil ($x10^3$)	5.28 (3.20 - 11.92)
Lymphocyte ($x10^3$)	1.75 ± 0.82
Monocyte ($x10^3$)	0.78 ± 0.47
Eosinophil ($x10^3$)	0.18 (0.08 - 0.34)
Platelet ($x10^3$)	357.53 ± 168.95
NLR	4.06 (1.99 - 6.84)
PLR	180.46 (142.57 - 321.43)
SII ($x10^3$)	1045.39 (515.46 - 2598.73)

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

hematocrit (r=-0.369, p=0.001) levels and MCV (r=-0.257, p=0.024) values.

DFS was 73.54 ± 7.14 (95% CI: 59.54 - 87.54) months (Figure 1). Univariable cox regression analysis revealed that stage at diagnosis and Bulky disease were the only factors independently associated with poor prognosis. Multivariable cox regression revealed that stage at diagnosis was the only factor independently associated with poor prognosis. Patients with stage III & IV cHL at diagnosis had a 4.270-fold higher risk for refractory/ recurrent disease or death compared to patients with stage I & II cHL at diagnosis (HR: 4.270, 95% CI: 1.165 - 15.655, p=0.029, Figure 2) (Table 5).

Discussion

The main findings of the present study were as follows: Firstly, there were significant associations between SII and B symptoms, between NLR and stage IV disease, B symptoms and extranodal involvement, and between PLR and female sex. Secondly, SII, NLR and PLR were not found to be significant markers in predicting poor prognosis. Finally, only Stage III & IV disease and Bulky disease were associated with poor prognosis in the present study [7].

SII is assumed to reflect systemic inflammation in a balanced way, and has been claimed to be a stronger prognostic marker in some malignancies –compared to other systemic inflammation markers such as NLR, PLR and lymphocyte-to-monocyte ratio [1, 17, 21]. However, the relationship between SII and the clinicopathological and prognostic features of HL has not been adequately studied. In the present study, SII was only associated with the presence of B symptoms. There was also a weak correlation between SII and IPS-7 score. Although the presence of B symptoms and a high IPS-7 score are predictors of poor prognosis in HL, no strong relationship was found between SII and these factors of poor prognosis in our study. Mirilli and colleagues showed that SII was an independent predictive factor for both overall survival (OS) and progression free survival (PFS) in HL patients. They also found SII to be a more powerful indicator than other scores and inflammatory parameters including NLR, prognostic nutritional index and B2 microglobulin, as demonstrated by its predictive sensitivity of 73% and specificity of 73% [1]. To our knowledge, there have been no other studies investigating the role of SII in HL, whereas there has been research in patients with nHL [16, 22-24]. In the light of available data, although SII seems to have a prognostic role for nHL, it seems that more comprehensive studies are needed to ascertain its prognostic role in cHL.

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Table 3. Inflammation indices with regard to patient characteristics

	NLR	p	PLR	p	SII	p
Sex						
Male	3.40 (1.92 - 6.79)	0.223	155.02 (133.80 - 271.51)	**0.005**	950.60 (445.10 - 2890.10)	0.185
Female	4.88 (2.16 - 7.07)		227.92 (168.31 - 391.20)		1499.18 (794.92 - 2548.65)	
ECOG performance score						
0	4.14 (1.96 - 7.17)	0.778	171.24 (143.14 - 329.73)	0.615	963.64 (495.73 - 3281.13)	0.893
1 & 2	3.42 (2.54 - 6.57)		218.95 (141.00 - 321.43)		1212.39 (809.34 - 2246.51)	
Histological subtype						
Nodular sclerosis	6.02 (1.99 - 7.90)		195.00 (154.49 - 349.60)		2246.51 (476.77 - 3641.94)	
Mixed cellularity	3.30 (2.05 - 6.06)	0.195	163.62 (140.68 - 315.72)	0.355	902.81 (529.50 - 1425.97)	0.194
Other	2.41 (1.66 - 4.64)		157.32 (136.56 - 218.95)		797.19 (286.51 - 1928.93)	
EBV						
Negative	4.88 (1.66 - 7.07)	0.275	212.03 (158.48 - 310.00)	0.434	1352.75 (448.98 - 3454.05)	0.700
Positive	5.64 (3.11 - 10.42)		280.00 (150.79 - 418.02)		1204.61 (583.10 - 2598.73)	
Stage						
Stage I & II	2.75 (1.75 - 6.63) [a]		160.58 (138.45 - 229.60)		827.90 (402.35 - 2238.79)	
Stage III	4.47 (2.19 - 6.08) [ab]	**0.036**	181.08 (143.70 - 391.20)	0.115	1357.43 (562.49 - 2492.16)	0.118
Stage IV	6.80 (3.27 - 9.15) [b]		214.67 (159.77 - 347.31)		1425.97 (905.88 - 4232.40)	
Bulky disease						
No	3.55 (1.94 - 6.84)	0.345	170.31 (140.91 - 280.00)	0.107	941.92 (476.77 - 2548.65)	0.316
Yes	6.29 (3.19 - 6.84)		306.25 (158.48 - 391.20)		1483.56 (861.43 - 4143.38)	

Table 1 continued next page

B symptom						
No	2.99 (1.58 - 6.08)	**0.005**	155.66 (136.56 - 280.00)	**0.014**	640.06 (395.79 - 2492.16)	**0.009**
Yes	4.88 (2.62 - 8.12)		217.30 (168.75 - 391.20)		1274.81 (867.31 - 3380.79)	
Mediastinal mass						
No	3.25 (1.94 - 6.31)	0.111	157.20 (136.56 - 231.28)	**0.011**	940.11 (476.77 - 2492.16)	0.260
Yes	4.88 (2.43 - 9.37)		217.30 (163.55 - 418.02)		1499.18 (543.54 - 3641.94)	
Extranodal involvement						
No	3.34 (1.94 - 6.31)	**0.012**	170.31 (141.00 - 238.00)	0.058	938.30 (476.77 - 2492.16)	0.092
Yes	6.96 (5.03 - 10.29)		306.25 (157.98 - 385.94)		1479.67 (905.88 - 4963.06)	
R/R or Death						
No	3.78 (1.94 - 7.07)	0.911	180.77 (154.19 - 321.43)	0.408	940.11 (514.69 - 2548.65)	0.339
Yes	5.64 (2.19 - 6.63)		153.11 (126.87 - 396.88)		1499.18 (583.10 - 2689.67)	

Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. Same letters denote the lack of statistically significant difference between groups. The letters in the table represent pairwise comparison results. Each letter provides contextual information regarding the comparative groups and are coded with an approach that reduces clutter. For example: The lettering “a b b” indicates that the first measurement/group is different from the others, and there is no difference between the second and third measurements/groups. The lettering “a ab b” indicates that the first measurement/group and the third measurement/group are different, and the second measurement/group is similar to both other measurements/groups
Abbreviations: EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, R/R: Refractory/Recurrent, SII: Systemic immune inflammation index.

Table 4. Relationships between inflammation indices and other continuous variables

		NLR	PLR	SII
Age at diagnosis	r	**-0.226**	-0.142	**-0.278**
	p	**0.048**	0.219	**0.014**
IPS-7	r	**0.378**	**0.294**	**0.271**
	p	**0.001**	**0.010**	**0.017**
GFR (mL/min/1.73 m2)	r	0.192	0.150	**0.252**
	p	0.095	0.192	**0.027**
AST (IU/L)	r	-0.172	-0.068	**-0.300**
	p	0.135	0.555	**0.008**
ALT (IU/L)	r	-0.155	-0.123	**-0.263**
	p	0.178	0.287	**0.021**
Albumin (g/dL)	r	**-0.280**	**-0.264**	-0.221
	p	**0.014**	**0.020**	0.054
ESR (mm/h)	r	**0.416**	**0.446**	**0.390**
	p	**<0.001**	**<0.001**	**<0.001**
LDH (mg/dL)	r	0.009	-0.105	-0.024
	p	0.939	0.365	0.835
CRP (mg/L)	r	**0.452**	**0.541**	**0.519**
	p	**<0.001**	**<0.001**	**<0.001**
Hemoglobin (g/dL)	r	**-0.387**	**-0.519**	**-0.369**
	p	**0.001**	**<0.001**	**0.001**
Hematocrit (%)	r	**-0.387**	**-0.515**	**-0.369**
	p	**<0.001**	**<0.001**	**0.001**
MCV (fl)	r	-0.193	**-0.367**	**-0.257**
	p	0.093	**0.001**	**0.024**

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, r: Spearman correlation coefficient

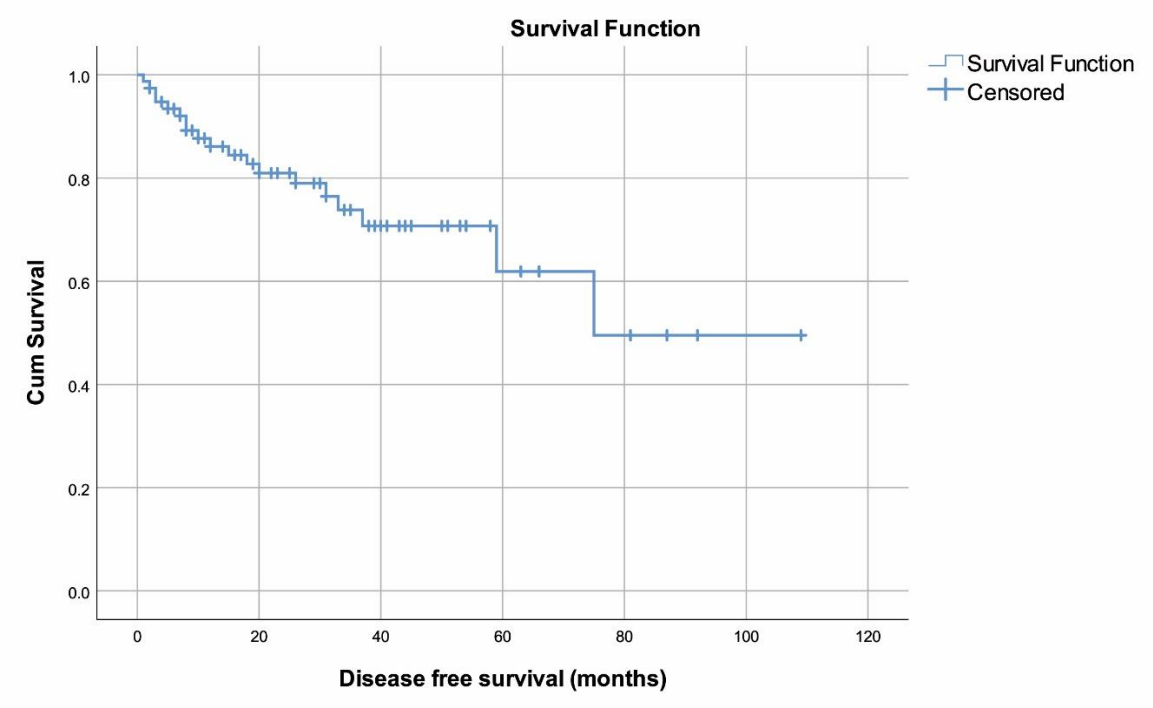

Figure 1. Disease free survival plot

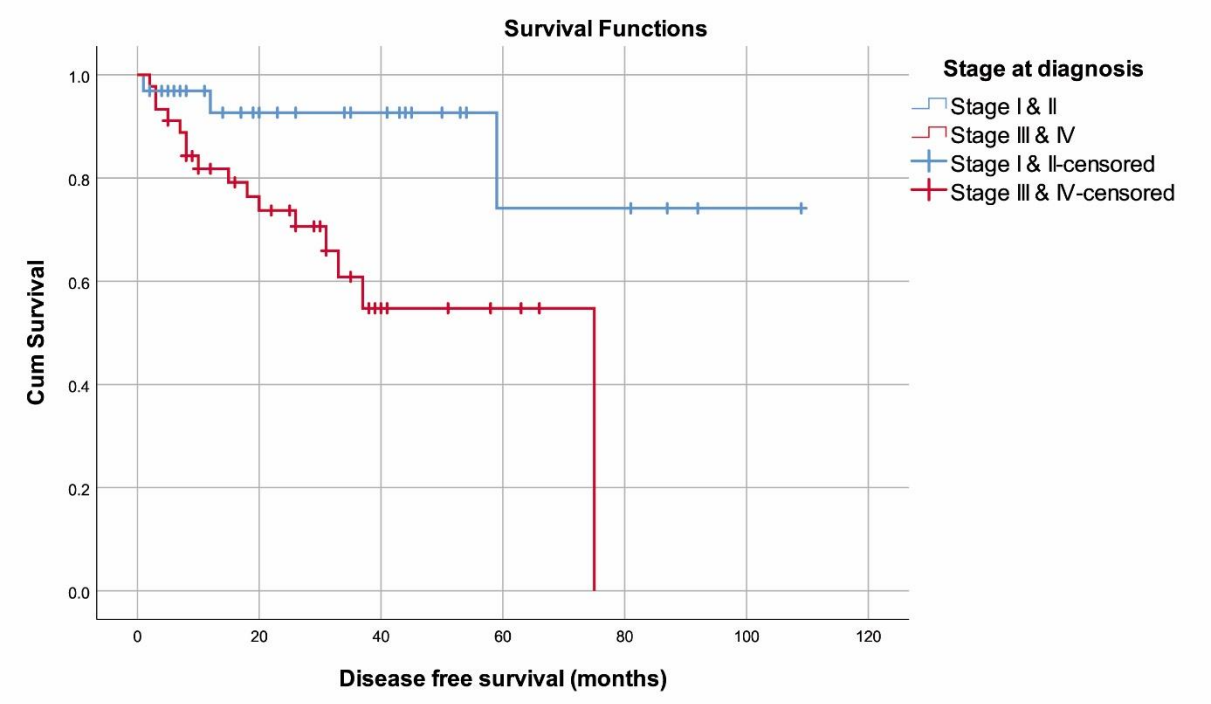

Figure 2. Disease free survival plot with regard to stage

Table 5. Association between variables and poor prognosis (refractory/recurrent disease or death), Cox Regression

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis	0.981 (0.948 - 1.014)	0.255		
Sex (based female)	0.538 (0.192 - 1.505)	0.237		
ECOG performance score (based ECOG≥1)	1.328 (0.472 - 3.738)	0.591		
Histological subtype (based mixed cellularity)	1.440 (0.577 - 3.590)	0.434		
EBV (based positive)	2.453 (0.651 - 9.252)	0.185		
Stage (based stage III & IV)	4.970 (1.407 - 17.564)	**0.013**	4.270 (1.165 - 15.655)	**0.029**
Bulky disease (based present)	2.986 (1.098 - 8.119)	**0.032**	2.004 (0.722 - 5.557)	0.182
B symptom (based present)	1.662 (0.674 - 4.100)	0.270		
IPS-7	1.027 (0.725 - 1.454)	0.882		
Mediastinal mass (based present)	1.526 (0.594 - 3.924)	0.380		
Extranodal involvement (based present)	1.982 (0.693 - 5.671)	0.202		
Chemotherapy (based ABVD)	0.773 (0.101 - 5.894)	0.803		
Radiotherapy (based present)	0.507 (0.147 - 1.755)	0.284		
GFR (mL/min/1.73 m2)	1.015 (0.991 - 1.039)	0.231		
AST (IU/L)	0.987 (0.953 - 1.023)	0.480		
ALT (IU/L)	0.990 (0.965 - 1.016)	0.445		
Albumin (g/dL)	1.230 (0.598 - 2.529)	0.574		
ESR (mm/h)	1.003 (0.989 - 1.018)	0.655		
LDH (mg/dL)	1.000 (0.997 - 1.003)	0.947		
CRP (mg/L)	1.002 (0.995 - 1.010)	0.583		
Hemoglobin (g/dL)	0.951 (0.802 - 1.128)	0.567		
Hematocrit (%)	0.984 (0.922 - 1.052)	0.642		
MCV (fl)	1.078 (0.994 - 1.168)	0.070		
WBC ($x10^3$)	1.045 (0.986 - 1.108)	0.141		
Neutrophil ($x10^3$)	1.047 (0.977 - 1.123)	0.193		
Lymphocyte ($x10^3$)	1.628 (0.918 - 2.885)	0.095		
Monocyte ($x10^3$)	1.681 (0.717 - 3.939)	0.232		
Eosinophil ($x10^3$)	1.327 (0.546 - 3.228)	0.533		
Platelet ($x10^3$)	1.002 (0.999 - 1.004)	0.197		
NLR	0.990 (0.913 - 1.074)	0.811		
PLR	0.999 (0.997 - 1.002)	0.656		
SII ($x10^3$)	1.000 (1.000 - 1.000)	0.917		

Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CI: Confidence interval, CRP: C-reactive protein, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, HR: Hazard ratio, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

It is known that platelets play an important role in the spread and growth of tumors [25] and platelet related markers are suggested to be prognostic factors for solid tumors [26, 27]It has also been shown that platelets play a critical role in the spread of Hodgkin-Reed Sternberg cells, especially in the spleen [28]. In the current study, a significant association was found between PLR and B symptoms and mediastinal mass. There was also a weak correlation between PLR and IPS-7 score. However, PLR was not found to be a significant marker for cHL prognosis. Reddy et al. showed that 2-year PFS was 84.3% for early cHL patients with a PLR of ≥266.2, which was significantly lower compared to the 96.1% 2-year PFS of patients with a PLR of <266.2. PLR remained a significant, independent prognostic factor. Also, high PLR (≥266.2) was also associated with advanced Ann-Arbor stage, B symptoms, and Bulky disease [12]. In another study high PLR was shown to be associated with lower likelihood of complete treatment response in patients with HL, and high PLR was independently associated with shorter PFS [15]. In contrast, similar to our findings, PLR was not found to be a prognostic factor for HL in other studies [29]. PLR seems to have the potential to be a prognostic marker for HL but available evidence needs to be supported by randomized controlled trials.

NLR has also been used for the prognostication of many types of

malignancies, including lymphomas [1, 6, 12]. Our results showed that NLR was associated with Stage IV disease, B symptoms, and extranodal involvement. Also, there was a weak correlation between NLR and IPS-7 score, but NLR was not a reliable predictor for poor cHL prognosis. In a comprehensive retrospective study, it was reported that 2-year PFS for early cHL patients with an NLR of ≥6.4 was 82.2% versus 95.7% among those with an NLR of <6.4. Similar to high PLR, having high NLR (≥6.4) was also associated with advanced Ann-Arbor stage, B symptoms and Bulky disease [12]. In another study in pediatric HL patients, it was reported that patients with an NLR of >3.5 had significantly higher stage and greater frequency of Bulky disease and B symptoms [14]. High NLR values have also been associated with disease stage, early-stage risk scoring, and response to treatment [6]. We did not find any notable association between prognostic characteristics and NLR in the present study, which has been reported before in patients with HL [29].

As a general comment, unfortunately, current prognostic models have not shown satisfactory success in early detection of HL patients at high risk of shortened survival [30]. For example, IPS has little clinical benefit, because only 19% of patients with scores of 4 and 5 are found to have a less than 50% probability of 7-year PFS [31, 32]. IPS calculation is usually preferred for high-stage HLs. Considering these disadvantages, it is undoubtedly crucial to obtain further data to assess the roles of inflammation markers such as NLR, PLR and SII in cHL, particularly since these markers are readily-available, easy to access and low cost.

Despite being one of the first studies to assess these markers in patients with cHL, the limitations of the present study must be considered when interpreting the results. This is a single-center retrospective study with a relatively small sample size, and thus, there were a low number of deaths in the study group which made OS-related analyses impossible. In addition, the number of recurrences may be considered insufficient, which may impact the results concerning DFS. Although factors thought to affect the inflammatory markers were assessed to exclude patients, some relevant data of patients may not have been recorded in the database. The follow-up period of the patients who were diagnosed towards the end of the study may have been short. The patients included in the study were diagnosed between 2012 and 2021, and changes or advances in patient management may have affected the findings. As the number of similar studies was limited (especially for SII), there were inadequacies in comparative analyses with the literature.

Conclusion

SII was associated with B symptoms, NLR with Stage IV disease, and PLR with B symptoms and mediastinal mass. There were weak correlations between all three markers and IPS-7; however, none of the inflammation indices were found to be prognostic for cHL. Taken together with the limited literature, it is evident that current data is insufficient for the use of pretreatment SII, NLR, and PLR in the prognostication of cHL disease

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REFERENCES

1. Mirili C, Paydas S, Kapukaya TK, Yılmaz A. Systemic immune-inflammation index predicting survival outcome in patients with classical Hodgkin lymphoma. Biomark Med. 2019; 13(18): 1565-75.
2. Yung L, Linch D. Hodgkin's lymphoma. Lancet. 2003; 361(9361): 943-51.
3. Momotow J, Borchmann S, Eichenauer DA, Engert A, Sasse S. Hodgkin Lymphoma-Review on Pathogenesis, Diagnosis, Current and Future Treatment Approaches for Adult Patients. J Clin Med. 2021; 10(5): 1125.
4. Brice P, De Kerviler E, Friedberg JW. Classical Hodgkin lymphoma. Lancet. 2021; 398(10310): 1518-27.
5. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016; 91(4): 434-42.
6. Dogan A, Demircioglu S. Assessment of the Neutrophil-Lymphocyte Ratio in Classic Hodgkin Lymphoma Patients. Pak J Med Sci. 2019; 35(5): 1270-5.
7. Kumar A, Burger IA, Zhang Z, Drill EN, Migliacci JC, Ng A, et al. Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes. Haematologica. 2016; 101(10): 1237-43.
8. Diefenbach CS, Li H, Hong F, Gordon LI, Fisher RI, Bartlett NL, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. Br J Haematol. 2015; 171(4): 530-8.
9. Chu Y, Liu Y, Jiang Y, Ge X, Yuan D, Ding M, et al. Prognosis and complications of patients with primary gastrointestinal diffuse large B-cell lymphoma: Development and validation of the systemic inflammation response index-covered score. Cancer Med. 2023; 00:1–13.
10. Samadi A, Sabuncuoglu S, Samadi M, Isikhan SY, Chirumbolo S, Peana M, et al. A comprehensive review on oxysterols and related diseases. Curr Med Chem. 2021; 28(1): 110-36.
11. Luo Q, Yang C, Fu C, Wu W, Wei Y, Zou L. Prognostic Role of Blood Markers in Primary Central Nervous System Lymphoma Patients Treated With High-Dose Methotrexate-Based Therapy. Front Oncol. 2021; 11: 639644.
12. Reddy JP, Hernandez M, Gunther JR, Dabaja BS, Martin GV, Jiang W, et al. Pre-treatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are prognostic of progression in early stage classical Hodgkin lymphoma. Br J Haematol. 2018; 180(4): 545-9.
13. Tao Y, He X, Qin Y, Liu P, Zhou S, Yang J, et al. Low platelet/platelet distribution width and high platelet/lymphocyte ratio are adverse prognostic factors in patients with newly diagnosed advanced Hodgkin lymphoma. Leuk Lymphoma. 2021; 62(13): 3119-29.
14. Jan S, Mustafa O, Elgaml A, Ahmad N, Abbas A, Althubaiti S. Neutrophil-to-Lymphocyte Ratio and Ferritin as Measurable Tools for Disease Burden and B Symptoms in Pediatric Patients With Hodgkin Lymphoma. J Pediatr Hematol Oncol. 2022; 44(2): e567-e71.
15. Tao Y, Zhou Y, Chen H, Qin Y, He X, Liu P, et al. Prognostic role of red blood cell distribution width and platelet/lymphocyte ratio in early-stage classical Hodgkin lymphoma. Future Oncol. 2022; 18(15): 1817-27.
16. Wang Z, Zhang J, Luo S, Zhao X. Prognostic Significance of Systemic Immune-Inflammation Index in Patients With Diffuse Large B-Cell Lymphoma. Front Oncol. 2021; 11: 655259.
17. Yang J, Guo X, Hao J, Dong Y, Zhang T, Ma X. The Prognostic Value of Blood-Based Biomarkers in Patients With Testicular Diffuse Large B-Cell Lymphoma. Front Oncol. 2019; 9: 1392.
18. Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. Cancer. 1990; 65(8): 1864-6.
19. Tarella C, Cuttica A, Vitolo U, Liberati M, Di Nicola M, Cortelazzo S, et al. High-dose sequential chemotherapy and peripheral blood progenitor cell autografting in patients with refractory and/or recurrent Hodgkin lymphoma: a multicenter study of the intergruppo Italiano Linfomi showing prolonged disease free survival in patients treated at first recurrence. Cancer. 2003; 97(11): 2748-59.
20. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. Crit Rev Oncol Hematol. 2013; 85(2): 216-37.
21. Fu X, Li T, Dai Y, Li J. Preoperative systemic inflammation score (SIS) is superior to neutrophil to lymphocyte ratio (NLR) as a predicting indicator in patients with esophageal squamous cell carcinoma. BMC Cancer. 2019; 19(1): 721.
22. Wu XB, Hou SL, Liu H. Systemic immune inflammation index, ratio of lymphocytes to monocytes, lactate dehydrogenase and prognosis of diffuse large B-cell lymphoma patients. World J Clin Cases. 2021; 9(32): 9825-34.
23. Wu J, Zhu H, Zhang Q, Sun Y, He X, Liao J, et al. Nomogram based on the systemic immune-inflammation

index for predicting the prognosis of diffuse large B-cell lymphoma. Asia Pac J Clin Oncol. 2023; 19(2): e138-e48.
24. Feng Y, Liu Y, Zhong M, Wang L. Complete blood count score model predicts ınferior prognosis in primary central nervous system lymphoma. Front Oncol. 2021; 11: 618694.
25. Nash GF, Turner LF, Scully MF, Kakkar AK. Platelets and cancer. Lancet Oncol. 2002; 3(7): 425-30.
26. Sahin F, Yildiz P. Serum platelet, MPV, PCT and PDW values, neutrophil to lymphocyte and platelet to lymphocyte ratios in lung cancer diagnosis. Eur Respiratory Soc; 2015; 46: PA4279
27. Aksoy EK, Kantarcı S, Torgutalp M, Akpınar MY, Sapmaz FP, Yalçın G, et al. The importance of complete blood count parameters in the screening of gastric cancer. Prz Gastroenterol. 2019; 14(3): 183-7.
28. Ohana OM, Ozer J, Prinsloo I, Benharroch D, Gopas J. Hodgkin lymphoma cell lines bind to platelets. Incubation with platelets induces CD15 and P-selectin dependent adhesion of the cell lines to Human Umbilical Vein Endothelial cells (HUVEC). Cancer Biol Ther. 2015; 16(11): 1651-9.
29. Ertan K, Dogru A, Kara B, Koksal Y. Impact on the survival of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and monocyte-lymphocyte ratio on prognosis in children with Hodgkin lymphoma. Saudi Med J. 2022; 43(5): 451-7.
30. Romano A, Parrinello NL, Vetro C, Chiarenza A, Cerchione C, Ippolito M, et al. Prognostic meaning of neutrophil to lymphocyte ratio (NLR) and lymphocyte to monocyte ration (LMR) in newly diagnosed Hodgkin lymphoma patients treated upfront with a PET-2 based strategy. Ann Hematol. 2018; 97(6): 1009-18.
31. Hasenclever D. The disappearance of prognostic factors in Hodgkin's disease. Ann Oncol. 2002; 13 Suppl 1: 75-8.
32. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998; 339(21): 1506-14..

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Doi: 10.5505/aot.2023.62582

Case Report

Anaplastic Multiple Myeloma: A Report of a Rare Case with CD38 and CD117 Positivity

Anaplastik Multipl Miyelom: CD38 ve CD117 Pozitifliği Olan Nadir Bir Olgu Sunumu

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ABSTRACT

Anaplastic multiple myeloma (AMM), which comprises anaplastic multiple myeloma and anaplastic plasmacytoma, is a rare illness that aggressively advances as a morphological subtype of multiple myeloma (MM). It has a poor prognosis and is believed to be particularly resistant to treatment. In this case report, we presented a 66-year-old woman diagnosed with AMM. The anaplastic morphology of MM may pose a diagnostic challenge. The need for a multidisciplinary approach to detect hematological neoplasms is highlighted in this example. For AMM instances, prompt radiographic, flowcytometry, and histological examination may assist guide effective treatment strategies.

Keywords: Anaplastic myeloma, multiple myeloma, monoclonal antibody

ÖZET

Anaplastik multipl miyelom ve anaplastik plazmasitoma içeren anaplastik multipl miyelom (AMM), multipl miyelomun (MM) morfolojik bir alt tip olarak agresif bir şekilde ilerleyen nadir bir hastalıktır. Kötü bir prognoza sahiptir ve tedaviye özellikle dirençli olduğuna inanılmaktadır. Bu olgu sunumunda AMM tanısı alan 66 yaşında bir kadın hastayı sunduk. MM'nin anaplastik morfolojisi tanısal bir zorluk teşkil edebilir. Bu örnekte hematolojik neoplazmları tespit etmek için multidisipliner bir yaklaşıma olan ihtiyaç vurgulanmıştır. AMM vakaları için hızlı radyografik, akım sitometri ve histolojik inceleme, etkili tedavi stratejilerini yönlendirmeye yardımcı olabilir.

Anahtar kelimeler: Anaplastik myelom, multiple myelom, monoklonal antikor

Introduction

Anaplastic multiple myeloma (AMM), which comprises anaplastic multiple myeloma and anaplastic plasmacytoma, is a rare illness that aggressively advances as a morphological subtype of multiple myeloma (MM). In newly-diagnosed instances of MM aberrant morphology and asynchronous immuno-phenotypic expression of plasma cells might be detected, leading to error in the initial diagnosis. It has a poor prognosis and is believed to be particularly resistant to treatment [1]. All ethnic groups and both sexes are impacted by AMM. AMM is far more common in younger patients than traditional multiple myeloma (median age of 69 years old), with a median age of 57.02 years [2, 3]. Because of its rarity, the clinical and pathological aspects of AMM have not been thoroughly understood yet. AMM

First Received: 09.02.2023, Accepted: 28.03.2023 doi: 10.5505/aot.2023.43925

patients are often young, with anemia or pancytopenia, dramatically reduced Ig, IgA isotype blood levels, and quickly developing extramedullary diseases [4]. Even in the presence of clinical, radiographic, and biochemical indications of the disease, a bone marrow test is necessary for the diagnosis of AMM. Using immunophenotyping, the bone marrow is evaluated both qualitatively and quantitatively. Myeloma cells are divided into 4 kinds based on their cytomorphology: mature, immature, pleomorphic, and plasmablastic [5]. AMM cells are atypical plasmacytoid differentiated cells that are widely dispersed. They have the following morphological characteristics: More than one big and irregular nucleolus; nucleoli with numerous distributed vacuoles; pleomorphic cells with significantly enriched cytoplasm [6]. Conventional chemotherapy and radiation are ineffective in the majority of AMM patients [1]. Immunotherapy, such as chimeric antigen receptor T cell immunotherapy, monoclonal antibodies, and potentially hematopoietic stem cell transplantation, might give these patients hope [1]. Chemotherapy has not been very effective in the past against this illness. It has been proposed that this aggressive phase may be the consequence of clonal evolution of the initial malignant cell rather than the emergence of a brand-new neoplasia on its own [7]. In this case report, we presented a 66-year-old woman diagnosed with AMM.

Case report

A 66-year-old female was admitted to the hematology clinic with increased fatiguability and night sweats. Physical examination revealed splenomegaly but was otherwise unremarkable. Hemogram revealed anemia (Hemoglobin = 9.1 g/dL), and thrombocytopenia (Platelet count = 74 × 10^6/L). Biochemical tests resulted in total protein: 105 g/L, albumin level of 35 g/L, creatinine 0.9 mg/dL, LDH 250 U/L. Roll formation was observed in erythrocytes in peripheral blood smear as depicted in Figure 1 (A). High lambda (207 mg/L) compared to kappa (10.8 mg/L) with a ratio of 19.1 verified the lambda light chain limitation in neoplastic cells by free light chain test. IgG isotype blood level was 64.12 g/L (7-16 g/L). Hypercellular particles with decreased trilineage hematopoiesis were seen on bone marrow aspiration. The aspirate smear of bone marrow was densely infiltrated with cohesive clusters/sheets of extremely pleomorphic neoplastic cells, many of which had anaplastic shape. There are numerous big atypical pleomorphic cells with a high nucleo-cytoplasmic ratio, basophilic cytoplasm, and a central eccentric nucleus with an uneven nuclear border as depicted in Figure 1 (B). Flowcytometric evaluation of bone marrow showed a CD45 negative cell population expressing CD38, CD117, and lambda on their surface without CD138 and CD56 expressions. (Figure 2). These cells were plasma cells and negative for surface expressions of CD19, CD20, CD22, and CD23, and also negative for intracytoplasmic CD79a. Positron emission tomography was reported as pleural nodular thickening, spleen 25 cm, diffusely increased involvement, multiple soft tissue lesions in the pelvic region, and multiple foci of involvement in bone structures and bone marrow as depicted in Figure 3 (maximum SUVmax value: 13.6). Based on the morphological and immuno-phenotypic findings, the patient was diagnosed with AMM. The patient is now being treated with bortezomib, lenalidomide, and dexamethasone, and is being followed up. After chemotherapy, autologous stem cell transplantation treatment is planned.

Discussion

AMM is a kind of plasma cell myeloma that has a very aggressive clinical course and a poor prognosis. One of the most frequent signs of AMM was anemia, and 9.6% of patients had thrombocytopenia when they were diagnosed, which is probably due to the

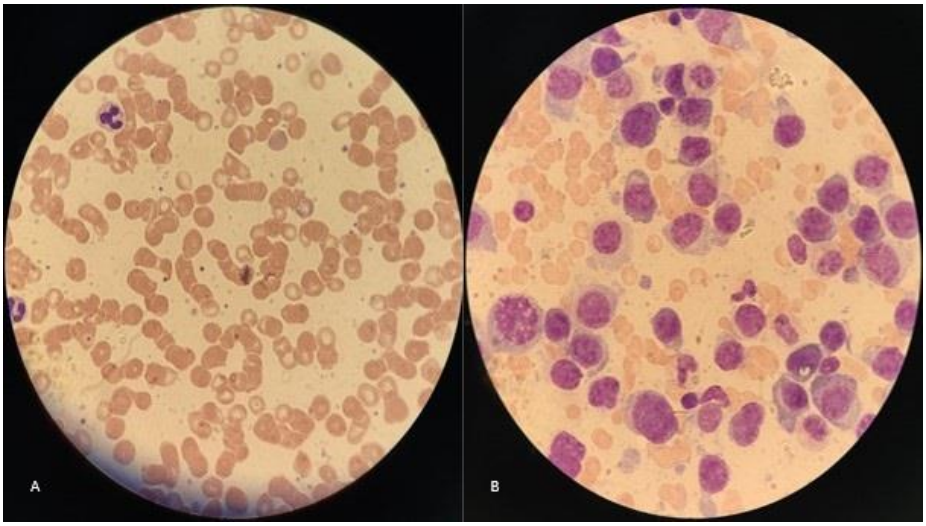

Figure 1. (A) Roll formation was observed in erythrocytes in peripheral blood smear, (B) Numerous big atypical pleomorphic cells with a high nucleocytoplasmic ratio, basophilic cytoplasm, and a central eccentric nucleus with an uneven nuclear border were seen in bone marrow aspiration.

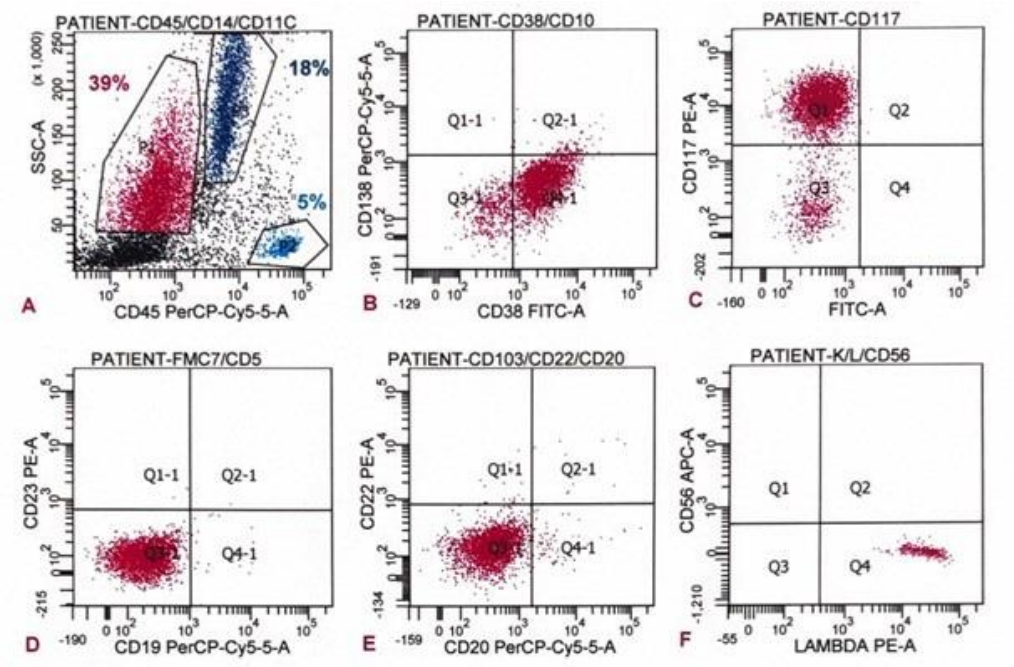

Figure 2. Flowcytometry showed (A) plasma cells account for 39%; were negative for CD45; (B) positive for CD38, negative for 138; (C) positive for CD117, (D) negative for CD19 and CD23; (E) negative for CD20 and CD22; (F) negative for CD56 and positive for lambda chain (FACS Canto, Becton Dickenson).

disease's aggressiveness and the significant anaplastic plasma cell infiltration of the bone marrow [3, 8]. Because of their unusual form, they might be difficult to diagnose. By morphology, they might seem like high-grade lymphoma or non-hematopoietic cancer. Anaplastic morphology can be detected in the early stages of myeloma or as the disease progresses. Infiltration of the extramedullary space is prevalent [9]. For the proper diagnosis, a combination of clinical symptoms, morphology, biochemical data, and immunophenotype are required. We reported a 66-year-old woman diagnosed with AMM in this case report. After further examination, multiple extramedullary infiltrates were detected in the patient. AM cells resemble "immunoblasts" at times, and

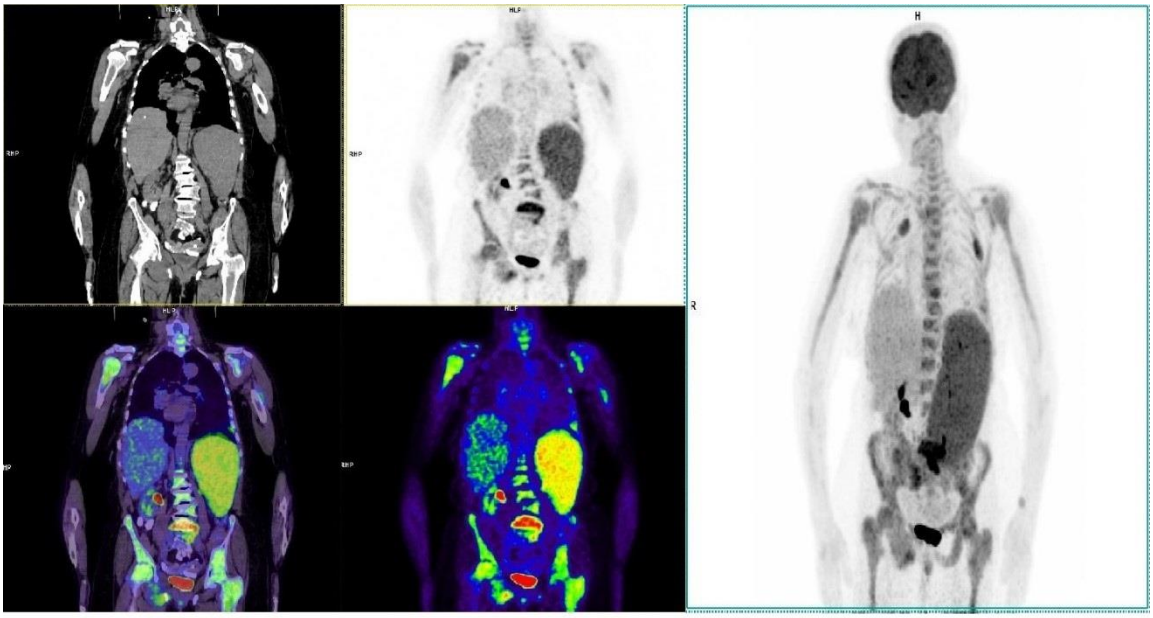

Figure 3. FDG uptake of tumor tissue in the skeletal system, spleen, bilateral pleura, and the lesion adjacent to L5 vertebra anterior in the coronal plane and MIP images observed in 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT)

they're frequently mistaken as other low-differentiated malignancies such as malignant melanoma, Burkitt lymphoma, and sarcoma. As a result, immunohistochemistry and flow-cytometry play a crucial role in differential diagnosis. AM cells typically express CD38, CD138, and MUM1 with little light chain expression, while lymphocyte markers CD20, CD19, and CD3 are absent [1]. This is in line with our findings. AM cells may also express CD56 and CD117 on their surface. Vinho Do et al. reported a case of AMM. In this case, flow cytometric analysis was positive in an expanded panel of CD138, CD56, and CD117 together with the kappa light chain. They reported that plasma cells account for 81.0% and those cells are negative for CD45, positive for CD138, negative for CD38, and positive for CD117 [10]. After this case report reported by Vinho Do et al. in the literature, flowcytometric analysis of the bone marrow showed CD117 positivity in our case.1q21 amplification [13], 17p (p53) deletion, t(4;14), and/or chromosomal 13 abnormalities are all prevalent [11]. Conventional chemotherapy and radiation are ineffective in the majority of AMM patients. As a result, combining stronger chemotherapies with new drugs may increase response. According to one case series, 66.7% of patients receiving VRD (Bortezomib, Lenalidomide, and Dexa-methasone) and VCD (Bortezomib, Cyclophosphamide, and Dexamethasone) conventional myeloma treatment regimens had an inadequate response. In two patients, VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) regimen was used along with VRD prior to hematopoietic stem cell transplantation consolidation and was able to achieve remission for over 2 years [3]. Immunotherapy, such as chimeric antigen receptor T cell immunotherapy, monoclonal antibodies, and potentially hematopoietic stem cell transplantation, may offer these patients fresh therapeutic hope [1]. We applied bortezomib (1.3 mg/m^2), lenalidomide (25 mg), and dexamethasone (40 mg) chemotherapeutic in this case we presented. In conclusion, the anaplastic morphology of MM

may pose a diagnostic challenge. The need for a multidisciplinary approach to detect hematological neoplasms is highlighted in this example. For AMM instances, prompt radiographic, flow cytometry, and histological examination may assist the diagnosis

REFERENCES

1. Huang J-X, Meng F-J, Feng X-Q, Lyu X, Wang X. Clinical and histopathological analyses of anaplastic myeloma. Chinese Medical Journal. 2020; 133(13): 1614-6.
2. Dimopoulos MA, Stewart AK, Masszi T, Špička I, Oriol A, Hájek R, et al. Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age: secondary analysis from the phase 3 ASPIRE study. British Journal of Haematology. 2017; 177(3): 404-13.
3. Wu J, Chu E, Chase CC, Choi T, Gasparetto C, Young K, et al. Anaplastic Multiple Myeloma: Case Series and Literature Review. Asploro Journal of Biomedical and Clinical Case Reports. 2022; 5(1): 1-11.
4. Jain BB, Majumdar A, Chowdhary KM. Plasmablastic lymphoma versus anaplastic myeloma in a human immunodeficiency virus negative male: a diagnostic quandary. Archives of Iranian Medicine. 2013; 16(10): 608-610.
5. Fujino M. The histopathology of myeloma in the bone marrow. Journal of Clinical and Experimental Hematopathology. 2018; 58(2): 61-7.
6. Elsabah H, Soliman DS, Ibrahim F, Al-Sabbagh A, Yassin M, Moustafa A, et al. Plasma cell myeloma with an aggressive clinical course and anaplastic morphology in a 22-year-old patient: a case report and review of literature. The American Journal of Case Reports. 2020; 21: e920489-1.
7. Sakthisankari S, Kumar PN, Syed T. Anaplastic multiple myeloma-a morphological challenge–A case series. Indian Journal of Medical and Paediatric Oncology. 2020; 41(03): 430-3.
8. Taccone FS, Bouko Y, Robin V. Exceptional association of diffuse anaplastic myeloma with microangiopathic anemia. European Journal of Internal Medicine. 2007; 18(8): 607.
9. Ichikawa S, Fukuhara N, Hatta S, Himuro M, Nasu K, Ono K, et al. Anaplastic multiple myeloma: possible limitations of conventional chemotherapy for long-term remission. Journal of Clinical and Experimental Hematopathology. 2018; 58(1): 39-42.
10. Do ATV. CD38–Negative Anaplastic Plasma Cell Myeloma: A Rare Case Report. Cureus. 2022;14(1).
11. Sethi S, Miller I. Plasma cell myeloma with anaplastic transformation. Blood, 2016; 128(16): 2106.

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Doi: 10.5505/aot.2023.43925

Case Report

A Case of Diffuse Large B Cell Lymphoma with Unusual Extranodal Breast, Brain İnvolvement And Autoimmune Hemolytic Anemia: Clinical and Radiological Presentations

Ekstranodal Meme, Beyin Tutulumu ve Otoimmun Hemolitik Anemisi Olan Alışılmadık Bir Diffüz Büyük B Hücreli Lenfoma Olgusu: Klinik ve Radyolojik Prezentasyonlar

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ABSTRACT

Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all non-Hodgkin lymphomas. Extranodal breast involvement of DLBCL is very rare. We present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms. A 54-year-old female patient was admitted to the emergency department with complaints of weakness and palpitations. Hemolytic anemia was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There were an increased fluorodexiglucose uptake detected in the middle and upper quadrant of the left breast in positron emission to-mography–computed tomography. She had impaired consciousness, her speech was dysarth-ric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. Cranial magnetic resonance imaging revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient, and had an expansile feature that restricted the diffusion. In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infil-tration was observed. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings im-proved and regressed completely after one course of therapy. This patient makes a signifi-cant contribution to the literature in terms of referring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of autoim-mune hemolytic anemia etiology and treatment preference.

Keywords: Diffuse large B cell lymphoma, extranodal involvement, hemolytic anemia, prognosis

ÖZET

Diffüz büyük B hücreli lenfoma (DBBHL), tüm Hodgkin dışı lenfomaların %30-40'ını oluşturan büyük ve transforme B hücrelerinden oluşan heterojen bir tümör grubudur. DBBHL'nin ekstranodal meme tutulumu oldukça nadirdir. Coombs pozitif hemolitik anemi ve nörolojik semptomlarla başvuran, meme

First Received: 19.02.2023, Accepted: 13.04.2023 doi: 10.5505/aot.2023.14890

kaynaklı bir DBBHL olgusunu sunmaktayız. Elli dört yaşında kadın hasta acil servise halsizlik ve çarpıntı şikayetleri ile başvurdu. Periferik kan yaymasında atipik hücre görülmeyen hastada hemolitik anemi düşünüldü. Pozitron emisyon tomografi-bilgisayarlı tomografide sol meme orta ve üst kadranda florodeksiglikoz tutulumunda artış saptandı. Bilinci bozuk, konuşması dizartrik, oryantasyon kısıtlı, kas kuvveti ve duyu ise muayenesi doğaldı, patolojik refleksi yoktu. Kranial manyetik rezonans görüntülemede pons seviyesinde difüzyonu kısıtlayan ekspansil özellikte T2 ve FLAIR hiperintens lezyon saptandı. Meme ilişkili kitlenin tru-cut biyopsisinde CD20(+), PAX5(+), CD3(-), CD5(-) büyük B hücreli lenfoma infiltrasyonu görüldü. Bir kür R-CHOP ve MTX tedavisi sonrası hastanın transfüzyon ihtiyacı geriledi. Nörolojik semptomları ve radyolojik bulguları bir kür tedaviden sonra tamamen düzeldi. Bu hasta, nörolojik semptomlarla başvurması, otoimmun hemolitik anemi etiyolojisinin araştırılması sırasında meme ilişkili kitleden DBBHL tanısı alması ve tedavi tercihi açısından literatüre önemli bir katkı sağlamaktadır.

Anahtar Kelimeler: Diffüz büyük B hücreli lenfoma, ekstranodal tutulum, hemolitik anemi, prognoz

Introduction

Non-Hodgkin lymphoma (NHL) ranks first among all hematological malignancies. Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all NHL [1]. Its incidence increases with age, and the median age at diagnosis is 64 years old. It is more common in men and 55% of the patients are male [2, 3]. It can occur de novo or histologically transformed from indolent lymphomas. The disease typically pre-sents as a rapidly growing nodal or extranodal mass associated with systemic symptoms [4].

One of the most common extranodal involvement sites for DLBCL is central nervous system (CNS) involvement. Extra-nodal breast involvement of DLBCL is very rare. It accounts for 0.5% of all NHLs and 2% of extranodal lymphomas [5]. However, even if lymphoma is the most common hematological malignancy affecting the breast, it accounts for only about 0.04% to 0.7% of all breast cancer cases, and this rare involvement appears to be associated with very few lym-phoid tissues in the breast. It is often confused with breast-derived solid malignancies due to both clinical and imaging findings [6].

CNS involvement is seen in one third of NHL patients. Involvement can be considered as leptomeningeal, epidural and intra-parenchymal metastasis. CNS involvement of lymphomas may present in many different clinics. The most common neurological complication of NHL is leptomeningeal disease that develops due to lymphoma infiltration of the leptomeninges. It can manifest with different symptoms and signs such as headache, nausea, communicating hydrocephalus, cranial neuropathy (for example, hearing loss, imbalance, dizziness, dysphagia, and hoarseness), limb weakness, paresthesia and pain. On magnetic resonance imaging (MRI), focal and diffuse leptomeningeal contrast involvement, sub-arachnoid nodule or enlargement of the intradural filum terminale can be seen [7]. Primary CNS lymphomas mostly present with single and all paren-chymal lesions, systemic involvement is not expected due to the blood brain barrier; second-ary CNS lymphomas are mostly characterized by leptomeningeal involvement and multiple parenchymal lesions can be detected [8].

In autoimmune hemolytic anemia (AIHA), autoantibodies are produced in abnormal amounts as a result of hyperfunction of B lymphocytes and complement are absorbed by erythro-cytes. As a result, it is destroyed rapidly after antigen-antibody reaction. While there is no role of any disease in primary AIHA etiology, secondary AIHA causes include lymphoproliferative dis-eases, viruses

such as Ebstein-barr virus, measles or cytomegalovirus, leukemias, thymoma and colon cancers. The incidence of AIHA / NHL is extremely rare [9].

In this case presentation, we present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms.

Case Presentation

A 54-year-old female patient was admitted to the emergency department with complaints of weakness, shortness of breath and palpitations. In the systemic examination of the patient, whose medical history was unremarkable, her body temperature was 38.6 C, blood pressure 120/86 mmHg, heart rate 96 / min and respiratory rate was 16 / min. In her neurological exami-nation, she had impaired consciousness, her speech was dysarthric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. In the extended biochemical analysis of the patient, hemoglobin was 5.3 gr/dl, leukocyte: 5510/mm^3, neutrophil: 3710/mm^3, thrombo-cyte: 140,000 / mm^3, lactate dehydrogenase (LDH): 1588 IU / L, haptoglobulin: 1 mg / dl (normal range: 30-200 mg / dl), total bilirubin: 1.26 mg /dl, indirect bilirubin: 0.86 mg / dl, and corrected reticulocyte resulted in 5.9%. Direct and indirect coombs tests were resulted as positive; AIHA was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There was no focus for infec-tion that could cause fever, and there was no growth in the blood and urine cultures.

The antinuclear antibody test (ANA) and extractable nuclear antigen (ENA) profile (RNP, Sm, SS-A, SS-B, Scl-70, Jo-1, anti-histone, anti-nucleosome) for possible underlying collagen tissue and lympho-proliferative diseases were found to be negative. In thoracic and abdominal computed tomography (CT), the spleen as 137 mm in size, reactive lymphadenopathies in the paraaortic and bilateral inguinal areas, and thickening of the skin and subcutaneous areas in both breast tissues were detected. There were also an increased fluorodexiglucose (FDG) uptake detect-ed in the middle (sudmax: 7.8) and upper quadrant (sudmax: 8.4) of the left breast in positron emission tomography–computed tomography (PET / CT) (Figure 1), and 6 cm heterogeneous contrast enhancement evaluated as breast imaging reporting and data system (BI-RADS) 4A in breast magnetic resonance (MRI) (Figure 2).

A bone marrow biopsy was performed by investigating the etiology of anemia. As a result of biopsy, megakaryocytes without significant clustering and dysplasia were interpreted as hypercellular bone marrow with mild reticulin fiber increase and no blast increase.

Cranial MRI revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient (ADC), and had an expansile feature that restricted the diffusion (Figure 3.A). In addition, a non-contrast appearance was observed, consistent with leptomeningeal thickening (Figure 4.A). Glucose was 78 mg / dL and protein was 18 g/L in the CSF sampling performed on the patient, and no cells were observed in direct examination. CSF flow examination was normal.

In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infiltration was observed (Figure 5a. and 5b) In the second bone marrow biopsy performed for possible infiltration of lymphoma, large b-cell lymphoid infiltration in the interstitial pattern, showing strong CD20 and weak CD5 expression was also revealed (Figure 6). No cytogenetic or molecular features were revealed in the fluorescence in situ

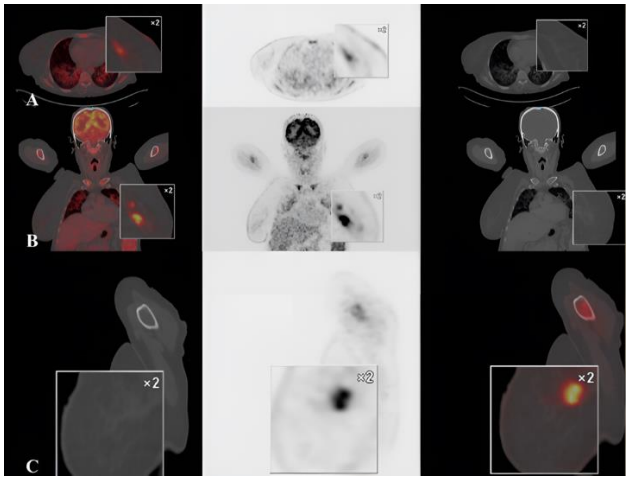

Figure 1.: Positron emission tomography–computed tomography (PET / CT) sections of patient: A. Axial (transverse), B. Coronal, C. Sagittal planes

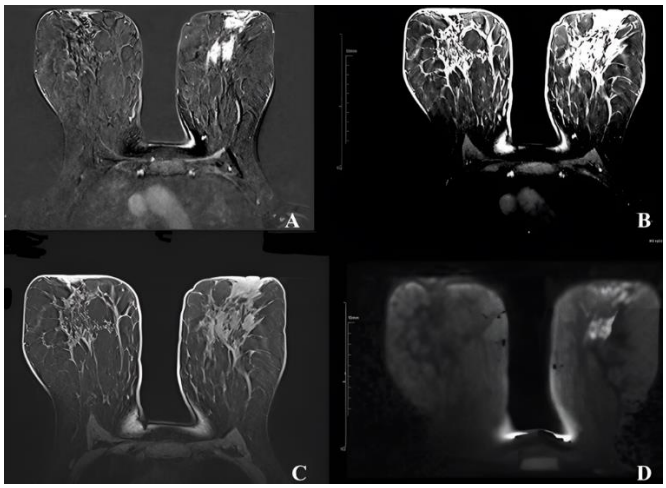

Figure 2.: Magnetic resonance (MRI) sections of breast associated mass: A. T1-weighted dynamic contrast-enhanced, B. Contrast-enhanced T1-weighted fat-suppressed subtraction, C. T1-weighted fat-saturated pre-contrast, D. Diffusion-weighted (DWI)

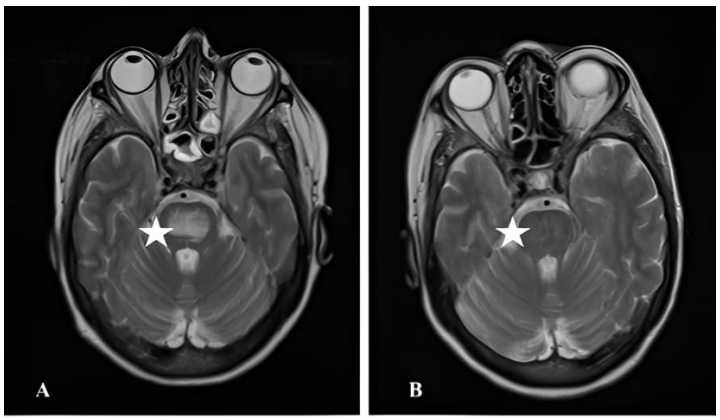

Figure 3: Hyperintense lesion on axial T2W MRI at pontin level. A.: Initial diagnosis, B.: After one course of therapy

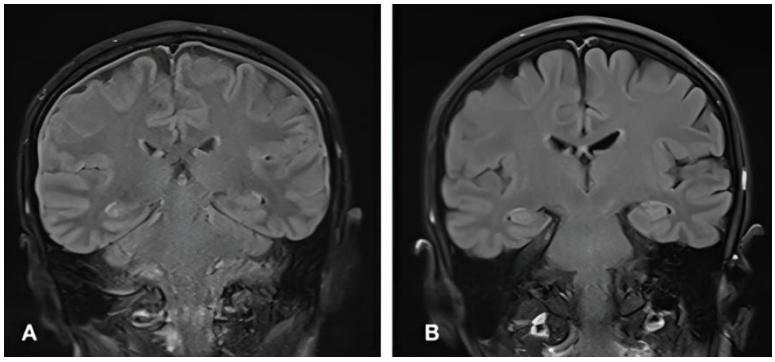

Figure 4: Leptomeningeal thickening on MRI. A.: Initial diagnosis, B.: After one course of therapy

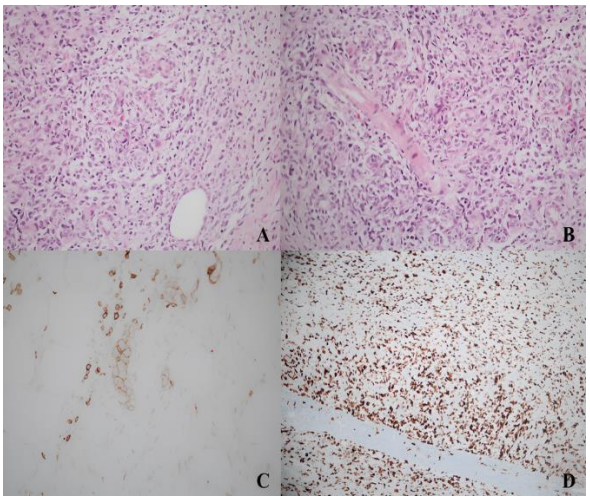

Figure 5a: Tru-cut biopsy sections of the breast associated mass: A. and B. Hematoxylin & eosin staining, C. CD-5 antibody staining, D. KI-67 staining

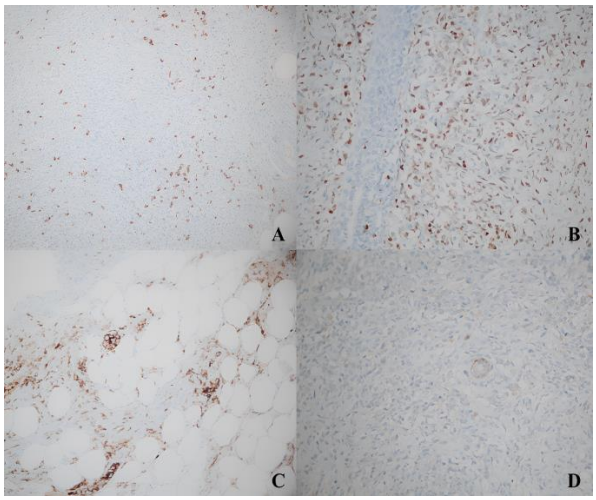

Figure 5b: Tru-cut biopsy sections of the breast associated mass: A. CD-3 staining, B. MUM-1 staining, C. CD-20 staining, D. CD-10 staining

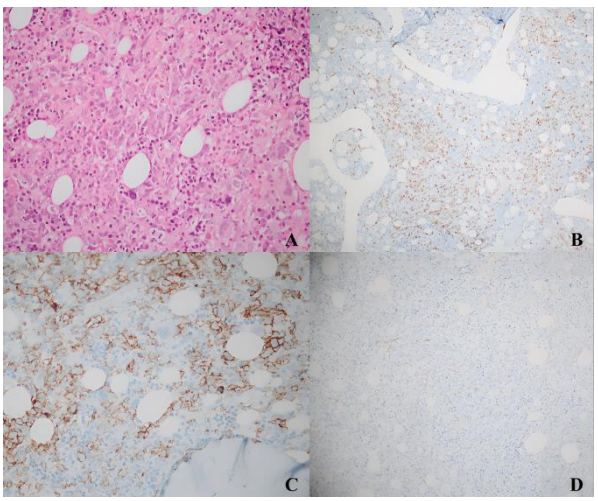

Figure 6: Bone marrow biopsy sections: A. Hematoxylin & eosin staining, B. MUM-1 staining, C. CD-20 staining, D. CD-34 staining

hybridization (FISH) analysis performed on both biopsy specimen and bone marrow samples.

Neurological clinical findings of the patient were considered as a result of neurological involvement of DLBCL. Methylprednisolone at a dose of 1 mg/kg was initiated due to hemolytic anemia and a treatment plan was made such as follows: Rituximab 375 mg/ m^2, cyclophosphamide 750 mg/m2, adriamycin 50 mg/m^2, vincristine 1,4 mg/m^2, prednisolone 100 mg (R-CHOP) every 21 days and on the 14th day, methotrexate (MTX) 3 gr/m^2, every 21 days. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings improved and regressed completely after one course of therapy (Figure 3.B., Figure 4.B.).

Discussion

Our case contributes significantly to the literature with its three features: AIHA, DLBCL diagnosed by a biopsy from breast associated mass, and CNS involvement associated or parane-oplastic neurological symptoms.

The incidence of AIHA and NHL is extremely rare. In a study by Ji-cheng Zhou et al., a total of 2204 NHL patients and 204 AIHA patients were screened between 2009 and 2018. AIHA and NHL association was observed in 20 of them. AIHA was detected in 0.91% of NHL patients, while NHL was detected in 9.8% of AIHA patients. Fourteen of the cases were male, 6 were fe-male and, the median age was 60 years old. All patients were stage 3-4 NHL. Lymphoma subtype with the highest incidence of AIHA was angioimmunoblastic t-cell lymphoma (AITL) with 7.31%, while marginal zone b-cell lymphoma was 6.25%, B cell lymphoma 4.25%, chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) 2.5% and mantle cell lymphoma 2.3% [9]. In another study, an AIHA serie was reported in patients diagnosed with splenic marginal zone lymphoma [10]. A total of 13 patients were complicated with AIHA in total and all patients died during follow-up. Patients with AIHA were found to have significantly ($p < 0.001$) shorter survival than those without AIHA [10]. In a study from 2000, a total of 16 patients with a diagnosis of NHL were found to be complicated with AIHA [11]. The treatment response for NHL was found to be significantly lower in this group, patients with NHL who did not develop AIHA had longer overall and median survival compared to the NHL/AIHA subgroup [11]. In another French multicenter retrospective cohort, all autoimmune manifestations were revealed in patients diagnosed with lymphoma and they were defined frequently together with CLL and DLBCL, while AIHA was the most common cause of autoimmune cytopenias [12]. The presence of autoimmune phenomena was associated with lower survival compared to non-autoimmune feature group when examining entire cohort. In general, it has been shown that the presence of AIHA or any autoimmune phe-nomenon has negative effects on treatment response and survival in patients diagnosed with lym-phoma. Although AIHA/ NHL coexisting is a rare condition, AIHA was detected as the first sign of the disease in our NHL patient.

Clinically, primary breast lymphomas manifest as painless palpable masses. Its distinction from other carcinomas is not clear radiologically. More than 95% of the primary breast lymphoma cases are B cell non hodgkin lymphomas, and 60% to 85% of them are DLBCL. Follicular lym-phoma, mucosa-associated lymphoma or marginal zone lymphoma are seen less common. Since these lymphomas are rare, there is no common approach to treatment. However, current treat-ments such as chemotherapy, immunotherapy and radiotherapy provide well designed disease con-trol in these patients. Average life

expectancy in 80% of the patients is 5 years [13].

It is difficult to differentiate breast lymphomas from benign and malignant breast diseases radiologically and clinically. However, differentiation of breast lymphomas from other malignan-cies (such as invasive breast cancer, inflammatory breast cancer or metastasis) is very important in terms of treatment preference. It is very important to know whether there is a systemic in-volvement. If the patient has systemic lymphoma, the risk of lymphoma involvement of breast increases.6 There was no finding in favor of systemic involvement in the different imaging results of our patient; the presence of only breast involvement was the most important clinical challenge.

Although DLBCL and neurological involvement has been widely reported, it is a difficult condition to diagnose. It often occurs as leptomeningeal involvement, intracranial and spinal me-tastasis, lymphomatosis cerebri and peripheral nervous system involvement causes different radi-ological appearances associated with these conditions.[7] Abe et al. evaluated cranial MRIs of 33 patients with intravascular DLBCL and found hyperintense lesions in the pons as the most com-mon finding (n = 19 (57.6%); leptomeningeal thickening was observed in 12.1% of cases [14]. Kawata et al. presented also a DLBCL case with central pontine myelinosis [15]. In our case, a lesion in pons and leptomeningeal thickening were observed together. However, flow cytometry and pathology of the patient's CSF sampling did not show any findings compatible with the DLBCL involvement. Also, sodium values measured in terms of central pontine myelinosis were normal during the clinical follow-up. High-dose systemic methotrexate ($3mg/m^2$) treatment was also administered, considering intracranial involvement, since it could not be differentiated in terms of etiology. Additionally, in our patient, the fact that a score that could objectively doc-ument the patient's neurological status before and after treatment was not recorded was an important limitation point.

As a result, our patient makes a significant contribution to the literature in terms of refer-ring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of AIHA etiology and treatment preference. Detailed screening of differ-ent organs and systems is of great importance in DLBCL cases where bone marrow biopsy is nor-mal and difficult to diagnose in the early period.

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REFERENCES

1. Iqbal J, Joshi S, Patel KN, Javed SI, Kucuk C, Aabida A, d'Amore F, Fu K. Clinical implication of genome-wide profiling in diffuse large B-cell lymphoma and other subtypes of B-cell lym-phoma. Indian J Cancer. 2007; 44(2): 72-86.

2. Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, Lipscomb J, Flowers CR. Ra-cial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the Unit-ed States. Cancer. 2011; 117(11): 2530-2540.

3. Morgan G, Vornanen M, Puitinen J, et al. Changing trends in the incidence of non-Hodgkin's lymphoma in Europe. Biomed Study Group. Ann Oncol. 1997; 8 Suppl 2: 49-54

4. Armitage JO. How I treat patients with diffuse large B-cell lymphoma. Blood. 2007; 110(1):29-36.

5. Candelaria M, Oñate-Ocaña LF, Corona-Herrera J, et al. Clinical characteristics of primary extranodal versus nodal diffuse large b-cell lymphoma: a retrospective cohort study in a cancer center. Rev Invest Clin. 2019; 71(5): 349-358.

6. Shim E, Song SE, Seo BK, Kim YS, Son GS. Lymphoma affecting the breast: a pictorial review of multimodal imaging findings. J Breast Cancer. 2013; 16(3): 254-265.

7. Mauermann ML. Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias. Continuum (Minneap Minn). 2017; 23(3): 669-690.
8. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. AJNR Am J Neuroradiol. 2011; 32(6): 984-92.
9. Zhou JC, Wu MQ, Peng ZM, Zhao WH, Bai ZJ. Clinical analysis of 20 patients with non-Hodgkin lymphoma and autoimmune hemolytic anemia: A retrospective study. Medicine (Balti-more). 2020; 99(7): 19015.
10. Fodor A, Molnar MZ, Krenacs L, Bagdi E, Csomor J, Matolcsy A, Demeter J. Autoimmune hemolytic anemia as a risk factor of poor outcome in patients with splenic marginal zone lymphoma. Pathol Oncol Res. 2009; 15(4): 597-603
11. Sallah S, Sigounas G, Vos P, Wan JY, Nguyen NP. Autoimmune hemolytic anemia in patients with non-Hodgkin's lymphoma: characteristics and significance. Ann Oncol. 2000; 11(12):1571-1577.
12. Jachiet V, Mekinian A, Carrat F, et al. French Network of systemic and immune disorders associated with hemopathies and cancer (MINHEMON). Autoimmune manifestations associated with lymphoma: characteristics and out-come in a multicenter retro-spective cohort study. Leuk Lymphoma. 2018; 59(6): 1399-1405.
13. Franco Pérez F, Lavernia J, Aguiar-Bujanda D, et al. Primary Breast Lymphoma: Analysis of 55 Cases of the Spanish Lymphoma Oncology Group. Clin Lymphoma Myeloma Leuk. 2017; 17(3): 186-191.
14. Abe Y, Narita K, Kobayashi H, et al. Clinical value of abnormal findings on brain magnetic resonance imaging in patients with intravascular large B-cell lymphoma. Ann Hematol. 2018; 97(12): 2345-2352.
15. Kawata E, Isa R, Yamaguchi J, et al. Diffuse large B-cell lymphoma presenting with central pontine myelinolysis: a case report. J Med Case Rep. 2015 Jun 5; 9: 131.

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Doi: 10.5505/aot.2023.14890

Original Article

The Prognostic Factors in Endometrial Cancers Treated with Radiotherapy: Retrospective Analysis

Radyoterapi Uygulanan Endometriyal Kanserlerinde Prognostik Faktörler: Retrospektif Analiz

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ABSTRACT

Introduction: Endometrial cancer is mostly diagnosed in the early stages and has a good prognosis. Surgery has main role in the treatment of patients with endometrial cancer and adjuvant radiotherapy (RT) is administered in certain risk groups. In this retrospective study, we analyzed the factors affecting the prognosis of patients with endometrial cancer who underwent RT.

Materials and methods: A total of 181 patients who were diagnosed with endometrial cancer were included in the study. Based on the prognostic factors, risk groups were recorded as low, intermediate, high-intermediate, high risk, and advanced/metastatic. Patients' overall survival (OS) was calculated using Kaplan– Meier method.

Results: Median age was 60 years (range, 28–82). The number of patients who received adjuvant RT alone, RT and chemotherapy, and chemotherapy alone were 77 (42.5%), 65 (36%), and 39 (21.5%), respectively. Median OS was 12.4 years (range, 0.1-21). Except for the advanced/metastatic risk group, OS was better in all the other risk groups who received RT alone ($p<0.001$).

Discussion: Risk groups (based on prognostic risk factors), p53, and treatment applied (RT alone) are the significant prognostic indicators for patients received adjuvant therapy in endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

Keywords: Chemotherapy, endometrial cancer, prognosis, radiotherapy

ÖZET

Giriş: Endometriyal kanser çoğunlukla erken evrelerde teşhis edilir ve iyi bir prognoza sahiptir. Endometriyal kanserli hastaların tedavisinde cerrahi tedavi temeldir ve belirli risk gruplarında adjuvan radyoterapi (RT) uygulanmaktadır. Bu retrospektif çalışmada, RT uygulanan endometriyal kanserli hastalada prognozu etkileyen faktörler inceledi.

Gereç ve yöntemler: Çalışmaya endometriyal kanser tanısı almış toplam 181 hasta dahil edildi. Prognostik faktörlere göre risk grupları düşük, orta, yüksek-orta, yüksek riskli ve ileri/metastatik olarak kaydedildi. Hastaların genel sağkalımı (GS), Kaplan-Meier yöntemi kullanılarak hesaplandı.

Bulgular: Ortanca yaş 60'tı (28-82). Tek başına adjuvan RT, RT ve kemoterapi ve tek başına kemoterapi alan hasta sayısı sırasıyla 77 (%42,5), 65 (%36) ve 39 (%21,5) idi. Ortanca GS 12.4 yıldı (0.1-21). İleri/metastatik risk grubu dışında diğer tüm risk gruplarında, tek başına RT alan hastalarda GS daha iyi bulundu ($p<0.001$).

Tartışma: Endometriyal kanserli hastalarda adjuvan tedavi alanlarda; risk grupları (prognostik risk faktörlerine göre), p53 ve uygulanan tedavi (yalnız RT) önemli prognostik göstergelerdir. RT'ye adjuvan kemoterapi eklenmesi prognozu olumsuz etkilemektedir.

Anahtar kelimeler: Endometriyal kanser, kemoterapi, prognoz, radyoterapi

First Received: 26.01.2023, Accepted: 17.03.2023 doi: 10.5505/aot.2023.02779

Introduction

Endometrial cancer is the most common gynecological cancer among women living in developed countries [1]. Most of the endometrial cancer patients are post-menopausal at the time of diagnosis, while the rate of disease in premenopausal period is only 25% [2]. Majority of the patients present with early-stage according to International Federation of Gynecology and Obstetrics (FIGO) at the time of diagnosis and survival time has been reported approximately 90% in these patients due to favorable prognosis [3]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) (including regional lymph node dissection or not) is the definitive management for early-stage endometrial cancer, but not for locally advanced or metastatic disease.

Numerous previous studies have identified the important prognostic factors in endometrial carcinoma. These are tumor stage, patient age, histological type, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. Additionally, prognostic effects of p53 and ki67 on endometrial cancer have been shown by certain studies, however, it has not been established clear enough yet. [6,7]. Risk groups that have different prognoses have been identified based on the prognostic factors and adjuvant management is set according to this classification [4,5,8].

Adjuvant management of endometrial cancer includes radiotherapy (RT), chemotherapy and/or hormonal therapy in patients who have certain risk factors [9]. RT plays a significant role in the treatment of endometrial cancer and commonly administered in postoperative setting; however, definitive RT may be considered for patients who are medically inoperable or in case of local recurrence. Treatment decision with adjuvant RT is related to certain risk factors, such as higher tumor grade, deep myometrium invasion, and lymphovascular invasion [9]. In this retrospective study, we analyzed the risk factors affecting the prognosis of patients with endometrial cancer who received adjuvant therapy.

Patients and Methods

A total of 203 patients who were diagnosed with endometrial cancer and referred to the Department of Radiation Oncology between January 2010 and January 2020 were included in the retrospective study. Twenty-one patients were excluded from the study because of unavailable medical records. The study was approved by the local ethics committee (Date: 15.11.2022, Decision Number: 2022/289502) and conducted by principles of the Helsinki Declaration 2013.

Surgical procedure was TAH+BSO with or without pelvic and paraaortic lymph-adenectomy. Histopathology of the tumor, FIGO stage (2009), lymph node status, depth of myometrial invasion, tumor grade, lymphovascular invasion and metastatic sites were recorded. Risk groups according to these prognostic factors were recorded as in Table 1[8].

Percentage of cells presenting with positive nuclear staining was expressed as ki67 and p53 scores. Ki67 positivity was defined as positive ki67 staining in >40% of tumor cells and p53 positivity was defined as positive p53 staining in >25% of tumor cells [10].

Number of patients treated with adjuvant and definitive RT were 77 (42.5%) and three (1.7%), respectively. Consecutive chemo-therapy was administered to 36% (n=65) of the patients who received adjuvant RT. Simultaneous chemoradiotherapy was administered to one patient. Thirty-nine patients (21.5%) received chemotherapy alone. Radiation fields en-compassed tumor bed and regional nodes with a treatment dose of 45-50.4 Gy in adjuvant setting. Total dose was 70-75 Gy with brachytherapy in patients who underwent definitive treatment.

Table 1 Risk groups of endometrial carcinoma

Risk group	ESMO-ESGO-ESTRO consensus
Low risk	Endometrioid endometrial cancer, grade 1–2, <50% myometrial invasion, without lymphovascular space invasion
Low- intermediate risk	Endometrioid endometrial cancer, grade 1–2, ≥50% myometrial invasion, without lymphovascular space invasion
High- intermediate risk	Endometrioid endometrial cancer, grade 3, <50% myometrial invasion, any lymphovascular space invasion Endometrioid endometrial cancer, grade 1–2, with unequivocally lymphovascular space invasion, any myometrial invasion
High risk	Endometrioid endometrial cancer, grade 3, ≥50% myometrial invasion, any lymphovascular space invasion Stage II–III endometrioid endometrial cancer, no residual disease Stage I-III non-endometrioid endometrial cancer (serous, clear cell, or undifferentiated carcinosarcoma)
Advanced/metastatic	Stage III with residual disease and, stage IVa Stage IVb

ESGO, European Society of Gynecological Oncology
ESMO, European Society for Medical Oncology
ESTRO, European Society for Radiation Oncology

Overall survival (OS) was defined as the period (years) from the time of the patient's diagnosis until the last visit or death.

Statistical analysis

Statistical analyses were done using SPSS (Statistical Package for Social Sciences) for Windows 23.0 IBM SPSS Statistics, New York, USA). P value less than 0.05 was defined statistically significant. Data measurements were represented by the mean, median and range. Categorical data were expressed as frequency and percentage, and chi-square test was used for comparison between groups. Patients' OS was determined using Kaplan– Meier method. Multivariate Cox regression model was used to determine the independent prognostic predictors of survival with the variables which were statistically significant by univariate Cox regression model.

Results

Median age was 60 years (range, 28–82). The predominant histologic subtype was endometrioid adenocarcinoma in 69.1% of the patients. Median tumor size was 4.5 cm (range, 0.3-16). Lymphovascular invasion was detected in 39.2% of the patients and hormone receptor was positive in 64.6%. Most of the patients were with high risk disease (42.5%). p53 and Ki67 positivity were 32.5% and 67.8%, respectively. The clinico-pathologic characteristics of the patients receiving adjuvant therapy are shown in Table 2.

Advanced age (over 70 years) was associated with deep myometrial invasion (17.9% vs. 6.8%), advanced stage (42.9% vs. 18%), and higher rates of grade 2 and 3 tumors (78.4% vs. 57.3%) ($p<0.04$).

Non-endometrioid histology was associated with deep myometrial invasion (48.1% vs. 31.1%), advanced stage (42.6% vs. 12.9%), grade 3 tumor (50% vs. 25.6%), p53 positivity (53.3% vs. 7.9%), and hormone receptor negativity (29.3% vs. 2.2%) ($p<0.04$).

In addition, deep myometrial invasion was associated with lymph node involvement (29.1% vs. 9.4%), lymphovascular space invasion (55.6% vs. 26.5%), advanced stage (65.7% vs. 31.4%) and grade 3 tumor (40.5% vs. 16.7%) ($p<0.03$).

Table 2 The clinicopathologic characteristics of the patients

Characteristic	All patient % (n)	RT alone % (n)	CT+RT % (n)	CT alone % (n)
Histologic type				
Endometroid	69.1 (125)	55.2 (69)	31.2 (39)	13.6 (17)
Papillary serous	10 (18)	5.6 (1)	55.6 (10)	38.9 (7)
Carcinosarcoma	6.6 (12)	16.7 (2)	25 (3)	58.3 (7)
ESS	6.6 (12)	16.7 (2)	41.7 (5)	41.7 (5)
Other types	7.7 (14)	21.4 (3)	57.1 (8)	21.4 (3)
T stage				
T1a	19.9 (36)	52.8 (19)	30.6 (11)	16.7 (6)
T1b	38.7 (70)	51.4 (36)	35.7 (25)	12.9 (9)
T2	22.1 (40)	50 (20)	42.5 (17)	7.5 (3)
T3	7.7 (14)	14.3 (2)	50 (7)	35.7 (5)
T4	8.8 (16)	-	25 (4)	75 (12)
Unknown	2.8 (5)			
FIGO stage				
I	56.4 (102)	54.9 (56)	34.3 (35)	10.8 (11)
II	20.4 (37)	48.6 (18)	43.2 (16)	8.1 (3)
III	9.4 (17)	17.6 (3)	47.1 (8)	35.3 (6)
IV	12.2 (22)	-	27.3 (6)	72.7 (16)
Unknown	1.7 (3)			
Tumor grade				
I	11 (20)	55 (11)	35 (7)	10 (2)
II	44.8 (81)	56.8 (46)	33.3 (27)	9.9 (8)
III	23.2 (42)	33.3 (14)	40.5 (17)	26.2 (11)
Unknown	21 (38)			
LVI				
Positive	39.2 (71)	38 (27)	43.7 (31)	18.3 (13)
Negative	47.5 (86)	50 (43)	31.4 (27)	18.6 (16)
Unknown	13.3 (24)			
LN metastasis				
Positive	22.1 (40)	2.5 (1)	65 (26)	32.5 (13)
Negative	60.2 (109)	56.9 (62)	26.6 (29)	16.5 (18)
Unknown	17.7 (32)			
Risk categories				
Low	11 (20)	65 (13)	25 (5)	10 (2)
Low-intermediate	13.8 (25)	68 (17)	20 (5)	12 (3)
High-intermediate	19.3 (35)	42.9 (15)	51.4 (18)	5.7 (2)
High	42.5 (77)	41.6 (32)	39 (30)	19.5 (15)
Advanced/metastatic	12.2 (22)	-	31.8 (7)	68.2 (15)

ESS, Endometrial stromal sarcoma; *LN*, Lymph node; *LVI,* Lymph-vascular invasion; *CT*, Chemotherapy; *RT*, Radiotherapy

Ki67 positivity was correlated with advanced stage, grade 3 tumor, hormone receptor negativity, lymph node involvement, and paraaortic metastasis ($p<0.04$), and p53 positivity was correlated with non-endometroid histology, hormone receptor negativity, and advanced stage ($p<0.02$).

Locoregional recurrence and/or distant metastasis occurred in 50 patients (27.6%). Lymphatic recurrences were seen in abdominal paraaortic, pelvic and mediastinal nodal regions in 12 (6.6%), 6 (3.3%) and seven patients (3.9%), respectively. Vaginal recurrence was seen in only three patients (1.7%).

Median OS was 12.4 years (range, 0.1-21), and 5- and 10-year survival rates were 70.5% and 56.8%, respectively. Patients with high and advanced/metastatic risk had shorter OS (Figure 1). Except for the advanced/metastatic risk group, survival was better in the all of the other risk groups who received RT alone (Table 3).

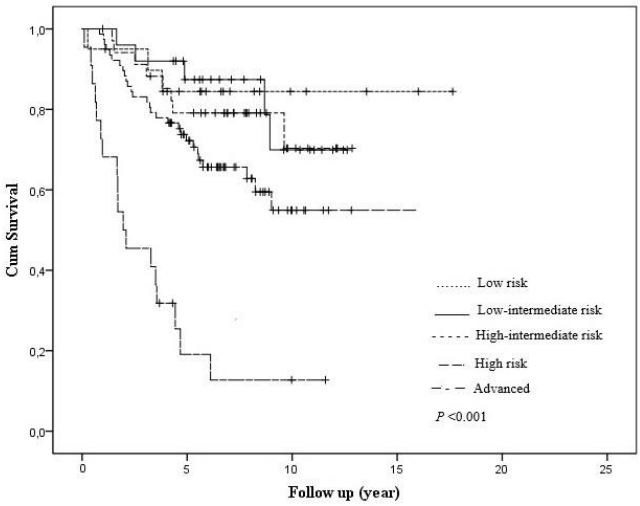

Figure 1. Overall survival by risk groups

Table 3. Median for Survival Time

				95% CI		
Risk group	Treatment	Time (year)	SE	Lower	Upper	*P value*
LIR	RT alone	16.5	1.5	13.3	19.8	0.004*
	RT-CT	9.5	1.7	6.1	12.5	
	CT	6.4	2.5	1.2	11.3	
HIR	RT alone	11.8	0.7	10.6	13.6	0.041*
	RT-CT	7.2	0.8	5.8	9.2	
	CT	5.6	1.3	3.4	7.8	
High risk	RT alone	12.5	0.4	10.8	13.2	0.042*
	RT-CT	6.7	0.7	5.7	8.4	
	CT	6.2	1.3	11.2	8.6	
Advanced	RT-CT	5	1.5	2	7.8	0.26
	CT	2.8	0.9	1.3	4.1	

HIR, High-intermediate risk; LIR, Low-intermediate risk; CT, Chemotherapy; RT, Radiotherapy; CI, Confidence interval; SE, Standard error
* P<0.05 was regarded statistically significant

Table 4 Cox regression analysis for prognosis

	Univariate			Multivariate		
Variable	HR	95%CI	P value	HR	95%CI	P Value
LNI (Yes vs No)	2.87	1.6-5.02	<0.001	0.77	0.39-1.49	0.44
Stage	1.97	1.6-2.4	<0.001	2.84	1.21-6.64	0.02*
PAND (Yes vs No)	2.14	1.25-3.65	0.006	0.54	0.12-2.49	0.43
PANM (Yes vs No)	2.6	1.3-5.2	0.007	1.07	0.20-5.70	0.94
Tumor size (≤4 cm vs >4 cm)	1.99	2.08-3.7	0.03	1.35	0.35-5.26	0.67
Age (≤70 vs >70)	1.05	1.02-1.08	0.04	0.65	0.10-4.25	0.66
P53 (≤25% vs >25%)	1.02	1.01-1.03	<0.001	0.16	0.05-0.53	0.003*
Ki67 (≤40% vs >40%)	3.18	1.44-7.02	0.004	0.41	0.08-1.95	0.26
Histology	1.3	1.12-1.5	0.001	0.84	0.44-1.62	0.60
Treatment	3.07	2.2-4.26	<0.001	4.39	1.65-11.70	0.003*
Risk groups	1.99	1.48-2.68	<0.001	0.29	0.11-0.79	0.02*

CI: Confidence interval; *HR*: Hazard Ratio; LNI, Lymph node involvement; PAND, Paraaortic node dissection; PANM, Paraaortic node metastasis
* *P<0.05* was regarded statistically significant

Prognosis was not found associated with lymphovascular space invasion (p= 0.08), extra-nodal spread (p= 0.6), and tumor grade (p= 0.2) by the univariate analysis. In the multivariate analysis, p53 (p= 0.003), tumor stage (p = 0.002), risk groups (p=0.02) and the treatment administered (adjuvant RT alone) (p<0.001) were significantly associated with prognosis. The results of univariate and multivariate analyses for prognosis are shown in Table 4.

Discussion

Endometrial cancer is predominantly diagnosed at earlier stages and has a good prognosis. Only 15–20% of the patients with endometrial cancer present with high-risk disease/distant metastases and poor prognosis. Surgery is the cornerstone of the endometrial cancer treatment and consists of TAH+BSO with or without pelvic and paraaortic lymphadenectomy [11]. Major factors affecting the prognosis of endometrial cancer have been established by previous studies and defined as age, tumor stage, histolopathology, tumor grade, deep myometrial invasion, and lymphovascular invasion [4,5]. After surgery, indications for adjuvant treatment are commonly related to these clinicopathological risk factors. In this study, factors affecting the prognosis of endometrial cancer were analyzed in patients received adjuvant therapy and it was found that tumor stage, and treatment applied (RT alone) were associated with prognosis in multivariate analysis.

Importance of RT in the adjuvant management of endometrial cancer was established by multiple studies. Recent studies have been concentrated upon the high-intermediate and high-risk diseases, whereas the adjuvant treatment in low-risk endometrial cancer is not indicated [8]. In our study, patients with high and high-intermediate risk diseases who received RT alone had a better prognosis than the patients who received chemotherapy with RT or chemotherapy alone. Addition of chemotherapy to RT also affected survival negatively in other risk groups except for the advanced/metastatic risk group.

The correlation between advanced age and poor prognosis is well established. The adverse impact of advanced age on worse progress of the disease is often explained by frequency of aggressive histology and advanced disease at diagnosis. Treatment with less aggressive regimens are another reason of the shorter survival in elderly patients [12]. In the present study, advanced stage, non-endometrioid histology and grade 2, 3 tumors were more frequent in patients over 70 years of age.

According to the FIGO annual report, serous and clear cell histologic types present with more advanced stages which explains the poorer survival in patients with non-endometrioid histology [13]. In our study, non-endometrioid histology was associated with higher rates of deep myometrial invasion and advanced stage resulting in shorter survival.

Myometrial invasion more than the half of the myometrial wall is defined as deep myometrial invasion which increases the risk of relapse and results in worse outcome [14]. In the present study, deep myometrial invasion was associated with non-endometrial types, advanced stage, lymphovascular invasion and higher grade. As a result, deep myometrial invasion and/or advanced stage were associated with poor survival.

Lymph node involvement has a potent impact on the outcome of the endometrial cancer which decreases the 5- year disease-free survival time to 65% to 70% alone. Presence of pelvic nodal metastases is an important indicator for the involvement of paraaortic nodes which decreases the 5-year disease-free survival rates to 30% [15]. In our study, whole patients with involved paraaortic nodes had

also involvement in pelvic nodes. However, prognosis was similar in patients who had only pelvic or pelvic plus paraaortic nodal involvements.

Increased ki67 or p53 expression in endometrial cancer was associated with more aggressive clinicopathological features and these markers were reported as indicators of poor prognosis [6,7]. In the present study, both markers were also associated with negative prognostic factors.

Prognosis of endometrial cancer is mainly affected by tumor grade which has a strong correlation with depth of myometrial invasion and metastasis to the lymph nodes. Grade 3 tumor for all stages has been reported to be an independent factor in predicting poor survival in the FIGO annual report [13]. Lympho-vascular invasion is also an important prognostic factor and indicates pelvic recurrence and distant metastasis which results in poor survival [16]. However, in our study, lymphovascular invasion and tumor grade was not associated with prognosis.

In univariate analysis, age, stage, histology, ki67, p53, pelvic or paraaortic nodal involvement, paraaortic lymphadenectomy, adjuvant RT alone, and risk groups were statistically associated with prognosis, however, only p53, stage, risk groups, and adjuvant RT alone were found statistically significant in multivariate analysis. Other prognostic factors, lymphovascular invasion and tumor grade, were not significantly associated with prognosis.

Conclusion

Tumor stage, p53, risk groups (based on prognostic risk factors), and RT alone are the most important prognostic indicators for patients received adjuvant therapy in the postoperative setting of endometrial cancer. Adding adjuvant chemotherapy to RT adversely affects the prognosis.

REFERENCES

1. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002; 97(1): 72-81.
2. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol. 1984; 64(3): 417-20.
3. Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. Gynecol Oncol. 1990; 38(1): 99-104.
4. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000; 355(9213): 1404-11.
5. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004; 92(3): 744-51.
6. Lundgren C, Auer G, Frankendal B, Moberger B, Nilsson B, Nordstrom B. Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. Int J Gynecol Cancer. 2002; 12(1): 110-8.
7. Coronado PJ, Vidart JA, Lopez-asenjo JA, et al. P53 overexpression predicts endometrial carcinoma recurrence better than HER-2/neu overexpression. Eur J Obstet Gynecol Reprod Biol. 2001; 98(1): 103-8
8. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016; 26(1): 2-30.
9. Lybeert ML, van Putten WL, Brolmann HA, Coebergh JW. Postoperative radiotherapy for endometrial carcinoma. Stage I. Wide variation in referral patterns but no effect on long-term survival in a retrospective study in the southeast Netherlands. Eur J Cancer. 1998; 34(4): 586-90.
10. Ferrandina G, Ranelletti FO, Gallotta V, et al. Expression of cyclooxygenase-2 (COX-2), receptors for estrogen (ER), and progesterone (PR), p53, ki67, and neu

protein in endometrial cancer. Gynecol Oncol. 2005; 98(3): 383-9.
11. van den Heerik A, Horeweg N, de Boer SM, Bosse T, Creutzberg CL. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. Int J Gynecol Cancer. 2021; 31(4): 594-604.
12. Bishop EA, Java JJ, Moore KN, Walker JL. Pathologic and Treatment Outcomes Among a Geriatric Population of Endometrial Cancer Patients: An NRG Oncology/Gynecologic Oncology Group Ancillary Data Analysis of LAP2. Int J Gynecol Cancer. 2017;27(4):730-7.
13. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006; 95 Suppl 1: S105-43.
14. Carien LC, Gini FF. Endometrial cancer. In: Joel ET, Robert LF, Jeff MM, editors. Gunderson & Tepper's Clinical Radiation Oncology. 5th ed. Philadelphia: Elsevier; 2021. p. 1213-1242.
15. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991; 40(1): 55-65.
16. Bosse T, Peters EE, Creutzberg CL, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015; 51(13): 1742-50.

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Doi: 10.5505/aot.2023.02779

Original Article

Investigation of the Effect of Adjuvant Endocrine Treatment on Depression, Sleep Quality and Sexual Function in Hormone Receptor-Positive Early-Stage Breast Cancer

Hormon Reseptör Pozitif Erken Evre Meme Kanserinde Adjuvan Hormonal Tedavinin Depresyon, Uyku Kalitesi ve Cinsel Fonksiyon Üzerine Etkinliğinin Araştırılması

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ABSTRACT

Aim: Questioning and recognizing depression, sleep and sexual dysfunctions in breast cancer patients improves the patients' quality of life. We aimed to evaluate the effects of adjuvant endocrine treatment and other variables on depression, sleep quality and sexual dysfunction in patients with early-stage breast cancer.

Materials and Methods: Our study was performed with the participation of 105 patients who were diagnosed with hormone receptor positive, early stage (stage I-III) breast cancer and at least 3 months followed by the medical oncology outpatient clinic. Sociodemographic form, Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI) and Female Sexual Function Index (FSFI) were used as data collection tools.

Results: According to the results obtained in our study, 55.8% patients had depression, 60.6% patients had poor sleep quality, 77.1% had poor sexual function. A tendency to sexual dysfunction was observed in patients with PR positivity and it was found to be statistically significant (P=0.005). There was a strong ($p<0.001$) correlation between the PSQI and BDI values of the patients. There was no significant relationship between different endocrine therapy agents (tamoxifen/anastrozole/letrozole) in patients with depression, sleep and sexual dysfunction ($p> 0.05$).

Conclusion: In our study, we found a tendency to depression, sleep disturbance, and sexual dysfunction in most patients. It was found that sleep disorders and sexual dysfunction increased in patients with depression. It was also statistically significant that hormone receptor status could affect sexual function. Therefore, symptoms related to depression, sleep and sexual problems should be questioned in patients followed up with a diagnosis of breast cancer.

Key Words: Breast cancer, endocrine treatment, BDI, PSQI, FSFI

ÖZET

Giriş ve Amaç: Meme kanseri hastalarında depresyon, uyku ve cinsel işlev bozukluklarını sorgulamak ve tanımak hastaların yaşam kalitesini iyileştirmektedir. Erken evre meme kanserli hastalarda adjuvan endokrin tedavisi ve diğer değişkenlerin depresyon, uyku kalitesi ve cinsel işlev bozukluğu üzerine etkilerini değerlendirmeyi amaçladık.

Yöntem ve Gereçler: Çalışmamız, hormon reseptörü pozitif, erken evre (evre I-III) meme kanseri tanısı almış ve medikal onkoloji polikliniğinde en az 3 ay takip edilen 105 hastanın katılımıyla gerçekleştirildi. Veri toplama aracı olarak sosyodemografik form, Beck Depresyon Envanteri (BDI), Pittsburgh Uyku Kalitesi İndeksi (PSQI) ve Kadın Cinsel İşlev İndeksi (FSFI) kullanıldı.

First Received: 28.11.2022, Accepted: 02.05.2023 doi: 10.5505/aot.2023.24654

Bulgular: Çalışmamızda elde ettiğimiz sonuçlara göre hastaların %55.8'inde depresyon, %60,6'sında kötü uyku kalitesi, %77.1'inde cinsel işlev bozukluğu saptandı. PR pozitif olan hastalarda cinsel işlev bozukluğuna eğilim gözlendi ve istatistiksel olarak anlamlı bulundu (P=0,005). Hastaların PUKİ ve BDI değerleri arasında güçlü (p<0,001) bir korelasyon vardı. Depresyon, uyku ve cinsel işlev bozukluğu olan hastalarda farklı endokrin tedavi ajanları (tamoksifen/anastrozol/letrozol) arasında ise anlamlı bir ilişki yoktu (p> 0.05).
Tartışma ve Sonuç: Çalışmamızda çoğu hastada depresyon, uyku bozukluğu ve cinsel işlev bozukluğuna eğilim saptadık. Bazı sosyodemografik özelliklerin ve hormon reseptör durumunun cinsel işlevselliği etkileyebileceği ortaya çıktı. Bu nedenle meme kanseri tanısı ile takip edilen hastalarda bu belirtilerin sorgulanması ve değerlendirilmesi önemlidir.

Anahtar Kelimeler: meme kanseri, hormonoterapi, depresyon, uyku, cinsel fonksiyon

Introduction

Breast cancer is the most common type of cancer in women, and it is a disease that has heterogeneous features both biologically and clinically [1].

From the moment of the diagnosis of breast cancer, it creates a crisis that affects the patient's life in different aspects such as physical, psychological, spiritual, and social. In this crisis, some reactions are common in every patient, regardless of age, ethnicity, and stage of the disease [2].

Adjuvant endocrine treatment reduces recurrence and increases survival rates in receptor-positive tumors [3]. However, endocrine treatments (eg ovarian suppression, SERMs such as tamoxifen) reduce estrogen levels and can modulate the central nervous system by their estrogen antagonist actions, which can inhibit serotonergic mechanisms in the brain, causing mood and sleep disturbances [4, 5]

Also, side effects of tamoxifen are known as hot flashes, vaginal dryness, cataracts, thromboembolism, and increased risk of endometrial cancer [6]. These side effects may also reduce the patient's interest and desire for sexual life.

Sexual problems observed in women with breast cancer may be the result of anxiety and depression experienced when diagnosed with cancer, as well as side effects of surgery, chemotherapy, radiotherapy, and endocrine treatment [7].

Depression and anxiety are very common in breast cancer patients, which could reduce adherence to the treatment, and is associated with significant functional impairment and increased risk of mortality [8]. Despite all these harms and high frequency; depression, insomnia, and sexual problems that occur in patients can be ignored by both healthcare professionals and researchers. In this context, emphasizing the importance of the follow-up and treatment of depression, sleep and sexual dysfunctions in early-stage breast cancer patients receiving endocrine treatment can improve the quality of life of patients by struggling against the poor quality of life.

Therefore, in this study, we aimed to evaluate the effects of adjuvant endocrine treatment and other variables on depression, sleep quality, and sexual dysfunction in patients with early-stage breast cancer.

Materials and Methods

Our study is conducted between September 2018 and March 2020 with the participation of 105 patients who were diagnosed with hormone receptor-positive early-stage (stage I-III) breast cancer who were receiving endocrine treatment for at least 3 months and still receiving in the department of oncology of our hospital.

The inclusion criteria of the study are being 18 years of age and older, being diagnosed with stage I-III breast cancer according to the TNM Staging System, having received endocrine treatment for at least 3 months, volunteering to participate in the study. Patients were selected regardless of their previous chemotherapy or radiotherapy history, and patients with distant organ metastasis were not included in the study.

This study is a cross-sectional study conducted to detect depression, sleep quality, and sexual dysfunction in women with breast cancer who are receiving endocrine treatment. The questionnaires were administered in a single interview by interviewing the patients one-on-one and taking verbal consent from the patient, paying attention to the principle of voluntary participation. Cancer type and stage, chemotherapy, radiotherapy information is obtained from the patient file.

Potential study participants were approached at the oncology outpatient clinic. The heads and interns of clinics of oncology were informed about the study by one of the researchers. In this way, the interns became able to answer questions if the participants would ask. The investigators explained the purpose of the study to patients who met the inclusion criteria, and face to face questionnaire was administered after obtaining the consent of the patients. They were assured of their anonymity and of confidentially, and they were told that they could drop out at any time. The subjects were administered three questionnaires that look around 20 to 30 min to complete. The data collected from patients and questionnaire forms were preserved in the research folder in the paper. Sociodemographic form, Beck Depression Inventory, Pittsburgh Sleep Quality Index (PSQI), and Female Sexual Function Index (FSFI) were used as data collection methods. The study was approved by the institutional ethics committee. All procedures performed under the national research committee's ethical standarts and Helsinki declaration updated in 2013.

Methods of Assessment

Beck Depression Inventory (BDI)

The main version of the scale was prepared by Beck et al. [9]. In this study, the 1978 version of the Beck form adapted by Hisli was used [10].

There are 21 questions with four options for each in the Beck Depression Inventory form. The patient is asked to select and mark the sentence that best describes how the person felt in the last week, including the day of the questionnaire, and each item gets a score between 0 and 3. The highest score that can be obtained on the scale is 63. In this study revise Beck depression inventory was used. According to the Beck Depression Inventory (BDI-II) scoring system, 0–13 points indicate minimal depression, 14-19 points indicate mild depression, 20-28 points indicate moderate depression and 29-63 indicate severe depression [9].

Pittsburgh Sleep Quality Index (PSQI)

PSQI is a self-report measure that evaluates sleep quality and disorder over one month period. According to the Pittsburgh Sleep Quality Index (PSQI), a global PSQI score ≤5 indicates ''good sleep quality'', and >5 indicates ''poor sleep quality''. PSQI, which is an effective tool used to measure sleep quality in cancer patients, was developed by Buysse et al. in 1989. Reliability and validity studies in our country were performed by Ağargün et al. (1996) [11].

Female Sexual Function Index (FSFI)

Female Sexual Function Index is a Likert-type scale consisting of 19 items developed by Rosen et al. to evaluate female sexual functions. The scale was created by the researchers who developed the sexual functions of women in the last month, 6 subgroup scores, and FSFI score calculation scale, and it is made according to a scoring index [12]. The Turkish validity and reliability analysis of the scale were conducted by Öksüz and Malhan (2005). In the study performed by Taş et al. in 2006 in Turkey the functional status; If FSFI score is >30, it is stated as good, if between 23-29 it is stated as medium, if <23 it is stated as bad [13]. (Table 1)

Statistical methods

IBM SPSS (Statistical Programme for Social Scientists) version 20.0 (IBM Corp., Armonk, Newyork, USA) program was used for the statistical analysis of the study. The Kolmogorov Smirnov test was used to evaluate the compatibility of the data for normal distribution. Continuous data matching to normal distribution were given as

Table 1. Female Sexual Function Index scoring chart [14].

FSFI domain	Questions	Score range	Factor number	Minimum score	Maximum score	Total score
Desire	1,2	1-5	0.6	1.2	6.0	
Arousal	3,4,5,6	0-5	0.3	0	6.0	
Lubrication	7,8,9,10	0-5	0.3	0	6.0	
Orgasm	11,12,13	0-5	0.4	0	6.0	
Satisfaction	14,15,16	0/1-5	0.4	0.8	6.0	
Pain	17,18,19	0-5	0.4	0	6.0	
Total score (FSFI score)				2.0	36.0	

Mean ± Standard Deviation, continuous data not matching to a normal distribution as Median (highest - lowest value or interquartile range), and categorical data as frequency (percentage). Mann Whitney U test was used to compare the data of two groups that did not match with the normal distribution between independent groups. Independent samples t-test was used to compare the data of two groups with normal distribution. Chi-square or Fisher's Exact test was used to compare independent categorical variables. Spearmen correlation test was used between BDI, PSQI and FSFI. All statistical tests were done bilaterally and $p < 0.05$ was considered statistically significant.

Results

The demographic characteristics of the patients included in the study are examined; 105 women were included in the study, and the median age of the individuals was 53 (34-79). 80% of the patients were married, 19% were divorced, and the median number of children they had was found to be 2 (0-9). The single patients didn't declare that they have sexual partners. 67% of the cases are housewives, 21% are retired and 17% continue to work actively.

When the patients were evaluated in terms of their menopausal status at the time of the interview, the menopausal status of seven patients was unknown, 61.9% were in the postmenopausal stage, 17.1% were in the premenopausal stage, and 14.3% were in the perimenopausal stage.

The surgery and pathology information of the patients included in the study are shown in Table 2 below.

Surgery type are unknown for four patients because data was missing. Tumor stage for 8 patients and Her2 value of nine patients are also unknown because data was missing. Perineural invasion is also unknown in 22 patients and extracapsular extension is unknown in 26 patients because pathological data could not be reached.

When the endocrine treatment agents taken by the patients were examined, 62 (59.6%) patients used tamoxifen, 29 (27.9%) patients used letrozole, and 13 (12.5%) patients used anastrozole. The median duration of endocrine treatment of the patients included in the study was followed for 24 months (3-120). Detailed data on Adjuvant treatments and their durations are shown in Table 3.

When we look at the BDI score information of the patients, 46.5% had minimal depression, 26.7% had mild depression, 24.7% had moderate depression, and 1.9% had severe depression. BDI value was below the median value of 10 in 55.8% of the patients, and above the median value of 10 in 44.2% of the patients.

When the sleep quality rates were examined, 41 (39.4%) patients had good and 63 (60.6%)

Table 2. Surgery and pathology information of patients

Number of patients		105
Surgery type, n (%)	Breast-Conserving Surgery (BCS)	33 (31,4)
	Modified Radical Mastectomy (MRM)	68 (64,8)
	unknown	4 (3,8)
Stage T, n (%)	T0	2 (1,9)
	T1	38 (36,2)
	T2	48 (45,7)
	T3	7 (6,7)
	T4	2 (1,9)
	unknown	8 (7,6)
Stage N, n (%)	N0	46 (43,8)
	N1	22 (21,0)
	N2	11 (10,5)
	N3	16 (15,2)
	unknown	10 (9,5)
ER, n (%)	positive	98 (93,3)
	negative	7 (6,7)
PR, n (%)	positive	93 (88,6)
	negative	12 (11,4)
Her-2, n (%)	positive	51 (48,5)
	negative	45 (42,9)
	unknown	9 (8,6)
Grade, n (%)	1	13 (12,4)
	2	39 (37,1)
	3	16 (15,2)
	unknown	37 (35,2)
LVI, n (%)	Yes	39 (37,1)
	No	49 (46,7)
	unknown	17 (16,2)
PNI, n (%)	available	15 (14,3)
	umavailable	68 (64,7)
	unknown	22 (21,0)

Table 2. continue next page

ECE, n (%)	Yes	21 (20,0)
	No	58 (55,2)
	unknown	26 (24,8)
Stage, n (%)	1A	24 (25,5)
	1B	22 (23,4)
	2A	25 (26,6)
	2B	3 (3,2)
	3A	8 (8,5)
	3B	12 (12,8)

T: Tumor, N: Lymph Node, ER: Estrogen Receptor, PR: Progesterone Receptor, Her2: Human Epidermal Growth Factor Receptor 2, LVI: Lymphovascular invasion, PNI: Perineural Invasion, ECE: Extracapsular Extension

patients had poor sleep quality. As a result, a tendency towards sleep disorder was observed in the patients who participated in the study.

When the FSFI scores of the patients were examined, low scores were found in the majority of the patients, and a tendency to sexual dysfunction was observed. According to the FSFI scores, 81 (77.1%) patients scored bad, 16 (15.2%) patients were found to be fair, and 8 (7.6%) patients scored well in terms of sexual function.

BDI, PSQI, and FSFI score information of the patients are summarized in Table 4.

When demographic characteristics of the patients with low and high BDI, PSQI, and FSFI scores were compared, no statistically significant relationship was found with the age, the number of children, social security, the menopausal status of the patients ($p>0.05$). However, the relationship between marital status and FSFI score was found to be statistically significant, and in 70% of married patients, sexual function was found to be poor ($p=0.04$).

When the patients' ER and PR positivity percentage rates were examined, no significant relationship was observed between the BDI scores and positivity percentage ($p=1.0$ for ER, $p=0.26$ for PR). However, although it was not statistically significant, a decrease in the ER percentage and an increase in the BDI score, that is, a tendency to depression, was observed ($p=0.06$). There was no significant effect of ER positivity ($p= 0.15$) and ER percentage ($p=0.35$) on sexual function. A tendency to sexual dysfunction was observed in patients with PR positivity and it was found to be statistically significant ($p=0.005$). There was no significant correlation between PR percentages and FSFI score ($p=0.55$).

No significant relationship was found between adjuvant chemotherapy, radio-therapy, trastuzumab, Luteinizing hormone releasing hormone (LHRH) treatment status, duration of treatment and BDI, PSQI and FSFI score values. There was no significant relationship between different endocrine therapy agents (tamoxifen/ anastrozole/ letrozole) in patients with depression, sleep and sexual dysfunction ($p> 0.05$). However, although not statistically significant, patients using aromatase inhibitors had a higher tendency to sleep disorder. Poor sleep quality was found in 29 (69%) of 42 patients using aromatase inhibitors. However, although not statistically significant, 90% of the patients who took aromatase inhibitors tended to sexual dysfunction.

Comparison of BDI, PSQI, and FSFI scores with adjuvant treatments is summarized in Table 5.

There was a strong correlation between PSQI and BDI ($p<0.001$), and a moderate inverse

Table 3. Adjuvant treatments and their durations

Adjuvant CT, n (%)	Yes	76 (72,4)
	No	28 (26,7)
	unknown	1 (1,0)
Adjuvant CT regimen, n (%)	Anthracycline and taxane	58 (55,2)
	Anthracycline	12 (11,4)
	Taxane	2 (1,9)
	Other	33 (31,4)
Adjuvant CT duration, the median day		149 (25-462)
Adjuvant trastuzumab, n (%)	Yes	32 (30,5)
	No	69 (65,7)
	unknown	4 (3,8)
Adjuvant RT, n (%)	Yes	81 (78,6)
	No	22 (21,4)
Adjuvant RT duration, the median day		35 (4-56)
Adjuvant Endocrine Treatment type, n (%)	Tamoxifen	62 (59.6)
	Letrozole	29 (27.9)
	Anastrozole	13 (12.5)
Adjuvant Endocrine Treatment duration, median month		24 (3-120)
Adjuvant LHRH, n (%)	Yes	10 (9,5)
	No	95 (90,5)

CT: Chemotherapy, RT: Radiotherapthy, LHRH: Luteinizing hormone releasing hormone

correlation (P=0.001) between FSFI-BDI scores. In summary, it was found that sleep disorders and sexual dysfunction increased in patients with depression. The correlation analysis of BDI, PSQI, and FSFI scores is summarized in Table 6.

Discussion

First of all, if we examine the results obtained with the Beck Depression Inventory, our first questionnaire, 44.2% of the patients tended to depression with a BDI score of 10 and above. In a study, results confirmed that side effects of endocrine treatment were significantly associated with anxiety and depression [8]. The prevalence of depression and anxiety in that study were 33.4% (133) and 13.3% (53), respectively. In another study by Weitzner et al., based on BDI questionnaires in a population of patients with 5 years of disease-free period, they found 29% depression among breast cancer patients. [15]. The reason why this rate was found to be higher in our study may be that our patient group consisted of patients who still received endocrine treatment and did not reach the disease-free period. In another study based on HADS (Hospital Anxiety and Depression Scale) score, comorbid depression was found in approximately one-quarter of all breast cancer patients, and this rate was estimated to be between 20% and 30% in early breast cancer and more than 50% in advanced and palliative stages [16]. Although all of the patients in our

Table 4. Beck, PSQI, and FSFI score information of the patients

Beck Depression score, median (min-max)		10 (0-33) if you want average 11,5±7,8
Beck Depression score, n (%)	Low	58 (55,8)
	High	46 (44,2)
	Minimal depression	47 (%46,5)
	Mild depression	27 (%26,7)
	Moderate depression	25 (%24,7)
	Severe depression	2 (%1,9)
PSQI score, median (min-max)		7 (1-16) if you want average 7.2 ±3.3
PSQI score, n (%)	Good	41 (39,4)
	Poor	63 (60,6)
FSFI score, median (min-max)		2,6 (2-34) if you want average 11,7±11,3
FSFI score, n (%)	Good	8 (7,6)
	Fair	16 (15,2)
	Bad	81 (77,1)

BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index,
FSFI: Female Sexual Function Index

Table 5. Comparison of BDI, PSQI, and FSFI Scores with Adjuvant Treatment.

	BDI	PSQI	FSFI
Adjuvant Chemotherapy (Yes/No)	P = 0,18	P = 1,00	P = 0,86
Adjuvant Chemotherapy regimen type	P = 0,11	P = 0,39	P = 0,54
Adjuvant Chemotherapy duration	P = 0,62	P = 0,93	P = 0,59
Adjuvant Trastuzumab (Yes/No)	P = 0,61	P = 0,60	P = 0,80
Adjuvant RT (Yes/No)	P = 0,92	P = 0,75	P = 0,84
Adjuvant Endocrine Treatment type	P = 0,74	P = 0,34	P = 0,09
Adjuvan Endocrine Treatment duration	P = 0,56	P = 0,78	P = 0,15
Adjuvant LHRH (Yes/No)	P = 0,33	P = 0,51	P = 0,39

RT: Radiotherapy, LHRH: Luteinizing hormone releasing hormone

Table 6. Correlation relationship

		FSFI score	BDI score
PSQI score	r	-0,04	0,57
	p	0,71	<0,001
FSFI score	r		-0,36
	p		<0,001
r: correlation coefficient			

BDI: Beck Depression Inventory, PSQI: Pittsburgh Sleep Quality Index,
FSFI: Female Sexual Function Index

study were in the early stage, the reason for the higher prevalence of depression compared to this study may be that the number of patients who received chemotherapy in our study was higher. On the other hand, the prevalence in our study was significantly lower than a study conducted in Iran which reported the prevalence of depression among cancer patients to be 95.9% [17] Different living environments and medical conditions may explain such a large difference.

In a recent meta-analysis of 16,298 women from 17 countries between 2000 and 2019, the prevalence of anxiety in breast cancer patients was found to be 41.9%. The meta-analysis showed a high level of anxiety among breast cancer patients [18]. The different prevalence rates of depression or anxiety in different studies may be due to the type of cancer, the stage of cancer treatment, the severity of the disease, the status of family support, patient's economic level and cultural context and education level among the patients studied.

In our study, the depression status of the patients before endocrine treatment is not known, since the cases were analyzed in cross-section. However, in a retrospective analysis study examining the development of depression in patients in whom tamoxifen treatment was initiated, it was shown that no statistically significant relationship was found between the initiation of tamoxifen treatment and the subsequent development of depressive symptoms [19].

In the literature, it has been reported that the prevalence of depressive symptoms increases in breast cancer patients receiving chemotherapy and radiotherapy [20, 21]. In our study, no significant difference was found between BDI, PSQI and FSFI score values levels in the group that received adjuvant chemotherapy and radiotherapy and the group that did not. It was thought that the reason for the lack of a significant relationship between chemotherapy and depression in our study may be since most of the patients completed the chemotherapy period and at least 3 months had passed.

Sleep disorders, one of the most important cancer-related problems affecting the quality of life, are observed with a rate of 30-50% in cancer patients [22]. In our study, patients with breast cancer under endocrine treatment were evaluated with the Pittsburgh Sleep Quality Index, and 60.6% of patients had poor sleep quality, and sleep disorders were observed in the vast majority of patients.

In a meta-analysis evaluating the relationship between sleep disorders and other symptoms in cancer patients, especially fatigue and depression, it was shown that the connection of insomnia with depression was moderate [23]. In the study of Palesh et al., it was found that sleep problems were positively correlated

with depression and fatigue [24]. In our study, parallel to previous studies, there was a high correlation between BDI and PSQI scores, and a significant correlation was found between sleep disturbance and depression disposition in patients.

When the sexual function index results of our study were examined, a tendency to sexual dysfunction was observed in the majority of the patients (77.1%). Similar to the result obtained in our study Joanne et al. observed that women treated with tamoxifen may experience symptoms of sexual dysfunction [25]. However, the effect of tamoxifen on sexual function is uncertain, and conflicting publications are showing that endocrine treatment causes sexual dysfunction. In the study of McCaughan et al., it was found that women who received endocrine treatment did not experience a significantly different sexual dysfunction than women who did not receive endocrine treatment [26]. Similarly, Ganz et al. examined the relationship between tamoxifen use and sexual function in breast cancer patients and found that there was no difference in sexual functioning among women treated without tamoxifen [27].

When the effect of demographic characteristics of the patients on sexual function was examined, no significant relationship was found, except being married which was found as a negative effect on sexual functionality (P=0.04). There are not enough studies on this subject but this result suggested that the disease may have affected their sexual life worse in married patients than in single or divorced patients since they experienced the entire disease process and difficulties with their sexual partners.

In our study, when the effects of ER and PR positivity on sexual function were compared, patients with PR positivity showed a tendency to sexual dysfunction, and it was found to be statistically significant. However, its clinical significance is not clear. In a different study based on FSFI questionnaires similar to our study, no relationship was found between ER status and sexual function in breast cancer patients. However, only postmenopausal patients were included in the study [28].

In the literature, it is known that sexual dysfunction and depression are associated with both cause and effect in breast cancer patients [29, 30]. In our study supporting the literature, a moderate correlation was observed between depression and sexual dysfunction. In our study, we evaluated the cross-sectional status of breast cancer patients who were hormone receptor-positive and were receiving endocrine treatment, and we found sexual dysfunction in most of the patients. However, we found no difference in the effects of different endocrine treatment agents (tamoxifen, anastrozole, and letrozole) on sexual function. The limited number of patients and different follow-up intervals were the main limitations of our study. The other limitation was that we did not know the anxiety and depression scores of the patients before taking endocrine treatment. An additional limitation was that we could not accurately evaluate the menopausal status of patients using LHRH analogs.

Although endocrine treatment is not a risk factor, we found a tendency to depression, sleep disturbance, and sexual dysfunction in most patients. The high incidence of depression in breast cancer itself makes it particularly difficult to isolate and measure the psychological impact of endocrine treatments on patients. In our study, it was revealed that some sociodemographic features and hormone receptor status may affect sexual functionality. Future research may shed light on the size of these independent risk factors and as a result, it may guide treatment decisions for breast cancer patients in the coming years.

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REFERENCES

1. R. L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1): 7-30.
2. B. Kara, H. Fesci, Kanserde öz-bakım ve yaşam kalitesi. Hematoloji–Onkoloji. 2004; 6(3): 124–129.
3. A.E. Giuliano, J.L. Connolly, S.B Edge, E.A. Mittendorf, H.S. Rugo, L.J. Solin, Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67(4): 290–303.
4. U. Halbreich, N. Rojansky, S. Palter, H. Tworek, P. Hissin, K. Wang, Estrogen augments serotonergic activity in postmenopausal women. Biol Psychiatry. 1995; 37(7): 434–441.
5. B.E.H. Sumner, K.E. Grant, R. Rosie, C. Hegele-Hartung, K.H. Fritzemeier, G. Fink, Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites and mRNA levels in the brain of ovariectomized rats with or without acute estradiol replacement. Mol Brain Res. 1999; 73(1-2): 119–128.
6. T.C. Moynihan, T.M. Habermann, A.K. Gosh, Breast cancer. In: Mayo Clinic Internal Medicine: Concise Textbook; 2009. p. 661–665.
7. B.P.A. Ganz, K.A. Desmond, T.R. Belin, B.E. Meyerowitz, J.H. Rowland, Predictors of Sexual Health in Women After a Breast Cancer Diagnosis. J Clin Oncol. 1999; 17(8): 2371-2380.
8. R. Zhao, H. Liu, J. Gao, Side Effects of Endocrine Therapy Are Associated with Depression and Anxiety in Breast Cancer Patients Accepting Endocrine Therapy: A Cross-Sectional Study in China. Frontiers in Psychology. 2022, 13.
9. A.T. Beck, R.A. Steer, G. Brown,BD I-II, Beck depression inventory manual. Psychological Corp.San Antonio, TX. 1996; 3: 601-608
10. N. Hisli, Beck Depresyon Envanteri'nin Geçerliği Üzerine Bir Çalışma. Psikol Derg. 1988; 6: 118–122.
11. M.Y. Ağargün, H. Kara, Ö. Anlar, Pittsburgh Uyku Kalitesi İndeksi'nin Geçerliği ve Güvenirliği. Türk Psikiyatr Derg. 1996; 7(2): 107–115.
12. R. Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, R. D'Agostino, The female sexual function index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26(2): 191–208.
13. E. Öksüz, S. Malhan, Kadin cinsel fonksiyon indeksi. Sendrom Derg. 2005; 17: 54–60.
14. B.B. Keseroğlu, B.C. Özgür, A.K. Yıldız, E. Gülen, Kadin Cinsel İşlev Ölçeğine Etki Eden Faktörler. Kırıkkale Üniversitesi Tıp Fakültesi Derg. 2008; 20(3): 269–273.
15. M.A. Weitzner, C.A. Meyers, K.K. Stuebing, A.K. Saleeba, Relationship between quality of life and mood in long-term survivors of breast cancer treated with mastectomy. Support Care Cancer. 1997; 5(3): 241–248.
16. L.J. Fallowfield, A. Hall, G.P. Maguire, M. Baum, Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. Br Med J. 1990; 301(6752): 575–580.
17. J. Shakeri, S. Golshani, E. Jalilian, V. Farnia, R. Nooripour, M. Alikhani, K. Yaghoobi, Studying the amount of depression and its role in predicting the quality of life of women with breast cancer. Asian Pac. J. Cancer Prev. 2016;17: 643–646.
18. S.M. Hashemi, H. Rafiemanesh, T. Aghamohammadi, et al. Prevalence of anxiety among breast cancer patients: a systematic review and meta-analysis. Breast Cancer. 2020; 27: 166–178.
19. K.C. Lee, G.T. Ray, E.M. Hunkeler, P.R. Finley, Tamoxifen treatment and new-onset depression in breast cancer patients. Psychosomatics. 2007; 48(3): 205–210.
20. A.M. Schreier, S.A. Williams, Anxiety and quality of life of women who receive radiation or chemotherapy for breast cancer. Oncol Nurs Forum. 2004; 31(1): 127–130.
21. S.E. Ward, G. Viergutz, D. Tormey, J. deMuth, A. Paulen, Patients' reactions to completion of adjuvant breast cancer therapy. Nurs Res. 1992; 41(6): 362–366.
22. M.J. Sateia, K. Doghramji, P.J. Hauri, C.M. Morin, Evaluation of Chronic Insomnia. Sleep. 2000; 23(2): 243–308.
23. K.A. Donovan, P.B. Jacobsen, Fatigue, Depression, and Insomnia. Evidence for a Symptom Cluster in Cancer. Semin Oncol Nurs. 2008; 23(2): 127–135.
24. O.G. Palesh, J.A. Roscoe, K.M. Mustian, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-community clinical oncology program. J Clin Oncol. 2010; 28(2): 292–298.
25. J.E. Mortimer, L. Boucher, J. Baty, D.L. Knapp, E. Ryan, J.H. Rowland, Effect of tamoxifen on sexual functioning in patients with breast cancer. J Clin Oncol. 1999; 17(5): 1488–1492.
26. S. Young-McCaughan, Sexual functioning in women with breast cancer after treatment with adjuvant therapy. Cancer Nurs. 1996; 19(4): 308–319.
27. P.A. Ganz, J.H. Rowland, K. Desmond, B.E. Meyerowitz, G.E. Wyatt, Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. J Clin Oncol. 1998; 16(2): 501–504.
28. J.A.C. Cavalheiro, A. Bittelbrunn, C.H. Menke, Jet al. Sexual function and chemotherapy in postmenopausal

women with breast cancer. BMC Womens Health. 2012; 12(1): 28.
29. E.N. Boswell, D.S. Dizon, Breast cancer and sexual function. Transl Androl Urol. 2015; 4(2): 160–168.
30. D. Buković, J. Fajdić, Z. Hrgović, M. Kaufmann, I. Hojsak, T. Stančerić, Sexual dysfunction in breast cancer survivors. Onkologie. 2005; 28(1): 29–34.

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Doi: 10.5505/aot.2023.24654

Original Article

Evaluation of Anesthesia Applications and Postoperative Care Results in Patients Who Underwent Reconstruction Surgery with Tumor Resection Prosthesis in Primary and Metastatic Bone Tumors

Primer ve Metastatik Kemik Tümörlerinde Tümör Rezeksiyon Protezi ile Rekonstrüksiyon Cerrahisi Yapılan Hastalarda Anestezi Uygulamaları ve Postoperatif Bakım Sonuçlarının Değerlendirilmesi

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ABSTRACT

Introduction: Patients scheduled for orthopedic oncological surgery often receive various treatments, such as chemotherapy or radiotherapy, before the operation. The treatments applied and related side effects, accompanying co-morbidities and the characteristics of the surgery to be performed affect the choice of anesthesia and require specificity. In this study, it was planned to retrospectively evaluate the patients who underwent tumor resection prosthesis with the diagnosis of primary or metastatic bone tumor in our hospital.
Materials and methods: 72 patients between the ages of 6-84 who underwent tumor resection prosthesis operation with the diagnosis of primary or metastatic bone tumor and who are in American Society of Anesthesiologists (ASA) I-III group were included in the present study. Demographic characteristics of patients, accompanying diseases, malignity diagnoses, ASA scores, surgical intervention carried out and anesthesia method, duration of anesthesia and operation, pre and postoperative hemoglobin values, amount of intraoperative bleeding, intraoperative fluid management and need for blood transfusion, need for and duration of postoperative intensive care and/or mechanic ventilation were recorded.
Results: The most frequently diagnosed primary bone tumor was osteosarcoma, and the most common operation was wide tumor resection and femoral proximal tumor resection prosthesis. Parameters such as duration of anesthesia, amount of bleeding, age, ASA, and comorbidity were shown to be associated with the need for postoperative mechanical ventilation or intensive care. In the postoperative analgesia methods applied to the patients, it was seen that the most frequently preferred method was intravenous analgesia.
Discussion: In orthopedic oncologic surgeries, anesthesia management should encompass evaluating the patient with a holistic approach starting from the preoperative period, and considering the need for postoperative analgesia and/or for intensive care in addition to intraoperative anesthesia. Communication between members of anesthesia and surgery teams is important for providing optimal surgical care.

Keywords: Bone neoplazms, reconstructıon surgery. anaesthesia. postoperatıve care, tumor resectıon, prosthesıs

ÖZET

Giriş: Ortopedik onkolojik cerrahi planlanan hastalar sıklıkla operasyondan önce kemoterapi veya radyoterapi gibi çeşitli tedaviler almaktadır. Uygulanan tedaviler ve bunlara bağlı yan etkiler, eşlik eden ko-morbiditeler ve yapılacak olan cerrahinin özellikleri anestezi seçimini etkileyerek spesifikleşmeyi

First Received: 04.02.2023, Accepted: 16.05.2023 doi: 10.5505/aot.2023.67689

gerektirir. Bu çalışmada, hastanemizde primer veya metastatik kemik tümörü tanısı ile tümör rezeksiyon protezi uygulanan hastaların retrospektif olarak değerlendirilmesi planlandı.
Gereç ve yöntemler: Çalışmaya hastanemiz Ortopedi ve Travmatoloji Kliniği tarafından Ocak 2015 ve Aralık 2016 tarihleri arasında Primer veya metastatik kemik tümörü tanısı ile tümör rezeksiyonu protez operasyonu uygulanan, American Society of Anesthesiologists (ASA) I-III grubunda yer alan 6-84 yaş arası 72 hasta bu çalışmaya dahil edildi. Hastaların demografik özellikleri, eşlik eden hastalıkları, malignite tanıları, ASA skorları, yapılan cerrahi girişim ve anestezi yöntemi, anestezi ve operasyon süresi, ameliyat öncesi ve sonrası hemoglobin değerleri, intraoperatif kanama miktarı, intraoperatif sıvı yönetimi ve kan transfüzyon ihtiyacı, ve postoperatif yoğun bakım ve/veya mekanik ventilasyon süreleri kaydedildi.
Bulgular: En sık tanı alan primer kemik tümörü osteosarkom, en çok yapılan ameliyat ise geniş tümör rezeksiyonu ve femur proksimal tümör rezeksiyon protezi olarak bulundu. Anestezi süresi, kanama miktarı, yaş, ASA ve ek hastalık gibi parametrelerin postoperatif mekanik ventilasyon veya yoğun bakım ihtiyacıyla ilişkili olduğu gösterildi. Hastalarda uygulanan postoperatif analjezi yöntemlerinde ise en sık olarak intravenöz analjezi yöntemi tercih edildiği görüldü.
Tartışma: Ortopedik onkolojik cerrahilerde anestezi yönetimi, preoperatif dönemden başlayarak hastayı bütüncül bir yaklaşımla değerlendirmeyi, intraoperatif anesteziyle birlikte postoperatif analjezi ve / veya yoğun bakım gereksinimini belirlemeyi kapsamalıdır. Anestezi ve cerrahi ekip üyeleri arasında iletişim optimal onkolojik cerrahi bakımın sağlanması açısından önemlidir.

Anahtar kelimeler: Kemik tümörleri, rekonstrüksiyon cerrahisi, anestezi, ameliyat sonrası bakım, tümör rezeksiyonu, protez

Introduction

In 2009, approximately 2600 new cases of primary bone malignancies and a more significant number of metastatic bone tumors were reported in the USA [1]. Osteosarcoma, Ewing sarcoma, and chondrosarcoma are the three most common types of sarcoma. The recent employment of new chemotherapy treatment agents and radiological imaging methods, treatment options conserving extremity have become more popular [2].

Patients planned to undergo orthopedical oncological surgery commonly receive treatments such as chemotherapy or radiotherapy before the operation. The treatment administered and associated side effects and the characteristics of the surgery influence choice of anesthesia, making it necessary to be more specific. In operations of tumors with rich vascular structure, fluid resuscitation, and adequate intravenous intervention for probable blood transfusion, invasive monitorization or preoperative tumor embolization may be required [3]. It is known that sufficient postoperative analgesic efficacy enables early mobilization and rehabilitation, decreasing morbidity [1].

In the present study, retrospective analysis of the patients who underwent tumor resection prosthesis between January 2015- December 2016 with the diagnosis of the primary or metastatic bone tumor was planned. It was aimed to evaluate demographic characteristics of patients, malignity diagnoses, surgical operation and anesthesia method used, amount of intraoperative bleeding and fluid management, need for blood transfusion, methods used for postoperative analgesia, duration of stay in postoperative ICU, complications developing and need for mechanic ventilation. In addition, the relation between duration of stay in intensive care and mechanic ventilation with other parameters were investigated.

Material and Method

The present study was carried out at University of Health Sciences Ankara Abdurrahman Yurtarslan Oncology Education and Research Hospital Anesthesiology and Reanimation Clinic after ethical approval numbered 2017-05/01 was obtained on 10/5/2017. The study was planned as a retrospective descriptive.72 patients between the ages of 6-84 who underwent tumor resection prosthesis operation with the

diagnosis of primary or metastatic bone tumor between January 2015 and December 2016 and who are in American Society of Anesthesiologists (ASA) I-III group were included in the present study. Cases who were planned to undergo tumor resection prosthesis but who turned out to have benign masses after biopsy were excluded from the study. The study was planned as a retrospective evaluation.

The files of patients who underwent tumor resection between the dates mentioned above were retrieved from hospıtal archive and preoperative anesthesia examination forms, anesthesia monitorization forms, post-operative anesthetic care unit monitorization forms and records of patients who needed monitorization in intensive care unit and/or mechanical ventilation were investigated.

Demographic characteristics of patients, accompanying diseases, malignity diagnoses, ASA scores, surgical intervention carried out and anesthesia method, duration of anesthesia and operation, pre and postoperative hemoglobin values, amount of intraoperative bleeding, intraoperative fluid management and need for blood transfusion, need for and duration of postoperative intensive care and/or mechanic ventilation duratıon were recorded. The relation between evaluated parameters and the need for postoperative intensive care duratıon and/or mechanical ventilation duratıon was investigated.

The number of patients administered regional or general anesthesia was determined and demographic characteristics and differences in the need for postoperative intensive care and/or mechanic ventilation between regional and general anesthesia groups were investigated (Group R, n:28, regional anesthesia - Group G, n:44, general anesthesia). Postoperative analgesia methods and drugs used and their doses were recorded

Statistical analysis

Statistical evaluation was made with SPSS 20.0 program using the tests listed below. $P<0.05$ was considered statistically significant. Statistical analysis was presented as follows: [mean ±standard deviation, minimum- maximum), median (minimum-maximum), n (%)]. Inter groups differences in age, hemoglobin levels, duration of anesthesia and surgical intervention, blood products and fluids used were evaluated with Student's t-test. Data on duration of stay in intensive care and mechanic ventilation, which were not normallly distributed, were evaluated with Mann Whitney U test. Data on ASA class, and additional disease, and the number of patients requiring intensive care and mechanic ventilation were evaluated with Chi-square or Fisher's exact tests.Correlation between data of patients that need intensive care and mechanic ventilation and duration of operation, ASA class, products used, and other parameters were evaluated with Spearman or Pearson correlation test.

Results

Demographic characteristics and accompanying diseases were as follows. 5.6% of the patients were in ASA I, 62.5% in ASA II and 31.9% in ASA III risk group. The most common accompanying disease was hypertension (13.9%) and 62.5% of patients had no additional disease (Table 1). Cancer diagnoses of the patients are shown in (Table 2).The most commonly diagnosed primary bone tumor was established to be osteosarcoma (21%) and the type of operation carried out most commonly wide tumor resection + Femur proximal tumor resection prosthesis with 32 (44%) patients. Upper extremity operation was performed in only one patient out of 72 patients. In 71 patients, the operation was in the lower extremities.

Postoperative analgesia methods used in patients. It was established that epidural PCA (Patient controlled analgesia) method was used in 33% of the patients. The most commonly used intravenous anesthesia method was tramadol bolus administration and PCA prepared with tramadol. (n=14, 19%). It was also determined that two patients underwent femoral plexus, and one patient brachial plexus block and two patients were administered i.v. NSAII (Non steroidal antiinflamatuar drug).

Table1.Demographic characteristics of patients and accompanying diseases [mean ± SD, n (%)]

		(n=72)
Age(year)		47.22±19.12
Weight(kg)		72.35±18.61
ASA(I/II/III)		4 (5.6)/45 (62.5)/23(31.9)
Additional diseases	Acute renal failure	1 (1.4)
	Asthma	1 (1.4)
	Asthma + Goitre	1 (1.4)
	Diabetes Mellitus	3 (4.2)
	Diabetes Mellitus + Hypertension	3 (4.2)
	Hepatitis B	1 (1.4)
	Hypertension	10 (13.9)
	Hypertension + Coronary Artery Disease	4(5.6)
	Hypertension + Chronic Obstructive Pulmonary Disease	1 (1.4)
	Obesity	1 (1.4)
	Pulmonary Hypertension	1 (1.4)
	No additional disease	45 (62.5)

Correlation between the need for duratıon of intensive care and evaluated parameters is shown in table 3. A positive correlation was found between the need for intensive care and duration of anesthesia, amount of bleeding and the amount of erythrocyte suspension used (p=0.025, p=0.003, p<0.0001, respectively). A negative correlation was found, however, between preoperative hemoglobin amount and need for duratıon of intensive care (p<0.0001). No correlation was found between the need for duratıon of intensive care and other parameters evaluated (Table 3).

The correlation between the need for duratıon of mechanic ventilation and the investigated parameters is demonstrated in (Table 4). A positive correlation was found between need for mechanic ventilation and age, ASA, additional disease, duration of anesthesia and amount of erythrocyte suspension used (p=0.005, p=0.012, p=0.041, p<0.0001, respectively). A negative correlation was found between the amount of preoperative hemoglobin and need for duration of mechanic ventilation (p<0.0001). No correlation was found between other parameters and the need for duratıon of mechanic ventilation (Table 4).

In the present study, the number of patients administered regional anesthesia was 28 (39%) (Group R), while the number of patients administered general anesthesia was 44 (61%) (Group G). Combined spinal epidural anesthesia was applied to 28 patients in the regional anesthesia group. Our rate of application of regional anesthesia was similar to the literatüre [1].

Table2.Cancer diagnoses of patients [n (%)]

Cancer diagnoses (n=72)	n (%)
Metastatic adenocarcinoma with unknown primary	4 (%5)
Lung Ca +Bone metastasis	4 (% 5)
Stage 4 Lung Ca+Primary bone malignant mesenchymal tumor	1 (% 1.4)
Giant cell tumor in Femur distal	1 (% 1.4)
Chondrosarcoma	10 (% 14)
Malignant melanoma bone metastasis+ Lung metastasis	1 (% 1.4)
Breast Ca +Bone metastasis	11 (% 15)
Bladder Ca+ left femur metastasis	2 (% 2.8)
Metastatic larynx Ca+ Right femur metastasis	1 (% 1.4)
Multiple myeloma+Humerus proximal carcinoma metastasis	3 (% 4.2)
Nasopharynx Ca +Right humerus proximal and left femur subtrochanteric fracture	1 (% 1.4)
Osteosarcoma	15 (% 21)
Prostat Ca + Bone metastasis	3 (% 4.2)
RCC +Bone metastasis	2 (% 2.8)
Right femur proximal fibrous dysplasia	1 (% 1.4)
Right tibia proximal Ewing sarcoma	1 (% 1.4)
Right tibia proximal giant cell tumor	1 (% 1.4)
Pleomorphic sarcoma in thigh	2 (% 2.8)
Femur malignant mesenchimal tumor	3 (% 4.2)
Left femur distal desmoid tumor	1 (% 1.4)
Left femur proximal pleomorphic rhabdomyosarcoma	1 (% 1.4)
Left thigh posterior mixoid liposarcoma	1 (% 1.4)
Tibia proximal malignant mesenchimal tumor	1 (% 1.4)
Thyroid carcinoma metastasis lytic lesion in proximal of left femur	1 (% 1.4)

Table 3. Correlation between the need for intensive care and other parameters

	R	*P*
Age(year)	0.139	*0.244*
Weight (kg)	0.108	*0.367*
ASA(I/II/III)	0.137	*0.251*
Additional disease	0.085	*0.489*
Duration of anesthesia (min)	0.265	*0.025**
Duration of operation (min)	0.211	*0.075*
Preoperative hemoglobin(g/dl)	-0.403	*<0.0001**
Postoperative hemoglobin(g/dl)	-0.163	*0.173*
Amount of bleeding (ml)	0.340	*0.003**
Erithrocyte suspension (unit)	0.490	*<0.0001**
Cristalloid (ml)	0.185	*0.119*
Colloid (ml)	0.191	*0.331*

Table 4. Correlation between the need for mechanic ventilation and other parameters

	R	*P*
Age(year)	0.330	*0.005**
Weight (kg)	0.058	*0.627*
ASA(1/2/3)	0.259	*0.012**
Additional disease	0.283	*0.018**
Duration of anesthesia(min)	0.242	*0.041**
Duration ofsurgery(min)	0.183	*0.123*
Preoperative hemoglobin (g/dl)	-0.400	*0.001**
Postoperative hemoglobin (g/dl)	-0.184	*0.122*
Amount of bleeding (ml)	0.162	*0.309*
Erithrocyte suspension (unit)	0.613	*<0.0001**
Crystalloid(ml)	0.155	*0.194*
Colloid (ml)	0.206	*0.294*

The comparison of the amount of crystalloid, colloid fluids, erythrocyte suspension, pre and postoperative hemoglobin, and duration of surgical intervention and anesthesia between groups were similar between groups.The amount of preoperative hemoglobin was found to be significantly higher in Group R (p=0.015).

The need for duration of mechanical ventilation was found to be significantly higher in Group R than Group G (p=0.031). Mechanic ventilation was required in eight patients (28.8%) in Group R, and four patients (9.1%) in Group G. Other findings were found to be similar between groups. Death did not occur within 24 hours, preoperatively or postoperatively in any patient.

Discussion

The most commonly diagnosed primary bone tumor was established to be osteosarcoma, and the operation carried out most commonly was found to be wide tumor resection and femur proximal tumor resection prosthesis. Metastatic bone tumors occur more commonly than primary tumors. As many primary cancers metastasize to bone, it is difficult to determine the exact incidence of metastatic bone cancer. Breast and prostate cancers are those that metastasize most commonly to the bone and do so at the rate of 70% in advanced stages [4]. In the present study, metastatic bone cancer was detected in 46% of patients. Of these patients, 11 had breast cancer metastasis, which is similar to the incidence reported in other studies [4]. The increase in developed countries in the prevalence of cancer with the increasing elderly population necessitates more care to be given for cancer patients in the routine practice of health professionals. Anesthetists work with cancer patients not only in operating theaters but also in supportive treatment processes such as pain, nutrition, and intensive care. Although various surgical guidelines have been developed in oncology patients according to cancer types, there are not adequate studies on anesthesia management in these patients [5]. Patients planned to undergo an operation for bone tumors experience an intensive treatment process before surgery. Cancer patients are immune-suppressed due to their disease inducing apoptosis of immune cells,

chemotherapy, and radiotherapy they undergo, malnutrition and psychological stress [6]. Along with immunosuppressive factors, surgical inflammation, pain, hypoxia, hypothermia, hyperglycemia, and immuno-modulation triggered with blood transfusion markedly influence the function of T lymphocytes and natural killer cells (NK) which are active in antitumor activity [7,8]. Recognition of these immune factors and selection of suitable methods in anesthesia management will decrease perioperative risks leading to tumor progression in cancer patients. Volatile anesthetics, morphine and blood transfusion promote immune suppression directly, while propofol, regional anesthesia, and cyclooxygenase inhibitors have been reported to exert positive effects on the immune system [5]. In patients undergoing chemotherapy or radiotherapy, anemia and thrombocytopenia occur frequently. Tumors are generally of vascular structure and tend to bleed at intraoperative period. It has been reported that perioperative tumor embolization may be useful if abundant bleeding is expected associated with a highly vascular tumor [3]. Adequate intravenous access for fluid resuscitation and probable transfusions and preparations for invasive monitorization should be incorporated into preoperative planning. Accompanying co-morbidities such as hypertension, diabetes mellitus, and chronic obstructive lung disease, may make anesthesia management more difficult. Communication with the surgical team is important in that characteristics of the operation can be learned, and anesthesia preparations can be made appropriately [3]. In the present study, the highest amount of bleeding occurred in the case who underwent wide resection, femur and humerus proximal tumor prosthesis operation due to metastasis of the renal cell tumor. As there was about 3000 ml loss of blood in the patient, intensive fluid and blood transfusion was required.

As primary bone tumors and metastases may arise at different sites in the body, anesthesia techniques specialized for certain anatomic localizations provide postoperative analgesia in addition to intraoperative analgesia. In upper extremity tumor resections, regional anesthesia methods may be used as in other surgical operations. If there are a large surgical area and excessive blood loss, difficulty in positioning or long duration of the operation is expected, general anesthesia may be used. In operations carried out under general anesthesia, postoperative analgesia may be given by local anesthetic infiltration via placement of perineural, subfascial or subcutaneous catheters in wound region. In lower extremity tumor resections, regional anesthesia methods may be used on their own or along with general anesthesia[1]. In the present study, 39% of the patients (n=28) were administered regional anesthesia and the remaining patients 61% (n=44) were administered general anesthesia.

Among metastatic tumor resection operations, the most difficult ones are surgeries involving femur. It may be difficult to position patients and use regional anesthesia methods due to primary lesion and other present metastases [1,9]. In cases with excessive bleeding together with sympathetic block associated with neuraxial anesthesia, it may not be easy to control intraoperative blood pressure. In the present study, no significant difference was found between regional and general anesthesia groups in terms of bleeding and the amount of blood transfusion.

It is known that sufficient postoperative analgesia after surgery decreases morbidity by enabling early mobilization and rehabilitation and shortens the duration of hospitalization [10,11]. In oncological surgical operations, postoperative analgesia may be carried out with multimodal analgesia approach, in which drugs and methods exerting effect on different regions in pain pathway such as central or peripheric nerve blocks, local anesthetic infusion via catheters placed in nerve sheath, local infiltration and PCA are used in combination [1]. In the present study, it was established that 33% of the patients used epidural PCA method. Operating theaters with the heavy workload, lack of a separate room for the administration of peripheric blocks in advance, lack of time for the anesthetist and

surgeon, difficulties in the supply of material may be the reasons why peripheric nerve blocks are not used commonly. Orthopedic oncology patients usually use strong opioids due to their pain in the preoperative period. This should be considered when planning postoperative opioid doses and opioid need and tolerance characteristics should be adjusted according to patients. In the study of Chung et al in which pain patterns in recovery unit were investigated, it was reported that the highest pain was described by orthopedics patients in ambulatory surgery [12]. In the study of Barbosa et al, similar results were obtained and 65.6% of patients complained of pain. It was also suggested that physicians and nurses do not adequately evaluate the pain of patients [13]. The efficacy of adjuvant drugs in postoperative pain management has been demonstrated in various studies [14-16]. There are publications reporting the efficacy of alpha 2 agonists such as Dextro-methorphan, NMDA antagonists, gaba-pentinoids, and clonidine[15-17] . NSAII drugs are commonly added to treatment in order to enhance the analgesic efficacy of opioids. The multimodal analgesic approach will decrease the need for intravenous opioids and hence the incidence of probable opioid side effects such as nausea-vomiting, somnolence, ileus and urine retention will also decline.

Orthopedic tumors are quite vascular and may lead to massive intraoperative bleeding[18] . For control and management of intraoperative bleeding, many methods such as preoperative embolization, acute normovolemic hemo-dilution, preoperative blood transfusion, controlled hypotension and antifibrinolytic treatment have been tried and each has its own characteristics [1]. Blood transfusion is an important risk factor in-hospital morbidity[19]. Bower et al investigated the effect of blood transfusion in non-cardiac patients on hospitalization, recovery, and cost and demonstrated that in patients undergoing blood transfusion, duration of hospitalization and frequency of complications was higher [20]. They also reported that in such patients the risk of surgical wound infection increased two-fold and hospital mortality increased 1.4 fold for every unit of blood transfused. Ogura et al in their study on 5716 patients, reported that female sex, age over 80, Charlson Comorbidity Index score of 4 or over, duration of anesthesia longer than 240 minutes, and blood transfusion increased morbidity and mortality [21]. In the present study, a positive correlation was found between duration of anesthesia, amount of bleeding, and amount of erythrocyte suspension used and the need for duration intensive care ($p=0.025$, $p=0.003$, $p<0.0001$, respectively). However, a negative correlation was found between the amount of perioperative hemoglobin and need for intensive care ($p<0.0001$). In patients with high intraoperative bleeding and transfusion need, duration of admission to intensive care was longer. A positive correlation was also found between age, ASA class, additional disease, duration of anesthesia, and the amount of erythrocyte suspension used and the need for duratıon of mechanic ventilation. Similar to other studies, increasing age, comorbidity, high ASA values, prolonged duration of anesthesia and bleeding, and complications increase the need for intensive care [21-27]. In the present study, it was established that the need for duration of mechanic ventilation was higher in the regional anesthesia group (28.6%) than in the general anesthesia group. We believe that this is because ASA class and mean age was higher in the regional anesthesia group and that anesthetists prefer regional methods in patients considered risky.

Bone cancers are usually metastatic tumors rich in vascular structure and localized in various regions of the body. Intense medical treatment patients receive before operation, radiotherapy and accompanying diseases, malnutrition and immune suppression render the operation that will be carried out more critical, necessitating more care to be taken. Bleeding, transfusion and intraoperative complications such as hemodynamic disturbances or embolus may lead to the need for intensive care and mechanic ventilation. The limited number of patients included in the

study and the fact that almost all of the patients were in the lower extremities are the limitations of the study. If larger patient series and patients with tumors in the upper extremity were included in the study, different results could be obtained.

Conclusion

In orthopedic oncological surgery, the need for intensive care may be greater in groups of patients who are older,have a higher ASA score,the duration of anesthesia is longer,the amount of bleeding and the amount of erythrocyte suspension used is excessive. In addition, the hemoglobin value should be optimized in terms of postoperative results before such major surgeries.

In orthopedic oncologic surgeries, anesthesia management should encompass evaluating the patient with a holistic approach starting from the preoperative period, and considering the need for postoperative analgesia and/or for intensive care in addition to intraoperative anesthesia. Communication between members of anesthesia and surgery teams is important for providing optimal surgical care.

REFERENCES

1. Anderson MR, Jeng CL, Wittig JC, Rosenblatt MA. Anesthesia for patients undergoing orthopedic oncologic surgeries. J Clin Anesth. 2010; 22(7): 565-572

2.Winkler K, Beron G, Kotz R et al. Adjuvant chemo-therapy in osteosarcoma- Effects of cisplatinum, BCD, and fibroblast interferon in sequential combination with HD-MTX and adriamycin. J Cancer Res Clin Oncol. 1983; 106 sup:1-7.

3. Zhang L, Gong Q, Xiao H, Tu C, Liu J. Control of blood loss during sacral surgery by aortic balloon occlusion. Anesth Analg. 2007; 105: 700–703

4. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004; 350: 1655–1664

5.Kurosawa S. Anesthesia in patients with cancer disorders. Curr Opin Anesthesiology. 2012; 25: 376-384

6.Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. J Environ Pathol Toxicol Oncol. 2003; 22: 139–146.

7. Kurosawa S, Kato M. Anesthetics, immune cells, and immune responses. J Anesth. 2008; 22: 263–277.

8. Homburger JA, Meiler SE. Anesthesia drugs, immunity, and long-term outcome. Curr Opin Anesthesiol. 2006; 19:423–428.

9.Kawai VFA, Cortez PJO, Valenti VE, Oliveira FR, Vitorino LM. Pre and postoperative analgesia for orthopedic surgeries. Rev Dor. São Paulo. 2015; 16(3): 166-170

10. Chester JG, Rudolph JL. Vital signs in older patients: age-related changes. J Am Med Dir Assoc. 2011; 12(5): 337-43

11. Sharma V, Morgan PM, Cheng EY. Factors influencing early rehabilitation after THA: a systematic review. Clin Orthop Relat Res. 2009; 467(7): 1400-1411.

12. Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. Anesth Analg. 1997; 85: 808-816.

13. Barbosa MH, Araujo NF, Silva JA, Corrêa BT, Moreira MT, Andrade VE. Pain assessment intensity and pain relief in patients post-operative orthopedic surgery. Esc Anna Nery. 2014; 18(1): 143-147.

14. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002; 96: 725-741.

15.Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. Anesth Analg. 2008; 107: 1380-1383.

16.Mercadante S, Fulfaro F. Management of painful bone metastases. Curr Opin Oncol. 2007; 19: 308-314

17. Pinkerton PH, Covens A. Autologous blood transfusion in radical hysterectomy. Transfus Med. 1996 ;6: 223-225.

18.Nakai S, Yoshizawa H, Kobayashi S, Naga K, Ichinose H. Role of autologous blood transfusion in sacral tumor resection: patient selection and recovery after surgery and blood donation. J Orthop Sci. 2000; 5: 321-327

19. Hormozi AK, Mahdavi N, Foroozanfar MM et al. Effect of Perioperative Management on Outcome of Patients after Craniosynostosis Surgery. World J Plast Surg. 2017; 6(1): 48–53.

20. Bower WF, Jin L, Underwood MJ, Lam YH, Lai PB. Peri-operative blood transfusion increases length of hospital stay and number of postoperative complications in non-cardiac surgical patients. Hong Kong Med J. 2010; 16(2): 116-120.

21. Ogura K, Yasunaga H, Horiguchi H, Fushimi K, Kawano H. What Is the Effect of Advanced Age and Comorbidity on Postoperative Morbidity and Mortality After Musculoskeletal Tumor Surgery? Clin Orthop Relat Res. 2014; 472: 3971–3978

22. Lupei MI, Chipman JG, Beilman GJ, Oancea SC, Konia MR. The association between ASA status and other risk stratification models on postoperative intensive care unit outcomes. Anesth Analg. 2014; 118(5): 989-994.

23. Lahat G, Dhuka AR, Lahat S et al. Complete soft tissue sarcoma resection is a viable treatment option for select elderly patients. Ann Surg Oncol. 2009; 16: 2579–2586.

24. Al-Refaie WB, Habermann EB, Dudeja V et al. Extremity soft tissue sarcoma care in the elderly: insights into the generalizability of NCI Cancer Trials. Ann Surg Oncol. 2010; 17: 1732–1738.
25. Boden RA, Clark MA, Neuhaus SJ, A'Hern JR, Thomas JM, Hayes AJ. Surgical management of soft tissue sarcoma in patients over 80 years. Eur J Surg Oncol. 2006; 32: 1154–1158.
26. Buchner M, Bernd L, Zahlten-Hinguranage A, Sabo D. Primary malignant tumours of bone and soft tissue in the elderly. Eur J Surg Oncol. 2004; 30: 877–883.
27. Osaka S, Sugita H, Osaka E, Yoshida Y, Ryu J. Surgical management of malignant soft tissue tumours in patients aged 65 years or older. J Orthop Surg. 2003; 11: 28–33.

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Doi: 10.5505/aot.2023.67689

Original Article

Prognostic Role of Pan Immune Inflammation Value and Systemic Inflammation Response Index in Small Cell Lung Cancer

Küçük Hücreli Akciğer Kanserinde Pan İmmün Enflamasyon Değeri ve Sistemik Enflamasyon Yanıt İndeksinin Prognostik Rolü

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) is a highly lethal form of lung cancer with very poor prognosis. Systemic inflammation is an important risk factor for cancer development. Circulating immune cells play an important role in fighting against cancer. This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers as components of circulating immune cells in small cell lung cancer.

Materials and methods: A total of 81 SCLC patients followed up at Dokuz Eylül University Hospital Department of Medical Oncology between 2012 and 2021 were included in this study. Demographic characteristics and clinic-pathological features of each patient were recorded. Peripheral blood tests of patients were recorded at the time of diagnosis. Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count × platelet count × monocyte count)/lymphocyte count. The optimal cut-off values were determined according to the receiver operating characteristic (ROC) curve. These values were 2.8 and 585 in limited stage SCLC, and 1.33 and 497 in all-stage SCLC for SIRI and PIV, respectively. Overall survival (OS) was calculated by Kaplan-Meier method and compared by log rank test. Multivariate analysis was calculated using the Cox regression model.

Results: Among 81 SCLC patients,28 (34.6%) patients had LS-SCLC while 53 (65.4%) patients had extensive stage disease. In whole group, median SIRI was 2.37 (IQR, 0.34–18.59), while median PIV was 634.80 (IQR, 61.57–8320). Although there was a numerical difference between survival in analysis performed in the patient group including all stages, statistical significance could not be achieved for both markers (p=0.20 for SIRI; p=0.058 for PIV). While statistical significance was found for OS and ECOG; SIRI, and PIV status in univariate analysis ofpatients with limited stage SCLC, no significant difference was found between the variables with multivariate analysis..

Discussion: Our findings show that SIRI and PIV may be promising predictors for prognosis in SCLC.

Keywords: Small cell lung cancer; inflammation index; inflammation value

ÖZET

Giriş: Küçük hücreli akciğer kanseri (KHAK), çok kötü prognozlu, oldukça ölümcül bir akciğer kanseri türüdür. Sistemik inflamasyon, kanser gelişimi için önemli bir risk faktörüdür. Dolaşan bağışıklık hücreleri, kansere karşı mücadelede önemli bir rol oynar. Bu çalışma, küçük hücreli akciğer kanserinde dolaşımdaki bağışıklık hücrelerinin bileşenleri olarak farklı periferik kan lökosit biyobelirteçlerinin prognostik değerini araştırmak için tasarlanmıştır.

Gereç ve yöntemler: Bu çalışmaya 2012-2021 yılları arasında Dokuz Eylül Üniversitesi Hastanesi Tıbbi Onkoloji Anabilim Dalı'nda izlenen toplam 81 KHAK hastası dahil edildi. Her hastanın demografik özellikleri ve klinikopatolojik özellikleri kaydedildi. Hastaların tanı anında periferik kan testleri kaydedildi. Sistemik immün-inflamasyon indeksi (SIRI) (nötrofilsayısı×monosit sayısı)/lenfosit sayısı olarak tanımlandı. Pan-immüninflamasyon değeri (PIV) şu şekilde hesaplandı: (nötrofil

First Received: 22.03.2023, Accepted: 01.06.2023 doi: 10.5505/aot.2023.02703

sayısıxtrombosit sayısıxmonosit sayısı)/lenfosit sayısı. Optimal cut-off değerleri, ROC eğrisine göre belirlendi. Bu değerler SIRI ve PIV için sınırlı evreli KHAK'de sırasıyla 2,8 ve 585 ve yaygın evre KHAK'de 1,33 ve 497 idi. Genel sağkalım (GS), Kaplan-Meier yöntemiyle hesaplandı ve log rank testiyle karşılaştırıldı. Cox regresyon modeli kullanılarak çok değişkenli analiz tahmin edildi.
Bulgular: 81 KHAK'li hastanın 28'inde (%34,6) sınırlı evre KHAK, 53'ünde (%65,4) yaygın evre hastalık vardı. Tüm grupta medyan SIRI 2,37 (IQR, 0,34–18,59), medyan PIV ise 634,80'di (IQR, 61,57–8320). Tüm evreleri içeren hasta grubunda yapılan analizde sağkalım arasında nümerik fark olmasına rağmen her iki belirteç için istatistiksel anlamlılık elde edilememiştir (SIRI için p=0,20; PIV için p=0,058). Sınırlı evre KHAK'li hastaların GS, ECOG, SIRI ve PIV durumu için istatistiksel anlamlılık bulunurken, çok değişkenli analizde değişkenler arasında anlamlı bir fark bulunmadı.
Tartışma: Bulgularımız, SIRI ve PIV'in KHAK'de prognoz için umut verici belirleyiciler olabileceğini göstermektedir.

Anahtar kelimeler: Küçük hücreli akciğer kanseri; inflamasyon indeksi; inflamasyon değer

Introduction

Lung cancer is a subset of tumours with poor prognosis among various solid tumours due to its high morbidity and mortality rate and is divided into two main groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)[1]. SCLC represents the most aggressive form of lung cancer. Although it is characterized by a rapid response to chemotherapy and sensitivity to radiotherapy (RT), the 5-year survival rate is less than 10%[2]. The incidence of SCLC has decreased in the last decade, with a prevalence of 1-5/10,000 people in the European population, and is therefore considered an orphan disease[3,4]. According to a lung study group, SCLC is classified in two stages: limited stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC)[5]. Despite the advances in diagnosis and treatment, the prognosis remains poor and overall survival is short as the doubling tumor time is rapid, the growth fraction is high and development of metastasis is early [6].

The essential component of treatment for SCLC is systemic therapy.The primary treatment is chemo-radiotherapy for limited stage disease, whereas palliative chemo-therapy remains at the forefront for extensive stage disease[7]. Although SCLC is highly sensitive to chemotherapy, most patients relapse within 6 months. The response rate to second-line therapy depends on the treatment-free time following first-line therapy and response to first-line platinum-based induction therapy. The response rate to second-line therapy is usually around 20% to 30% in platinum-sensitive patients and 15% in platinum-resistant patients [8].

In terms of prognosis, the relationship between systemic immunity and cancer-related inflammation is important. Several blood and biochemical parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), cytokines and lactate dehydrogenase (LDH), have been studied as potential biomarkers associated with inflammation to predict drug efficacy and prognosis [9,10]. High lymphocyte and low neutrophil counts were associated with better prognosis in various tumor models[11]. Recently two immune biomarker models were developed: the systemic inflammation response index (SIRI) and the pan-immune-inflammation-value (PIV). SIRI, which integrates different inflammatory parameters (neutrophils, monocytes and lymphocytes), has proved to be a promising prognostic marker in different cancers[12,13], while PIVis derived from neutrophil, platelet, monocyte and lymphocyte counts. PIV, which has the potential to comprehensively reveal the state of systemic immune and cancer-related inflammation, has been recognised as a reliable marker for clinical outcomes in patients with advanced cancer[14]. In SCLC, some prognostic parameters such as poor performance score, extensive stage, higher lactate dehydrogenase (LDH), and weight loss

were recognized as major poor prognostic factors in retrospective studies.

This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers, as components of circulating immune cells, in small cell lung cancer. We analyzed the prognostic role of SIRI and PIV in patients with SCLC.

Materıals and Method

Study Population:

The study population included 81 SCLC patients (n=120), who applied to Medical Oncology Outpatient Clinic of Dokuz Eylül University Hospital between 2012 and 2021 for diagnosis and treatment. Medical information was retrieved retrospectively from patient files. Gender, age, comorbidities, albumin, hemoglobin, lymphocyte, monocyte, neutrophil and platelet levels at the time ofdiagnosis, disease stage, site of metastasis, treatments received and responses of patients were recorded. Tumor staging was evaluated according to the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines[15]. SCLC was defined in two stages: (a) limited stage: patients with Stage I-III disease that can be reliably treated with precise radiation doses (T any, N any, M0), and (b) extensive stage: patients with Stage IV disease (T any, N any, M 1a/b/c) or T3-4 tumor due to multiple lung nodules that are too extensive or have higher tumor/nodal volume. It includes tumors that are too large to be encompassed in a tolerable radiation plan. The end point of our study was overall survival (OS), whichwas defined as the time from diagnosis to date of death or last check-up visit.

The inclusion criteria were as follows: (1) pathologically diagnosed small cell lung adenocarcinoma; (2) suffering relapsed or metastasized disease; (3) suffering limited stage patients; (4) complete record of blood test results and follow-up data prior to initiation of therapy. The exclusion criteria were as follows: (1) history of other malignant tumors; (3) clinical evidence of recent acute infection or inflammation.

This study was approved byDokuz Eylül University Clinical Research Ethics Committee (dated: 28/09/2022, with decision number: 2022/31-05).

SIRI and PIV:

Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count×platelet count×monocyte count)/lymphocyte count. The optimal cut-off value was determined according to the receiver operating characteristic curve (ROC) and these values were 2.8 and 585 for SIRI and PIV in limited stage SCLC (LS-SCLC), while values were 1.33 and 497 for SIRI and PIV in all-stage SCLC, respectively.

Statistical Analysis:

Descriptive statistical analyses were performed for demographic, clinic-pathological and treatment modalities of patients. Analysis of study data was performed using IBM SPSS software version 24.0. Descriptive statistics of participants were shown as percentages and (n) for categorical variables, and as mean±SD for continuous variables. Before performing the hypothesis tests, the Kolmogorov Smirnov test was used to determine whether the data were normally distributed. The sensitivity and specificity of SIRI and PIV for prognosis prediction were evaluated using a time-dependent receiver operating characteristic (ROC) curve in R software. Multivariate Cox hazard regression analysis was performed on the factors that were found to be significant in the univariate analysis. Overall Survival was defined as the time from randomization to death. OS was estimated using the Kaplan-Meier method, and the results were compared using the log-rank test.The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

Table 1. Clinicopathological characteristics and inflammatory markers of patients

Variable	No of patients(%)/median(range)
Age(years)	
≤60	29(35.8)
>60	52(64.2)
Sex	
Male	67(82.7)
Female	14(17.3)
TNM stage	
LS-SCLC	28(34.6)
ES-SCLC	53(65.4)
ECOG performance score	
0	25(30.9)
1	28(34.6)
2	23(28.4)
3	5(6.2)
Death	
No	10(12.3)
Yes	71(87.7)
Neutrophils, $\times 10^9$/L	6.5(1-23.9)
Monocytes, $\times 10^9$/L	0.7(0.2-1.5)
Lymphocytes, $\times 10^9$/L	1.85(0.2-15)
Platelets, $\times 10^9$/L	274(105-687)
SIRI	2.37(0.34-18.59)
PIV	634.8(61.57-8320)
SIRI in LS-SCLC	
≤2.80	16(57.1)
>2.80	12(42.9)
PIV in LS-SCLC	
≤585	13(46.4)
>585	15(53.6)

Results

Patient Characteristics:

The characteristics of 81 patients included in this retrospective analysis aresummarized in Table 1. Among these 81 patients, 67(82.7%) were male, and 14 (17.3%) were female. The mean age was 63.38±8.7 years. Twenty eight (34.56%) patients had limited stage disease while53 (65.43%) patients had extensive stage disease.

Systemic Treatment:

In all patients, 32.1% received cisplatin+ etoposide and 38.3% received carboplatin+ etoposide chemotherapy regimens. For first-line treatment, platinum-based chemotherapy could be applied to 95.9% of all patients. Prophylactic cranial radiotherapy was applied to 3.8% of the patients and definitive radiotherapy was applied to 23.1%. In the LS-SCLC group, 9% of patients received concurrent radiotherapy with chemotherapy. After first-line chemotherapy, radiological complete response was obtained in 10 (15.3%) patients, partial response in 23 (28.4%) patients,

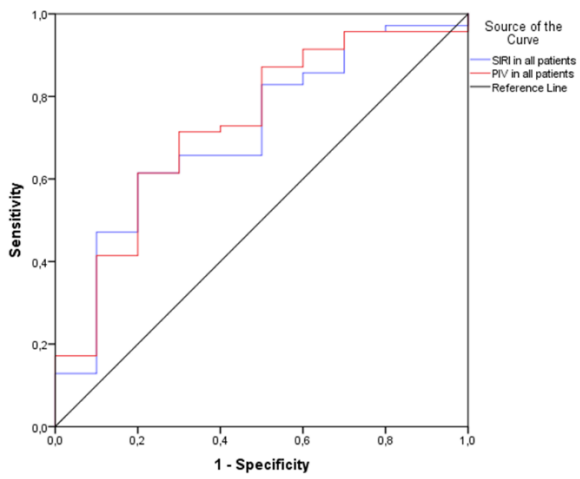


Figure 1. Receiver operating characteristic curve analysis of the optimal cut-off value for systemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 81patients with small cell lung cancer. Areas under the curve for overall survival were 0.711and 0.730 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

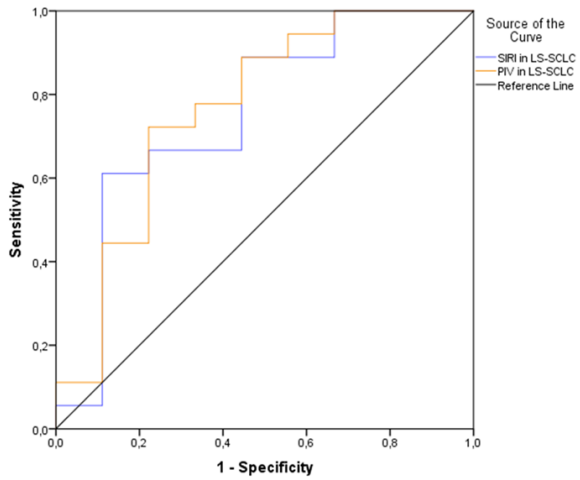


Figure 2. Receiver operating characteristic curve analysis of the optimal cut-off value forsystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 28 patients with limited stage small cell lung cancer. Areas under the curve for overall survival were 0.753and 0.765 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

progression in 20 (24.7%) patients, and stable response in the remaining patients.

Analysis of SIRI and PIV:

The median PIV of patients was 634.80 (IQR, 61.57–8320), while median SIRI was 2.37 (IQR, 0.34–18.59). For all stages, cut-off values were determined as ≥497 and ≥1.33 to establish the prediction of PIV and SIRI biomarkers and estimate prognosis for OS using the time-dependent ROC curves, respectively. In the limited stage group comprising 28 patients, the SIRI and PIV cut-off values were ≥2.80 and ≥585, respectively. Median follow-up was 29.73 (3-131) months. AUC for SIRI and PIV were 0.711(95%CI: 0.541-0.881, P=0.031) and 0.730 (95%CI:0.562-0.898, P=0.019), respectively, for all stages (Figure 1).

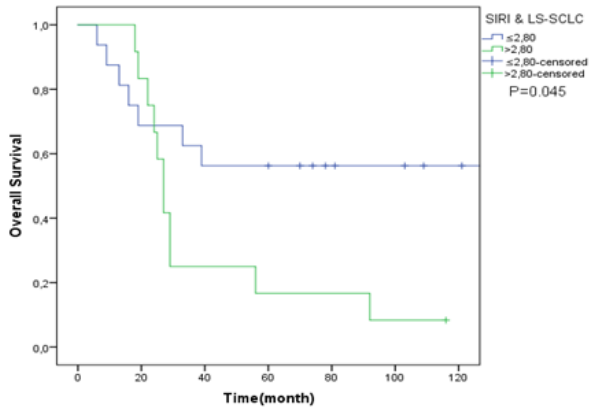
Survival Analyses:

At the end of follow-up, 87.7% of patients had died, and 12.3%were alive. For survival analysis, patients were stratified according to their optimal threshold values for SIRI and PIV. No statistically significant difference was found forsurvival between genders (p=0.67). Survival graphs for patients stratified for SIRI and PIV according to different cut-off values are shown in Figure 2. While the mOS for all patients were 17 months, the mOS were 31 months in the LS-SCLC group and 11 months in the ES-SCLC group.

Survival Analyses according to SIRI and PIV:

The mOS was 45.05 months for patients with SIRI value below 1.33, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 27.76 months for those with a value above 1.33. The mOS was 48.85 months for patients with a PIV value below 497, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 25.44 months for patients with PIV value above 497. The mOSwas 65 months in the patient group with

A



B

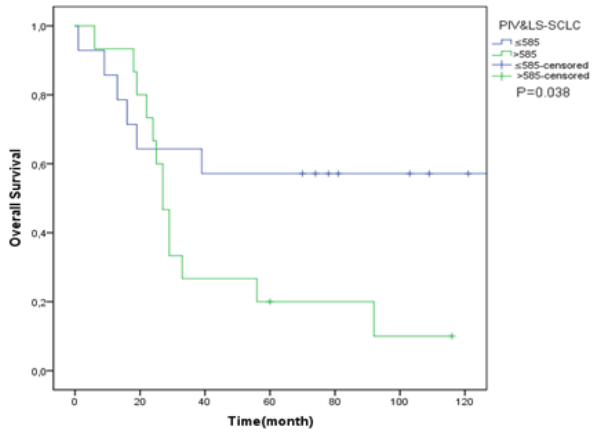


Figure 3. Kaplan-Meier curves for overall survival (OS) according tosystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV)in 28 patients with limited stage small cell lung cancer. (A) and (B).

a SIRI value below 2.80, the cut-off value determined for limited stage patients, while it was 31 for the patient group with SIRIvalue above 2.80 (p=0.045, Figure 3). Similarly, themOSwas 74 months in the patient group with a PIV value below 585, the cut-off value determined for limited stage patients, while it was 27 months for the patient group with a PIV value above 585 (p=0.038, Figure 3).

In this analysis, although there was a numerical difference between the survival rates for the patient group including all stages, statistical significance could not be obtained for both biomarkers (p=0.20 for SIRI; p=0.058 for PIV). However, when SIRI and PIV were evaluated individually in the limited and extensive stage patient groups, survival analysis showed no statistical significance in the patient group with extensive stage, whereas both biomarkers had statistically significant prediction power for prognosis in patients with limited stage disease. Univariate analysis showed statistically significant differences between OS and ECOG, SIRI and PIV status in patients with limited stage SCLC, while multivariate analysis showed no difference between the variables (Table 2).

Discussion

The markers with prognostic value in predicting the survival of the patients are lacking. Therefore, it is important to find reliable tumor markers of prognosis and facilitate treatment adjusting and patient stratification. In the present study, we evaluated prognostic effect of blood-based immune-inflammation indices, including SIRI and PIV, in small cell lung cancer. We think that SIRI and PIV may play a prognostic role especially in patients with limited stage SCLC. There is no study has examined the prognostic impact of the SIRI and PIV in SCLC patients. Consistent with these previously published data for other types of cancers, we found that a high SIRI and PIV was independently associated with worse patient OS.

Through recent advances in molecular biology, remarkable improvement has been achievedfor non-small-cell lung cancer with the use of targeted therapy and immuno-therapy. However, survival still remains short in SCLC due to the lack of effective new therapies and prognostic markers. The mean survival is 2 to 4 months in untreated patients, while it is prolonged with the use of platinum/etoposide or platinum/ irinotecan regimens to 10 months in extensive stage disease and up to 3 years in limited stage disease[16,17]. There is a lack of prognostic markers to predict survival of patients. As it is important to identify tumor markers to predict prognosis and facilitate treatment planning and patient classification, we investigated the prognostic power of two immune inflam-mation indices, SIRI and PIV, based on

Table 2.Univariate and multivariate Cox regression analyses for overall survival in LS-SCLC

Variables		Univariate analysis		Multivariate analysis	
	N(%)	HR (95% CI)	P value	HR (95% CI)	P value
Sex					
Male	26(92.9)	0.52(0.07-3.9)	0.53		
Female	2(7.1)				
Age					
≤60	11(39.3)	1.59(0.59-4.24)	0.35		
>60	17(60.7)				
ECOG PS					
0-1	19(67.9)	4.45(1.63-12.1)	**0.003**	0.22(0.04-1.02)	0.05
2-3	9(32.1)				
Hemoglobin					
≤12	8(28.6)	1.87(0.60-5.75)	0.27		
>12	20(71.4)				
SIRI					
≤2.80	16(57.1)	2.5(0.9-6.6)	**0.045**	1.90(028-12.5)	0.50
>2.80	12(42.9)				
PIV					
≤585	13(46.4)	2.8(1-8.1)	**0.04**	0.44(0.83-2.33)	0.33
>585	15(53.6)				

SIRI: systemic inflammation response index; HR: hazard ratio; CIL confidence interval; PIV: Pan-immune-inflammation value; ECOG PS: ECOG performance status scale

peripheral blood samples for SCLC. SIRI and PIV were found to be prognostic factors for OS in patients with limited stage SCLC. Inflammation is a hallmark of cancer[18]. Recent studies have shownthat prognosis is associated with patient-related factors such as inflammation, immune deficiency and nutrition in several types of cancer and the correlation between nutritional status and prognosis of cancer is particularly striking. Local and systemic inflammation is a significant promoter of tumorigenesis, tumor cell proliferation, invasion and metastasis, and it also plays a role in the response to therapeutic agents[19]. Based on this working principle of the immune system, a model consisting of peripheral blood inflammatory cells has been established. Grivennikov et al.suggest that tumor-induced inflammation results in peripheral hematological changes, including in neutrophils, lymphocytes, monocytes and platelets via release of various cytokines[20]. Therefore, blood cell count is an easy to obtain and cost-effective index to represent the host immune inflammation status. Li et al reported that SIRI is an independent prognostic factor in lung cancer patients after thoracoscopic surgery. However, the prognostic role of SIRI in advanced stage lung cancer patient remains unclear[21]. In our study, we found that SIRI can be a prognostic marker in limited-stage small cell lung cancer, both easily and cost-effectively. PIV is a biomarker that was recently developed based on neutrophils, monocytes, platelets and lymphocytes, and its relationship with OS has been well established[14]. High PIV was a strong predictor of poor PFS and OS in colorectal cancer, breast cancer, renal cancer, melanoma and NSCLC treated with immunotherapy [14,22,23]. Ligorio et al. reported that the PIV was a useful predictor of OS in HER2+ advanced breast cancer patients treated with first-line trastuzumab-pertuzumab containing biochemotherapy[24]. Our results demonstrate that there is a significant relation-ship between inflammatory markers and cancer. Our findings with SIRI and PIV reflecting the systemic immunological status

demonstrated that it is possible to predict prognosis. In the present study, we found a statistically insignificant difference in OS across all patient groups when patients with low SIRI and low PIV were compared to those with high SIRI and PIV. However, for limited stage SCLC patients, our results showed that patients in the low SIRI and PIV group (SIRI≤2.80; PIV≤585) had longer OS compared to those in the high SIRI and PIV group (p=0.045; p=0.038). We of course acknowledge that future studies are needed to confirm our findings, and also to examine other potential mechanism(s) by which SIRI and PIV affects clinical outcome in cancer patients. Besides SIRI and PIV, ECOG performance score (PS) and disease stage have also been shown to be independent prognostic factors. In our patients with extensive stage disease and poor ECOG PS, higher SIRI and PIV levels may reflect impairment in the overall status of systemic inflammation. While there was a statistical significance between OS and ECOG, SIRI and PIV status in univariate analysis, no significance was found between the variables with multivariate analysis. This may be associated with our restricted number of patients. Although our study included patients with all stages of SCLC, we suggest that SIRI and PIV may play prognostic roles, particularly in patients with limited stage SCLC.Considering that prognostic markers such as SIRI and PIV have been studied relatively lessin SCLC compared to other cancers in previous studies, we believe that our study will contribute to increasing knowledge in this field.

Although our study, together with previous researches, demonstrated that SIRI and PIV are promising tools for predicting prognosis in SCLCpatients, the results of our research should be interpreted with caution due to the obvious limitation of the research.The mainlimitations include its retrospective design and restricted patient population. To the best of our knowledge, the number of studies ofpatients with SCLC is low in this field.

Conclusion

In conclusion, SIRI and PIV may be suitable, cost-effective and reliable markers of immune inflammation, especially for predicting prognosis in patients with limited-stage SCLC. They may help therapeutic planning and patient classification. However, well-designed prospective studies are required.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin 2021; 71(3):209–49.
2. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society. 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed October 20, 2020.
3. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006; 24(28): 4539-4544.
4. Breitling LP, Rinke A, Gress TM. Recent survival trends in high-grad neuroendocrine neoplasms and lung cancer. Neuroendocrinology 2020; 110(3-4): 225-233.
5. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and Classification of SCLC. Cancers 2021: 13(4): 820.
6. World Health Organization. International Agency for Research on Cancer, Section of Cancer Information. Cancer Incidence and Mortality Worldwide, 2008.
7. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. Oncologist 2010; 15: 187-195.
8. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small cell lung cancer. J Thorac Oncol 2012; 7(5): 866-872.
9. Hardy-Werbin M, Rocha P, Arpi O, et al. Serum Cytokine Levels as Predictive Biomarkers of Benefit From

Ipilimumabin Small Cell Lung Cancer. Oncoimmunology 2019; 8(6): e1593810.
10. Russo A, Franchina T, Ricciardi GRR, et al. Baseline Neutrophilia, Derived Neutrophil-to-Lymphocyte Ratio (dNLR), Platelet-to-Lymphocyte Ratio (PLR), and Outcome in nonSmall Cell Lung Cancer (NSCLC) Treated with Nivolumab or Docetaxel. J CellPhysiol 2018; 233(10): 6337–43.
11. Deng M, Ma X, Liang X, et al. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? Oncotarget 2017; 8: 37200-7.
12. Geng Y, Zhu D, Wu C, et al. A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. Int Immunopharmacol 2018; 65: 503-10.
13. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 2016; 122: 2158-67.
14. Corti F, Lonardi S, Intini R, et al. The pan-immune-inflammation value in microsatellite instability-high metastatic colorectal cancer patients treated with immune checkpoint inhibitors. Eur J Cancer 2021; 150:155–67.
15. Rami-Porta R, Asamura H, Travis WD, et al. Lung cancer- major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer JClin 2017; 67: 138-55.
16. Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007; 12(1): 20–37
17. Kubota K, Hida T, Ishikura S, et al. Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with oposide and cisplatin plusc on current accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomized phase 3 study. Lancet Oncol. 2014; 15(1): 106–13.
18. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674.
19. Chen L, Kong X, Wang Z, et al. Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med. 2020; 24(5): 2993–3021
20. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140(6): 883–899.
21. Li S, Yang Z, Du H, Zhang W, Che G, Liu L. Novel systemic inflammation response index to predict prognosis after thoracoscopic lung cancer surgery: a propensity score-matching study. ANZ J Surg. 2019; 89(11): E507–E513.
22. Fucà G, Guarini V, Antoniotti C, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE First-Line Trials. Br J Cancer 2020; 123(3):403–9.
23. Prelaj A, Ferrara R, Rebuzzi SE, et al. EPSILoN: a prognostic score for immunotherapy in advanced non-small-cell lung cancer: a validation cohort. Cancers 2019, 11(12): 1954.
24. Ligorio F, Fucà G, Zattarin E, et al. The pan-immune-inflammation-value predicts the survival of patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive advanced breast cancer treated with first-line taxane-trastuzumab-pertuzumab. Cancers (Basel). 2021; 13: 1964.

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Doi: 10.5505/aot.2023.02703

Original Article

Prognostıc Factors and Changing Paradigms in Febrile Neutropenia Episodes

Febril Nötropeni Ataklarında Prognostik Faktörler ve Değişen Paradigmalar

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ABSTRACT

Introduction: The epidemiology of pathogens responsible for febrile neutropenia (FEN) has changed and so did the diagnostic tools in the field of infectious diseases. This study examined the changing paradigms and prognostic factors in FEN episodes.

Materials and methods: This was a prospective and observational study of 145 adult patients aged 18 and older with solid tumor and hematological malignancies and who received FEN treatment at our cancer center between April 2020 and April 2021; 176 FEN episodes developed in patients and were examined.

Results: Hematological malignancy was present in 70.3% (n=102) of the 145 patients. Microbiologically-confirmed infections were seen in 46% of FEN episodes. The most common focus of infection was lower respiratory tract infections with 27.1%. In 66.2% (n=45) of FEN episodes, only gram-negative microorganisms grew while only gram-positive microorganisms grew in 19.1% (n=13). Bacteremia was significantly higher in patients with hematological malignancies versus patients with solid organ tumors (p<0.001). Deep neutropenia on day zero was associated with bacteremia (p<0.001), but the relationship between prolonged neutropenia and bacteremia could not be demonstrated (p=0.34). FEN-related mortality was 9.7% (n=17). The risk of mortality in FEN was 10.25-fold higher in patients with pneumonia and 6.05-fold higher in patients with prolonged neutropenia.

Discussion: We determined that the frequency of pneumonia increased in the FEN clinic due to the effects of newly introduced chemotherapeutics. Gram-negative microorganisms were more common in the causative profile unlike the previous decade. Pneumonia and prolonged neutropenia increase mortality. Comprehensive multicenter studies will allow for the development of new management algorithms for changing paradigms.

Keywords: Febrile neutropenia, Hematological Malignancies, Mortality, Solid Tumor

ÖZET

Giriş: Enfeksiyon hastalıklarının klinik ve laboratuvar tanısındaki gelişmeler ve yıllar içinde değişen etken spektrumu kanser tedavisi süresince Febril nötropeni (FEN) ataklarının güncel takibini gerekli hale getirmiştir. Bu çalışmada FEN ataklarında değişen paradigmaların ve prognostik faktörlerin araştırılması amaçlanmıştır

Gereç ve yöntemler: Prospektif, gözlemsel yürütülen bu çalışmaya, Nisan 2020-Nisan 2021 tarihleri arasında kanser merkezimizde FEN nedeniyle yatarak tedavi gören 18 yaş ve üzeri solid tümörü ve hematolojik malignitesi olan 145 erişkin hasta alındı ve hastalarda gelişen 176 FEN atağı incelendi.

Bulgular: Çalışmaya dâhil edilen 145 hastanın %70.3'ünde (n=102) hematolojik malignite mevcuttu FEN ataklarının %46'sında mikrobiyolojik olarak kanıtlanmış enfeksiyon saptandı ve en sık enfeksiyon odağının %27.1 ile alt solunum yolu enfeksiyonları olduğu görüldü. FEN ataklarının %66.2'sinde (n=45) sadece gram negatif, %19.1'inde (n=13) sadece gram pozitif mikroorganizma üredi. Hematolojik maligniteli hastalarda solid organ tümörlü hastalara göre bakteriyemi istatistiksel olarak anlamlı olacak şekilde daha yüksekti (p<0.001). Sıfırıncı günde derin nötropeni olması bakteriyemi ile ilişkili

First Received: 01.04.2023, Accepted: 07.06.2023 doi: 10.5505/aot.2023.79990

bulunurken (p<0.001), uzamış nötropeninin bakteriyemi ile ilişkisi gösterilemedi (p=0.34). FEN'e bağlı mortalite %9.7 (n=17) oranında görüldü. FEN'de mortalite riski, pnömonisi bulunan hastalarda 10.25 kat ve uzamış nötropenisi olan hastalarda 6.05 kat daha fazlaydı.
Tartışma: FEN ataklarının klinik ve laboratuvar bulgularının araştırıldığı bu çalışmada yeni kullanıma giren kemoterapötiklerin etkisiyle FEN kliniğinde pnömoni sıklığının arttığı ve etken profilinde geçtiğimiz dekattan farklı olarak gram negatif mikroorganizmaların daha çok olduğu saptanmıştır. Ayrıca pnomoni ve uzamış nötropeni varlığının mortaliyeti arttırdığı görülmüştür. Kapsamlı multicenter çalışmalar, değişen paradigmalara yönelik yeni yönetim algoritmalarının oluşturulmasına olanak sağlayacaktır.

Anahtar kelimeler: Febril Nötropeni, Hematolojik maligniteler, Mortalite, solid tümör

Introduction

The development of multi-drug chemotherapy protocols and the use of higher doses in cancer treatment has increased treatment success, the resulting immunosuppression (especially neutropenia) predispose patients to severe infections. Infections occurring in the neutropenic period can cause rapid mortality due to the insufficiency of defense cells. Infection signs that are vague in the neutropenic patient group cause clinical complexity in the FEN period and delay the start of treatment. The most important approach reduces mortality in these patients and initiates empirical antibiotic therapy as soon as possible after taking the necessary samples for culture [1,2]. Therefore, it has become a priority to quickly interpret clinical and laboratory findings and proceed to the treatment phase without losing time.

The patient's primary disease, the chemotherapy protocol, the factors detected in the previous FEN attack, and the level and duration of neutropenia should all be considered during the empirical treatment decision. In addition, each clinic's causative profile is a crucial factor that should be considered when choosing an empirical antibiotic [3,4]. Therefore, surveillance data that includes causative microorganisms and antibiotic susceptibility play an important role in developing an effective empirical treatment protocol [5,6].

This study aimed to determine the clinical characteristics of FEN episodes, laboratory parameters, agents growing in culture, and growth rates to identify the causes of infection and review compatible treatment plans. We further aimed to determine the factors impacting mortality and prognosis in patients with solid tumor and hematological malignancies who were followed up prospectively for one year at the our cancer center.

Material and Methods

Patients

This study included 145 adult inpatients with solid tumors and hematological malignancies aged 18 and older and treated for FEN between April 2020 and April 2021 at the our cancer center; 176 FEN episodes developed in these patients and were examined prospectively. No intervention was made in the follow-up and treatment of the patients enrolled here. Permission was obtained from the Clinical Research Ethics Committee prior to the study (Decision no:2020-03/581).

In accordance with the Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) clinical guidelines, the episodes of patients who had a fever of ≥38.3°C determined with one oral measurement or a fever of ≥38.0°C for more than one hour, those who had an absolute neutrophile count of ≤500 cells/mm^3 or 500-1000 cells/mm^3 and expected to decrease to below 500 cells/mm^3 within 24-48 hours were included as FEN. People with more than one isolate during the same episodes were not included in the study. The study's criterion was that each FEN patient included in the study recovered completely from the previous neutropenia attack. If there was a period longer than four weeks between the two episodes in the same patient, then the

second attack was also considered a new neutropenic attack.

Data collection

All patients eligible for the study were followed up in the wards with daily visits, and their data were recorded in the patient data form after obtaining signed informed consent form. Laboratory data and microbiological data were recorded daily from the hospital automation system. Peripheral blood cultures, urine cultures, and catheter blood cultures, if any, were taken simultaneously from all patients included in the study prior to treatment. Peripheral blood culture was obtained as two blood samples from peripheral veins in patients without a catheter. There was at least half an hour between the two blood samples. Other cultures such as sputum and stool cultures were taken from the sites considered to be the focus of infection based on the clinical symptoms and findings. The samples taken for culture were examined using traditional microbiological methods. Isolated agents were identified using conventional methods and the automated VITEK 2 (bioMerieux, France) system. If a known pathogenic microorganism grew in at least one blood culture, then the blood culture was deemed positive. Two or more growths in the blood culture of coagulase-negative staphylococci were considered positive. According to the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the disc diffusion method or an automated system were used to determine the antibiotic susceptibility of these grown agents.

In the hematology and medical oncology clinics of our center, empirical antibiotic therapy was started by the doctor in charge of the ward or an infectious diseases specialist after considering the microorganism profile from the previous year and their antibiotic susceptibility. The patients were evaluated with clinical findings, physical examination findings, laboratory results, and micro-biological results at daily visits; daily changes were also recorded. Infectious diseases in FEN patients who were followed up were defined as primary bloodstream infection, catheter-related bloodstream infection, urinary tract infection, pneumonia, soft tissue infection, and gastrointestinal tract infection in accordance with the Centers for Disease Control and Prevention (CDC) definitions. Other patients in whom no focus could be detected with clinical, laboratory, microbiological, and radiological findings were evaluated as fever of unknown origin (FUO).

Statistical Method

Data were analyzed with the SPSS software (version 22.0. Armonk, NY: IBM Corp.). The conformity to normal distribution of the data was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrorov-Smirnov/Shapiro-Wilk tests). The arithmetic mean, standard deviation, median, minimum and maximum values were used for evaluation of numerical data while frequency distributions and percentages were used to summarize categorical data. A Chi-squared ($\chi 2$) test was used to compare categorical data. The relationship between non-normally distributed numerical data and categorical data was evaluated with the Mann-Whitney U test. The Kruskal-Wallis test was used to evaluate three or more groups with numerical data. A posthoc Mann-Whitney U-test and Bonferroni correction were performed for pairwise comparisons between groups with significant Kruskal-Wallis test results. Logistic regression analysis was used to examine potential risk factors and independent predictors of treatment outcomes in FEN patients. The Hosmer-Lemeshow test was used to determine the goodness of fit of the model. A p-value of <0.05 was considered statistically significant.

Results

Sociodemographic Characteristics of Patients

We found 176 FEN episodes in 145 adult inpatients. Of the 145 patients included in the study, 52.4% (n=76) were female. The mean age of the patients was 47.16±15.50 years ranging from 18 to 80 years old; 70.3% (n=102) of the patients had hematological

Table 1: Baseline Characteristics of Patients

	n	%
Mean age	47.16 (±15.50)	
Gender		
Female	76	52.4
Male	69	47.6
Malignancy Type		
Solid Organ Tumor	43	29.7
Hematological Malignancy	102	70.3
Comorbidities		
Diabetes Mellitus (DM)	16	11.0
Hypertension	28	19.3
Coronary Artery Disease	5	3.4
Other (Chronic kidney disease, COPD)	25	17.2

malignancies, while 29.7% (n=43) had a solid organ tumor. The characteristics and comorbidities of the patients are presented in Table 1.

Characteristics of the FEN Episodes

Of the 176 FEN episodes, 112(63.6%) were developed during hospitalization, while 64 (36.4%) began outside the hospital. Among the nosocomial FEN episodes, 108 (96%) occurred in patients with haematological malignancies and 84 (75%) were associated with prolonged neutropenia. Bacteremia was significantly more frequent in patients who had FEN episodes during hospital stay ($p<0.001$). The most common focus of infection in FEN episodes was pneumonia. This was followed by catheter infection (22.6%) and primary bloodstream infection (20.3%) (Table 2). The total mucositis rate was 17.0% (n=30). Diarrhea was seen in 19.9% (n=35) of the FEN episodes.

Considering neutropenic fever syndromes both clinically and microbiologically, 46% (n=81) of the FEN episodes were micro-biologically-proven infections (44.8% diagnosed with culture, 1.2% with PCR test); 29.5% (n=52) had clinically identified focus of infection. The FEN focus could not be detected in 24.5% (n=43) of the patients, and thus they were evaluated as FUO. The median duration of treatment in FEN episodes was 14 days (min: 2.00-max: 47.00) and 13 days (min:2.00 - max: 50.00) days, respectively, for microbiological and clinically-documented infections. This was significantly longer than

Table 2. Distribution of Infection Foci

Focus	n	%
Lung Infection	36	27.1
Catheter Infection	30	22.6
Primary Bloodstream Infection	27	20.3
Gastrointestinal System Infection	18	13.5
Soft Tissue Infection	17	12.8
Urinary Tract Infection	5	3.8

the treatment duration of patients with unexplained fever. The total FEN time and total neutropenia times were shorter in the group of patients with unexplained fever ($p<0.001$). The mean duration of FEN was 7 (min:1-max:141) days in patients with hematological malignancies, and 2 days (min:1-max:14) in patients with solid organ malignancies ($p<0.01$). Additionally, 96.2% (n=51) of patients with prolonged neutropenia (neutropenia lasting longer than 10 days) (n=53) had hematological malignancies.

Laboratory and Radiological Characteristics of Patients

The mean leukocyte count at the onset of FEN attack was 595.7 $x10^3$ cells/uL, the mean neutrophil count was 129.6 $x10^3$ cells/uL, and the mean CRP was 121.21 mg/L. The effects of leukocyte count, CRP, and procalcitonin level at the time of diagnosis on mortality and duration of neutropenia was not shown ($p>0.05$). Here, 64.8% (n=114) of the patients had deep neutropenia on day zero, and the mean duration of deep neutropenia in these patients was 8.15±13.34 days (min: 1.00 - max: 112.00). The laboratory findings of the patients during FEN are presented in Table 3. Computed tomography (CT) was performed in 64.8% (n=114) of the patients. The CT of 53.5% (n=61) of the patient did not reveal any findings of infection, while pneumonia findings were detected in 46.5% (n=53) of the patients.

Microbiological Characteristics of FEN Episodes

Culture samples were positive in 53.4% (n=94) of FEN episodes. Growth was observed in peripheral blood culture in 38.6% (n=68), catheter culture in 36.4% (n=64), urine culture in 9.1% (n=16), and sputum culture in 5.1% (n=9). Simultaneous growth

Table 3. Laboratory Values of Patients in the Neutropenic Fever Period

Value	Mean±SD	Median (Min-Max)
WBC (n=176)	595.79±771.53	340.00 (00.00-6180.00)
Neutrophil (n=176)	129.60±160.95	70.00 (0.00-500.00)
Lymphocyte (n=176)	476.16±2154.44	160.00 (00.00-27900.00)
Platelet (n=176)	57,256.00±74,344.96	26,000.00 (9.60-523,000.00)
Hemoglobin (n=176)	8.70±1.84	8.30 (5.00-14.30)
MPV (n=176)	9.98±2.35	10.00 (0.00-14.30)
AST (n=159)	29.14±35.99	17.80 (5.70-221.00)
ALT (n=161)	33.47±47.53	19.20 (3.00-412.00)
Creatinine (n=165)	0.85±0.90	0.66 (0.19-6.80)
CRP (n=164)	121.21±89.14	106.01 (0.24-517.00)
Procalcitonin (n=132)	6.34±21.99	0.39 (0.01-75.00)
Glucose (n = 131)	126.99±76.53	111.00 (67.00-888.00)

Abbreviations: WBC= White Blood Cell, MPV=Mean Platelet Volume, AST=Aspartate Aminotransferase, ALT=Alanine Transaminase, CRP=C-Reactive Protein

Table 4. Microorganisms in Blood Culture

Microorganism	**n**	**%**
Gram Negative Bacteria		
E. coli	28	41.2
K. pneumoniae	8	11.8
P. aeruginosa	7	10.3
Enterobacter cloacae	3	4.4
Achromobacter xylosoxidans	1	1.5
Aeromonas sobria	1	1.5
Gram Positive Bacteria		
Coagulase negative staphylococci	12	17.6
Enterococcus spp.	2	2.9
Streptococcus gordonii	2	2.9
Staphylococcus aureus	1	1.5
Other		
Candida spp.	3	4.4

Table 5: Comparison of Treatment Results and Characteristics of Patients

	Recovered		Ex			
	n	%	n	%	χ^2	*p*
Combined Treatment	115	72.8	16	94.1**	3.711	0.041
Comorbidities	46	29.1	4	23.5	0.235*	0.433
Hematological Malignancy	115	72.8	15	88.2	1.918*	0.135
Attack Developed at the Hospital	99	62.7	12	70.6	0.416	0.519
G-CSF prophylaxis	52	32.9	3	17.6	1.659	0.198
Antibiotic prophylaxis	112	70.9	15	88.2	2.321*	0.103
Mucositis Presence	27	17.1	3	17.6	0.003*	0.587
Pneumonia	30	19.0	13	76.5	27.364*	<0.001
Antifungal Therapy	27	17.1	10	58.8	16.035*	<0.001
Second Line Treatment	13	8.2	14	82.4	64.632*	<0.001
Final Focus Detected	116	73.4	16	94.1**	3.548*	0.046
Culture Positivity	81	51.3	13	76.5**	3.922	0.048
Prolonged Neutropenia	41	25.9	12	66.7	12.730	<0.001

Fisher's exact chi-square test was used.** Represents the group from which the difference originates

Table 6. Logistic regression model developed to predict treatment outcomes

Variables		B	Standard error	*p*	Exp (β)
Pneumonia presence	Yes (Ref)	2.328	0.638	0.000	10.25
Prolonged Neutropenia	Yes (Ref)	1.800	0.643	0.005	6.05
Hematological Malignancy	Yes (Ref)	1.363	1.352	0.313	3.910
G-CSF Prophylaxis	Yes (Ref)	0.143	0.928	0.878	1.154
Antifungal Therapy	Yes (Ref)	0.197	0.936	0.834	1.217
Final Focus Detected	Yes (Ref)	0.401	1.315	0.760	1.493
Blood Culture Positivity	Yes (Ref)	1.067	0.846	0.207	2.908

Ref= Reference Assessed by binary logistic regression analysis. Hosmer-Lemeshow test: 0.590 Nagelkerke R Square: 0.425

was observed in peripheral blood and catheter blood cultures in 27.27% (n=48) of the episodes. The most frequently isolated micro-organisms in blood cultures were E. coli and coagulase-negative staphylococci. Of fatal cases, 50% had P. aeruginose and 33% had Klebsiella pneumoniae (K. pneumoniae) (Table 4) in blood culture.

Bacteremia was detected in 47.7% (n=84) of the episodes. Bacteremia was significantly higher in patients with hematological malignancies compared to patients with solid organ tumors ($p<0.001$). While deep neutropenia on day zero was found to be associated with bacteremia ($p<0.001$), the relationship between prolonged neutropenia and bacteremia could not be demonstrated ($p=0.34$). A model was developed with the type of malignancy, the initial antibiotic treatment regimen (monotherapy or combination therapy), and the presence of deep neutropenia on the first day to predict the development of bacteremia in patients with FEN. The logistic regression model explained 28.9% of the bacteremia risk (Nagelkerke R Square= 0.289). According to the model, the risk of developing bacteremia in patients with hematological malignancies was 8.33-fold higher than the risk of developing bacteremia in patients with solid organ tumors. The risk of developing bacteremia was 2.77-fold higher in patients receiving combined therapy than in patients receiving monotherapy. Patients with deep neutropenia on the first day were 2.45-fold more likely to develop bacteremia than those without.

Treatment Characteristics

Monotherapy was started as an initial treatment in 68.7% (n=121) of 176 FEN episodes. Cefaperazone- sulbactam was used most frequently. Here, 76.3% of the patients who were started on combination therapy were given β-lactam/β-lactamase inhibitors. It was determined that 51.1% (n=90) of the patients who received the initial treatment had a treatment change. Growth in blood culture was detected in 61.8% of the patients whose treatment was changed, and patients with a growth in their blood culture required more treatment changes after isolation ($p<0.05$). Due to clinical course and/or culture results treatment success was achieved in 75.5% of the patients who underwent a treatment change but 24.4% of them underwent another treatment change

Factors Affecting Survival Outcomes and Mortality

It was observed that 18.2% (n=32) of the patients developed hypoxia during the given treatments, and 9.7% (n=17) of the patients were intubated. Another 12.5% (n=22) of the patients were treated in the intensive care unit for an average of 3.77±2.28 days (min: 1.00 - max: 10.00). It was determined that 89.8% (n=158) of the patients were discharged with full recovery, 9.7% (n=17) of the patients died due to infection, and 0.6% (n=1) died due to other causes. Table 5 compares the patient characteristics associated with mortality.

A model including pneumonia and prolonged neutropenia was developed to predict treatment success in FEN patients (Table 6). The logistic regression model can predict 42.5% of treatment success (death or discharge with cure) (Nagelkerke R Square= 0.425). Table 6 shows that the mortality risk of patients with pneumonia in the FEN period was 10.25-fold higher than that of those

without pneumonia. Patients with prolonged neutropenia during the FEN period had a 6.05-fold higher risk of dying after treatment than those without prolonged neutropenia.

Discussion

Our study prospectively examined FEN patients in our hematology, oncology, and bone marrow transplant (BMT) centers: 9.7% (n=17) of the patients died due to FEN. The mortality rates related to FEN vary according to the literature. Ghosh et al. studied hematological patients and found that mortality due to FEN was 19.5% [7]. Another study's mortality rate was 11.2% in 232 patients—56.6% of whom had hematological malignancies [8]. Hatamabadi et al. examined FEN episodes in patients with mostly solid organ tumors (97.8%), and the mortality rate was 5.3% [9]. These differences may be due to several factors such as malignancy types, chemotherapy regimens given, accompanying comorbid diseases, different microorganisms grown in the culture depending on flora of centers and demographic characteristics of the population.

The mean age of the patients in the study was 57, and 52.4% were female. Most patients had hematological malignancies, and one-third of them had comorbidities such as DM, hypertension, and coronary artery disease. Gender, type of malignancy and presence of additional diseases were not associated with mortality. The absence of differences between gender and mortality in the study by Hatamabadi et al. supports our study [9]. However, unlike our study, there are also publications in the literature suggesting that additional diseases affect mortality negatively [10,11]. While the rate of patients over 65 years of age in our study was 15%, it was 28.5% in the studies of Kuderer et al [10]. The entire population of Hosmer et al.'s study consists of elderly people [11]. Therefore, the reason for this difference with the literature can be because comorbidities are more common in the elderly population, and the elderly population in these studies is higher than in our study.

The use of granulocyte colony stimulating factor (G-CSF) in patients receiving chemotherapy leads to a decrease in the normalization of neutrophil counts and the duration of hospitalization but has no effect on mortality [12,13]. Renner et al. found evidence for the decrease of all-cause mortality during chemotherapy with prophylactic G-CSF administration, but this relationship was less reliable. In this study, there was no relationship between the use of G-CSF and the mortality associated with infection after the development of FEN [13]. We found that 31.8% of the patients were receiving primary G-CSF prophylaxis: No relationship between the use of primary G-CSF and mortality could be demonstrated, which is consistent with the literature.

The long duration of neutropenia during episodes not only facilitates the development of complications due to the long-term insufficiency of the immune system, but also leads to a dose reduction in subsequent chemotherapy and thus to the disruption of effective cancer treatment. The mean duration of neutropenia was 12 days in the study of Demirel et al., and 15 days in Mert et al [14,15]. The mean duration of neutropenia was shorter than in those studies. Özden et al. observed a short duration of neutropenia (mean 3.3 days) in their study similar to our study [16]. While no statistically significant difference was found in this study in the mean neutropenia duration between patients with hematological malignancies and patients with solid organ tumors, the neutropenia duration was significantly longer in patients with hematological malignancies in our study. Neutropenia duration is one of the factors that is directly associated with mortality [17,18]. We found that a prolonged neutropenia duration (longer than 10 days of neutropenia) was significantly associated with mortality ($p<0.001$). Ceken et al. reported that the duration of neutropenia was also a risk factor for mortality [19].

Leukocyte count, CRP, and procalcitonin had no effect on mortality or duration of neutropenia. On the other hand, there are

many publications in the literature reporting that CRP and procalcitonin are effective in predicting the course of FEN and mortality. A Turkish study by Sahin et al. showed that CRP was an important prognostic parameter in FEN episodes [20]. Another study conducted in hematological malignancies revealed that the procalcitonin measured on hour 24 and the CRP measured on hour 48 were helpful in detecting fungal infections. On the other hand a study found that CRP could be a better marker than procalcitonin in determining disease-related fever [21].

The focus of infection could not be detected by clinical, microbiological, and radiological methods in 24.5% of the episodes. Demirel et al. reported that the rate of clinically-proven infection was 36% [15]. Maybe the main reason why more clinically and microbiologically proven fever foci and fewer unknown fevers were seen in our study is that we have finest diagnostic tools now like procalcitonin, quicker CT scan, ultrasound, cultures etc.

The most common infection focus detected was pneumonia at 27.1%. In studies conducted on hematological and oncological patients, the rate of pneumonia was 12.3% and 18.6% [9,22]. Our study was conducted during the COVID-19 pandemic, and imaging studies were performed more frequently during episodes. Thorax CT was performed in 64.8% of the patients, and pneumonia was found in 46.5% of the images. Therefore, patients in our series may have been diagnosed with pneumonia more frequently.

An uprising of gram-positive infections was reported after the 2000s [23,24,25]. Gram negative infections are much more commonly reported lately [26,27]. This is consistent with our findings. It is known that the presence of mucositis is an important risk factor for the predominance of gram-positive micro-organisms [28,29]. Safia et al. found that the incidence of mucositis was 50% [30]. Similarly, the rate of mucositis was 36% in a multicenter Spanish study conducted by Aguilar-Guisada [31]. In our study, mucositis was present in 17% of FEN episodes. Reducing the incidence of mucositis with appropriate oral care in our center may have reduced the incidence of FEN episodes caused by gram-positive bacteria.

Bacteremia was significantly more frequent in patients with hematological malignancies than in patients with solid organ tumors. Patients with hematological malignancies are usually treated with high-dose cytotoxic chemo-therapy regimens: Thus, the length of hospitalization is longer, and immuno-suppression is deeper, which causes a high risk of bacteremia [32]. In support of this, the rate of bacteremia in our study was higher in patients with deep neutropenia at day zero versus those without. A Turkish study examined 164 FEN cases, and found that the rate of bacteremia was higher in the group with deep neutropenia at the beginning33. Although it is known that prolonged neutropenia increases the risk of bacteremia, no relationship between prolonged neutropenia and bacteremia was found in our study [34].

One of the most important factors reducing mortality in FEN is the rapid initiation of empirical antibiotic therapy [35]. Mono-therapy was started as the initial treatment in 68.7% of the episodes. A review of the literature identified studies showing that monotherapy has similar efficacy to combination therapy and is even more advantageous because it has fewer side effects [36,37,38]. We found that the mortality rate in the group in which combination therapy was initiated was higher than that in the monotherapy group. The need for glycopeptide group antibiotics in the clinical evaluation at the beginning of the treatment suggests that the clinical situation in these patients is severe. The cause of mortality depends on the severity of the patient's FEN attack rather than the inadequacy of the combination therapy.

Invasive fungal infections (IFI) are important causes of morbidity and mortality in febrile neutropenic patients and other immuno-compromised populations after intensive chemotherapy [39]. Candidemia was

observed in three FEN episodes (1.7%) in our study. Goldberg et al. showed in a systematic review that empirical treatment did not significantly reduce mortality but reduced IFIs [40]. In our study, antifungal treatment was started in 21% (n=37) of the patients. Mortality was statistically higher in the group that received antifungal therapy than in those who did not. This proves that the mortality of invasive fungal infection is high even with appropriate treatment protocols.

Limitations

Our study has several limitations. First, the empirical treatment change rates were high in episodes. The reasons for these treatment changes in patients could not be investigated. Second, we could not reported data regarding susceptibility patterns and colonization. Third, we could not report etiological data for pneumonia which was the major cause of death in the study. Furthermore, the single-center limited the study population. Multicenter studies can offer more detailed results.

Conclusion

We prospectively examined the clinical and laboratory findings of FEN episodes in patients with hematological and solid malignancies and found that the frequency of pneumonia increased in FEN. The mortality associated with pneumonia was high, and gram-negative microorganisms were more common in the causative profile. The increasing rates of resistance in gram-negative microorganisms worldwide have brought this agent profile change to an alarming level. For better management of the process in FEN episodes, centers should know their own causative pathogen profiles and antibiotic susceptibilities and develop treatment algorithms accordingly.

REFERENCES

1. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis 2005; 40: 246-252.
2. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580-637.
3. Demiraslan H, Yıldız O, Kaynar L, Altuntaş F, Eser B, Aygen B. Febril nötropenik hastalardan izole edilen mikroorganizmalar ve antimikrobiyal duyarlılıkları: 2005 yılı verileri. Erciyes Tıp Dergisi. 2007; 29: 376–380.
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52: 427-431.
5. Sigurdardottir K, Digranes A, Harthug S, et al. A multi-centre prospective study of febrile neutropenia in Norway: microbiological findings and antimicrobial susceptibility. Scand J Infect Dis 2005; 37: 455-464.
6. Deniz Yayla B, Azak E, Mutlu B, Dündar D. Febril nötropenik hastalardan izole edilen mikroorganizmaların dağılımı ve antimikrobiyal duyarlılıkları: Altı yıllık bir gözlemin sonuçları. Klimik Dergisi. 2019; 32: 71–77.
7. Ghosh S, Chakraborty M, Samanta S, et al. Analysis of blood stream infections, antibiograms and clinical outcomes in haematological patients with febrile neutropenia: data from a tertiary care haematology institute in India. Ann Hematol 2021; 100: 395-403.
8. Al-Tawfiq JA, Hinedi K, Khairallah H, et al. Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. J Infect Public Health. 2019; 12: 364-366.
9. Hatamabadi H, Arhami Dolatabadi A, Akhavan A, Safari S. Clinical Characteristics and Associated Factors of Mortality in Febrile Neutropenia Patients; a Cross Sectional Study. Arch Acad Emerg Med 2019; 7: 39.
10. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006; 106: 2258-2266.
11. Hosmer W, Malin J, Wong M. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer. 2011; 19: 333-341.
12. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Version 3.2021: Hematopoietic Growth Factors. http://www.nccn. org. 2021.

13. Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database Syst Rev 2012; 10: CD007913.
14. Mert D, Ceken S, Iskender G, et al Epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies. J Infect Dev Ctries 2019; 13: 727-735.
15. Demirel A, Tabak F, Ar MC, et al. Secondary Infections in Febrile Neutropenia in Hematological Malignancies: More Than Another Febrile Neutropenic Episode. Turk J Haematol 2015; 32: 243-50.
16. Özden M, Denk A, Demirağ K, Elkıran T. Febril Nötropenik Olgular ve Risk Faktörlerinin Değerlendirilmesi. Mediterr J Infect Microb Antimicrob 2013; 2: 1–7.
17. Bulut N, Kiki I, Sincan G, Yıldırım R, Polat M, Bilen Y, Gündogdu M. Akut myeloid lösemili hastalarda indüksiyon kemoterapisi sonrası gelişen nötropeni süresini etkileyen faktörler. Abant Tıp Dergisi. 2015; 4: 371–377.
18. Dale DC. Advances in the treatment of neutropenia. Curr Opin Support Palliat Care. 2009; 3: 207-212.
19. Ceken S, Gedik H, Iskender G, et al Evaluation of Risk Factors for Mortality in Febrile Neutropenia. J Infect Dev Ctries 2020; 14: 886-892.
20. Şahin S, Gençer S, Doğan M, Demirhan G, Özer S. Febril nötropenik olgularımızda C-reaktif proteinin infeksiyon ve mortalite göstergesi olarak incelenmesi. Flora. 2009; 14: 72–80.
21. Halder R, Seth T, Chaturvedi PK, et al. Comparison of CRP and procalcitonin for etiological diagnosis of fever during febrile neutropenia in hematology patients- an experience from a tertiary care center in Northern India. Blood Cells Mol Dis 2020; 84: 102445.
22. Parodi RL, Lagrutta M, Tortolo M, et al A multicenter prospective study of 515 febrile neutropenia episodes in Argentina during a 5-year period. PLoS One. 2019; 14: e0224299.
23. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. Virulence. 2016; 7: 280–297.
24. Eslami Nejad Z, Ghafouri E, Farahmandi-Nia Z, Kalantari B, Saffari, F. Isolation, Identification, and Profile of Antibiotic Resistance of Bacteria in Patients with Cancer. Iranian Journal of Medical Sciences. 2010; 35: 109-115.
25. Meidani M, Bagheri A, Khorvash F. A population-based study of bacterial spectrum in febrile neutropenic patients. Jundishapur J Microbiol 2013; 6:150–156.
26. Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile Neutropenia in Hematological Malignancies: Clinical and Microbiological Profile and Outcome in High Risk Patients. J Lab Physicians. 2015; 7:116-120.
27. Babu KG, Lokanatha D, Lakshmaiah KC, et al. Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. Indian J Med Paediatr Oncol 2016; 37: 174-182.
28. Hansen BA, Wendelbo Ø, Bruserud Ø, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. Mediterr J Hematol Infect Dis 2020; 12: e2020009.
29. van der Velden WJ, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol 2014; 167: 441-452.
30. Safia M, Khanfir A, Maalej-mezghani S, Hammami A, Frikha M. Chemotherapy-induced febrile neutropenia: About 186 episodes. Clinical, microbiological and therapeutic characteristics. La Tunisie Medicale. 2015; 93: 217–222.
31. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematology 2017; 4: e573-e583.
32. Rasmy A, al Mashiakhi M, Ameen A. Chemotherapy-induced febrile neutropenia in solid tumours. Gulf J Oncolog 2017; 1: 77–84.
33. Calik S, Ari A, Bilgir O, Cetintepe T, Yis R, Sonmez U, Tosun S. The relationship between mortality and microbiological parameters in febrile neutropenic patients with hematological malignancies. Saudi Med J 2018; 39: 878-885.
34. Menichetti F. Infectious complications in neutropenic cancer patients. Intern Emerg Med 2010; 5: 21–25.
35. Clarke RT, Warnick J, Stretton K, Littlewood TJ. Improving the immediate management of neutropenic sepsis in the UK: lessons from a national audit. Br J Haematol 2011; 153: 773-779.
36. Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, Tanimoto M, Masaoka T; Japan Febrile Neutropenia Study Group. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. Clin Infect Dis 2004; 39: 15-24.
37. Castagnola E, Mikulska M, Viscoli C. Prophylaxis and Empirical Therapy of Infection in Cancer Patients. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015: 3395–3413.e2.
38. Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta- lactam versus beta-lactam-aminoglycoside combination therapy

in cancer patients with neutropenia. Cochrane Database Syst Rev 2013; 2013: CD003038
39. Slobbe L, Polinder S, Doorduijn JK, Lugtenburg PJ, el Barzouhi A, Steyerberg EW, Rijnders BJ. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia- myelodysplastic syndrome treated with intensive chemotherapy: an observational study. Clin Infect Dis 2008; 47: 1507-1512.
40. Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. European Journal of Cancer. 2008; 44: 2192–2203.

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Doi: 10.5505/aot.2023.79990

Original Article

Naples Score May Predict Overall Survival in Metastatic Gastric Cancer and is Superior to CONUT

Naples Skoru Metastatik Mide Kanserinde Genel Sağkalımı Öngörebilir ve CONUT'a Üstündür

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ABSTRACT

Introduction: Gastric adenocarcinoma (GC) is a common malignancy with a poor prognosis. There is a need for prognostic markers to assist treatment decisions in GC. Naples prognostic score (NPS) and controlling nutritional status (CONUT) score are immune-nutritional scores that predict outcomes in different early-stage tumours. Data on the performance of these in metastatic GC are scarce. We evaluated the relationship of CONUT and NPS with prognosis in patients with metastatic GC.
Materials and methods: We retrospectively analysed 201 patients who received first-line platinum-based chemotherapy for metastatic GC between 2017-2021. NPS and CONUT were calculated depending on the pre-treatment laboratory. Overall survival (OS) analyses were performed regarding NPS and CONUT.
Results: Median survival negatively correlated with NPS and CONUT. Clinical parameters that may be associated with OS were evaluated. Liver metastases were associated with shorter survival, while peritoneal involvement did not. Tumour differentiation was not associated with OS. In the univariate analysis, the number of metastatic foci, the presence of hepatic metastases, increased Ca19-9, decreased albumin levels, extraperitoneal metastatic disease, NPS, and CONUT were associated with lower OS. Age, gender, tumour differentiation ECOG, and CEA levels did not affect survival. In multivariate analyses, lower albumin, higher Ca19-9, hepatic metastases, and NPS (OR:2.9) were independently associated with shorter survival. CONUT did not have an effect on OS in multivariate analysis.
Discussion: Among immuno-nutritional scores, CONUT and NPS, predict poor prognosis in metastatic GC patients. The NPS seems superior to the CONUT.

Keywords: Metastatic Gastric Cancer; Naples; CONUT; overall survival

ÖZET

Giriş: Gastrik adenokarsinom (GK), sık görülen ve kötü prognoza sahip bir malignitedir. GK'de tedavi kararlarına yardımcı olmak için prognostik belirteçlere ihtiyaç vardır. Naples prognostik skoru (NPS) ve beslenme durumunun kontrol edilmesi (CONUT) skoru, farklı tümörlerde prognoz ile ilişkili immün-beslenme skorlarıdır. Bunların metastatik GK'deki performansına ilişkin veriler ise azdır. Metastatik GK'li hastalarda CONUT ve NPS'nin prognoz ile ilişkisini değerlendirdik.
Gereç ve yöntemler: 2017-2021 yılları arasında metastatik GC için birinci basamak platin bazlı kemoterapi alan 201 hastayı geriye dönük olarak analiz ettik. Tedavi öncesi laboratuvar sonuçları değerlendirilerek NPS ve CONUT skorları hesaplandı. NPS ve CONUT ile ilgili genel sağkalım (OS) analizleri yapıldı.
Bulgular: Medyan sağkalım, NPS ve CONUT ile negatif korelasyona sahipti. OS ile ilişkili olabilecek klinik parametreler değerlendirildi. Karaciğer metastazları daha kısa sağkalım ile ilişkiliyken, peritoneal

First Received: 29.05.2023, Accepted: 16.06.2023 doi: 10.5505/aot.2023.80269

tutulum bunu göstermedi. Tümör farklılaşması OS ile ilişkili değildi. Tek değişkenli analizde, metastatik odakların sayısı, hepatik metastazların varlığı, artmış Ca19-9, azalmış albümin seviyeleri, ekstraperitoneal metastatik hastalık, NPS ve CONUT, daha düşük OS ile ilişkiliydi. Yaş, cinsiyet, tümör farklılaşması ECOG ve CEA seviyeleri sağkalımla ilişkili değildi. Çok değişkenli analizlerde, daha düşük albümin, daha yüksek Ca19-9, hepatik metastazlar ve NPS (OR:2.9) bağımsız olarak daha kısa sağkalım ile ilişkilendirildi. CONUT, çok değişkenli analizde OS üzerinde bir etkiye sahip değildi.
Tartışma: İmmüno-beslenme skorları arasında CONUT ve NPS, metastatik GK hastalarında kötü prognozu öngörür. Bu açıdan NPS, CONUT'tan üstün görünmektedir.

Anahtar kelimeler: Metastatik Gastrik Kanser; Naples; CONUT; Genel sağkalım

Introduction

Gastric adenocarcinoma (GC) is one of the most common malignancies with a poor prognosis. Although the incidence of GC has decreased compared to previous decades, it is among the leading causes of cancer-related deaths worldwide [1]. 5-year survival is below 30% due to high case fatality rates [2, 3]. There are regional differences in the prevalence and mortality of GC. Turkey is among the countries with high GC-related mortality [4]. Surgical resection is the curative treatment modality in patients with early-stage disease. However, patients with metastases at the time of diagnosis are unsuitable for surgery, and the expected survival is less than one year [5]. In parallel with the introduction of new biomarkers and treatment options, significant advances have been made in treating metastatic malignancies in the last decade. On the other hand, the treatment of GC needs further progress in this regard, given the poor prognosis of metastatic disease. There is also a need for better prognostic and/or predictive biomarkers to assist in making appropriate treatment decisions in GC.

The immune response, and thus associated systemic inflammatory markers, are associated with survival in different types of cancer. The prognostic significance of scores based on systemic inflammation has been investigated in cancers of different origins, such as lung, oesophagus, colorectal, and kidney, in recent years [6-8]. Also, in addition to inflammatory scores, some scores consider the negative effects of malnutrition on survival. Some of these inflammation or malnutrition-based scores can be listed as Glasgow Prognostic Score, CRP-based prognostic index, neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio, and controlling nutritional status (CONUT) score [9, 10]. We recently demonstrated the association of the Naples prognostic score (NPS) with survival in metastatic pancreatic carcinoma [11].

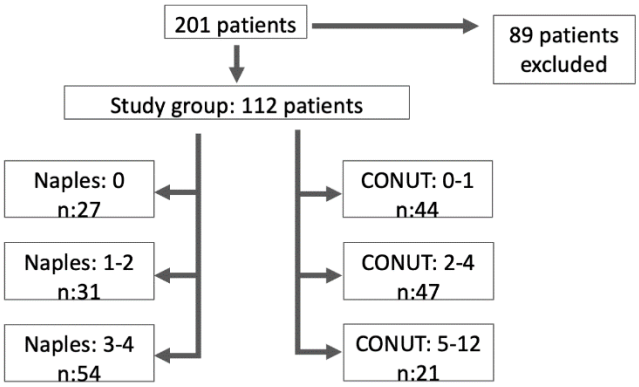
NPS was developed as a scoring system that assesses systemic inflammatory burden and malnutrition based on serum albumin, total cholesterol, lymphocyte-monocyte ratio (LMR), and NLR. NPS calculated before surgical treatment is associated with surgical outcomes in GC [12]. On the other hand, data on the prognostic, predictive power of immuno-nutritional scores in patients with metastatic disease are still scarce. Therefore, we aimed to evaluate the relationship of immuno-nutritional scores CONUT and NPS with prognosis in patients with metastatic GC who received first-line chemotherapy and the power of these scores to predict overall survival.

Material and methods

Patient group

The study was conducted in a tertiary referral centre in Turkey's largest city. We retrospectively analysed 201 consecutive patients who received first-line platinum-based chemotherapy for newly diagnosed metastatic GC between 2017 and 2021. Regarding treatment-related effects, only patients receiving FOLFOX chemotherapy were included in the study to ensure the homogeneity of study results.

Exclusion criteria for the study can be listed as follows: concomitant infectious processes,



Naples Score Factor Points		
Serum albumin, mg/dL	≥4	0
	<4	1
Total cholesterol, mg/dL	>180	0
	≤180	1
Neutrophil:lymphocyte ratio	>2.96	0
	≤2.96	1
Lymphocyte:monocyte ratio	>4.44	0
	≤4.44	1

CONUT Score Factor Points		
Serum albumin, mg/dL	≥3.5	0
	3-3.4.9	2
	2.5-2.9	4
	<2.5	6
Total cholesterol, mg/dL	≥180	0
	140-180	1
	100-139	2
	<100	3
Total lymphocyte (count/mm3)	≥1600	0
	1200-1599	1
	800-1199	2
	<800	3

Figure 1. Study design and patients according to Naples and CONUT groups. Factor points for Naples and CONUT scores

absence of laboratory parameters (complete blood count, serum albumin or total cholesterol levels) in the last two weeks before first-line chemotherapy, GC treatment other than the specified chemotherapy regimen, patients with insufficient follow-up data, and patients continuing their treatment in different centres. Eighty-nine patients who did not meet these criteria were excluded from the study. Accordingly, 112 patients were included in the final analysis (Figure 1). The local ethics committee approved the study protocol and was in accordance with the Declaration of Helsinki.

Data collecting

Values from the last 2 weeks before the start of chemotherapy were used as laboratory data. The parameters evaluated were: CA19-9 and CEA levels, serum albumin, total cholesterol, absolute neutrophil count, lymphocyte count, and monocyte count; NLR and LMR were calculated using these. To determine sub-scores of NPS parameters: Albumin concentration ≥4.0 g/dL was scored as 0, <4.0 g/dL as 1; total cholesterol >180 mg/dL as 0, ≤180 mg/dL as 1; NLR >2.96 as 0, NLR ≤2.96 as 1; LMR >4.44 was scored as 0 and LMR ≤4.44 as 1 (Figure -1). NPS was then calculated as the sum of the above-mentioned scores ranging from 0 to 4. Finally, the patients were divided into three groups based on their NPS scores: 0 points - group 1, 1 or 2 points - group 2, 3 or 4 points - group 3.

The CONUT score was calculated as the sum of albumin, cholesterol, and lymphocyte scores; albumin score (≥ 3.5 g/dL as 0; 3.0–3.49 g/dL as 2; 2.50–2.99 g/dL as 4; <2.50 g/dL as 6), total cholesterol score (≥180 mg/dL as 0; 140–179 mg/dL as 1; 100–139 mg/dL as 2; <100 mg/dL as 3), and lymphocyte score (≥1.6 103 /mm3 as 0; 1.20–1.59 103 /mm3 as 1; 0.80–1.19 as 2 g/L; <0.8 103 /mm3 as 3) (Figure 1)[13]. Patients were grouped according to their CONUT scores; scores 0-1: 1st group; scores 2-4: group 2 and 5-12: group 3[9]. In addition, the total number of metastatic sites, liver metastases, or peritoneal involvement of the patients was

Table 1. Demographic characteristics, laboratory parameters, and prognostic factors of the study groups

	Whole Group (n:112)	Naples 0 (n:27)	Naples 1-2 (n:31)	Naples 3-4 (n:54)	*p*	CONUT 0-1(n:44)	CONUT 2-4 (n:47)	CONUT 5-12(n:21)	p
Demography									
Sex (F%(n))	22.3 (25)	25.9	19.4	22.2	0.83	18.2	29.8	14.3	0.25
Age	60.1 (±10)	60.5(±9.4)	61(±10.3)	56.9 (±9.6)	0.22	61.3(±9.7)	59.4(11.3)	56.7(±6.9)	0.29
Age >65	34.8(39)	18.5	35.5	42.6	0.10	36.4	27.7	47.6	0.27
Ecog performance status									
0	10.7(12)	14.8	6.5	11.1		15.9	4.3	14.3	
1	71.4(80)	55.6	77.4	75.9	0.27	68.2	72.3	76.2	0.28
2-3	17.9 (20)	29.6	16.1	13		15.9	23.4	9.5	
Differentiation									
Poor	75.9	70.4	74.2	79.6	0.22	70.5	87.2	61.9	0.04
Metastasis									
Focus n	2(1)	1(2)	2(1)	2(1)	0.38	2(2)	2(2)	2(2)	0.44
Liver	43.8(49)	29.6	54.8	44.4	0.15	43.2	40.4	52.4	0.65
Peritoneal	54.5 (61)	85.2	48.4	42.6	<0.001	54.5	59.6	42.9	0.44
Laboratory									
Hgb	11.2 (±2.1)	12.3(±1.8)	11.3(±2.6)	10.7(±2)	0.08	11.7(±2)	11.1(±2.7)	10.8(±1.1)	0.13
Albumin	3.9(0.6)	4.1(0.3)	4 (0.5)	3.7(0.5)	<0.001	4.1(0.4)	3.9(0.7)	3.5 (1)	<0.001
C19-9	16.8(55.8)	44(83)	20 (127)	16.3(65)	0.137	16.6(49)	19.5(82)	15(80)	0.55
CEA	3.7 (21.2)	2.2(6)	2.8(5)	4.1(18.3)	0.03	3.1(21)	3.8(12)	5.8 (31)	0.81
OS	15 (19)	32(11)	16(6)	9(7)	<0.001	18(13)	11(16)	10 (7)	<0.001

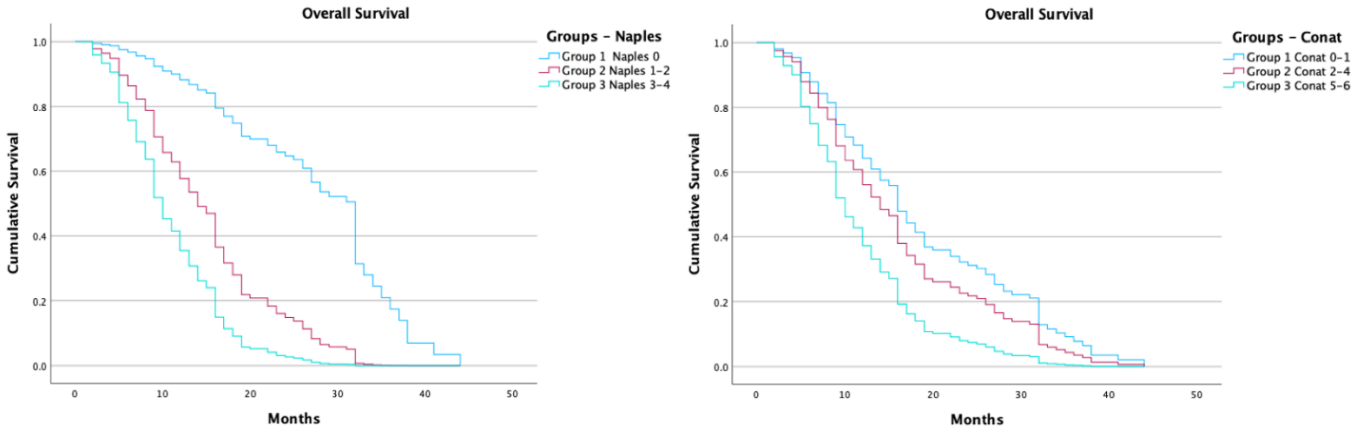


Figure 2. Overall survival of patients according to Naples (0; 1-2; 3-4) and CONUT (0-1; 2-4; 5-12) groups (Naples: Log Rank p<0.001; CONUT: Log Rank p:0.007)

noted. The overall survival (OS) was defined as the time from initiation of first-line chemotherapy to death (if happened) for each patient.

Statistical analysis

Parametric data were expressed as mean (standard deviation), and non-parametric data as median (distribution range). Non-parametric data comparisons between groups were made using independent sample tests, Kruskal-Wallis, and Mann-Whitney U tests. Survival analysis was performed by the Kaplan-Meier method using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Prognostic variables identified by univariate analysis with a $p < 0.1$ value were also evaluated by multivariate analysis. A $p<0.05$ value was accepted for statistical significance. IBM-SPSS v.29 program was used for statistical analysis.

Results:

Our study examined the overall survival and associated prognostic markers of 112 metastatic gastric adenocarcinoma patients who received first-line chemotherapy. 22.3% of the patient group was female, and we found the mean age to be 60.1. The median survival in the whole group was 15 months. Table- I summarises the demographic characteristics, laboratory parameters, and prognostic factors of the study group. The median number of metastasis foci of the patients in the study group was 2. Liver metastasis was observed in 43.8% of the patients, and peritoneal involvement was observed in 54.5% of the patients. Three-quarters of the patients had tumours showing poor differentiation.

Our study examined Naples and CONUT scores in terms of immuno-nutritional prognostic scores. We created three groups for each score. NPS 0 was defined as group 1 (n:27), NPS 1-2 group 2 (n:31), and NPS 3-4 group 3 (n:54). Similarly, CONUT 0-1 (n:44), CONUT 2-4 (n:47), CONUT 5-12 (n:21) were evaluated as three separate groups. Demo--graphic, laboratory, and clinical charac-teristics according to prognostic groups are summarised in Table - I. There was no difference between the NPS and CONUT groups in terms of demographic charac-teristics and ECOG performances of the patients (Table -1). Tumours with poor differentiation were significantly more common in the CONUT 2-4 group (87.2% vs 70.5-61.9; p: 0.04). Peritoneal involvement was found more frequently among the groups in the NPS 0 group (85.2% vs 48.4-42.6; p:<0.001). There was no difference between the groups regarding liver metastasis and the number of metastasis foci. Within the laboratory parameters, albumin decreased proportionately to the increasing scores for both (p<0.001). There was a significant difference in CEA levels between NPS groups (2.2 ng/mL - 2.8 - 4.1; p:0.03). Although haemoglobin values showed a decreasing

trend in parallel with increasing prognostic scores, the difference did not reach statistical significance (NPS p: 0.08; CONUT p: 0.13)

Median survival was negatively correlated with increasing scores in both NPS and CONUT groups (both p<0.001). The median survival was found to be 32-16-9 months in the NPS groups and 18-11-10 months in the CONUT groups, respectively. Clinical parameters that may be associated with patients' overall survival were evaluated by Kaplan-Meier analysis. There was no difference between ECOG performance scores and overall survival (Log Rank p:0.08). A significant relation was found between NPS groups and overall survival (Log Rank p<0.001); similarly, CONUT groups were also associated with survival (Log Rank p:0.007) (Figure 2). Liver metastases were associated with shorter survival (Log Rank p:0.004). Peritoneal involvement of metastatic disease showed a better prognosis than extraperitoneal metastatic disease (Log Rank p:0.008) (Figure 3). Tumour differentiation was not associated with overall survival (Log Rank p: 0.564).

We also analysed the parameters that may be related to overall survival by multivariate Cox regression analysis (Table –2). In the univariate analysis, the number of metastatic foci, the presence of hepatic metastases, increased Ca19-9 levels, decreased albumin levels, extraperitoneal metastatic disease, and both NPS (3-4) and CONUT (5-12) prognostic scores were associated with lower overall survival. Age, gender, tumour differentiation ECOG performance status, and CEA levels did not affect survival. In multivariate analyses, lower albumin, higher Ca19-9 levels, presence of hepatic metastases, and NPS (3-4) (OR:2.9) were found to be independently associated with shorter survival. CONUT (5-12) did not have a significant effect on overall survival in multivariate analysis (p:0.373)

Discussion:

Our study showed that scores evaluating the immuno-nutrition status before first-line chemotherapy can predict prognosis in patients with metastatic GC. The NPS score seems superior to the CONUT score in this respect. This association of NPS score with prognosis in patients with metastatic GC unsuitable for surgery is a novel contribution to the literature.

Many studies show that immune response and nutritional state are associated with malignancy. This has led to the research and development of new biomarkers or immune and nutrition-based prognostic scoring systems [14]. GC ranks among the top in cancer-related deaths worldwide [4]. The prognosis in metastatic patients is quite poor. The nutritional status of these patients is generally poor due to gastrointestinal involvement and cachexia of malignancy. This and the impaired immune response may be among the reasons for the shorter survival we encounter in these patients [15].

The inflammatory response in the tumour microenvironment may exert a role in the destruction of tumour cells, and angiogenesis. Thus, they may modify the response of tumours to radiotherapy and chemotherapy. Lymphocytes play a major role in this immune response. Lymphopenia is associated with adverse reactions and poor prognosis in many tumours, including GC [16, 17]. On the other hand, increased tumoural neutrophil infiltration generally has poor clinical outcomes. Neutrophils may participate actively in tumorigenesis by some cytokines, inducing tumor cell proliferation and even metastasis [18, 19]. Therefore, NLR and LMR have been evaluated in many studies, and increasing NLR and decreasing LMR are generally associated with worse outcomes [20].

Malnutrition is closely associated with angiogenesis and tumour growth, thus with disease progression. The serum albumin concentration is one of the important markers of nutritional status and inflammatory load as a negative acute phase reactant. Hypoalbuminemia is often associated with worse outcomes in various tumors[21]. Similarly, our study showed that hypoalbuminemia is related to poor prognosis

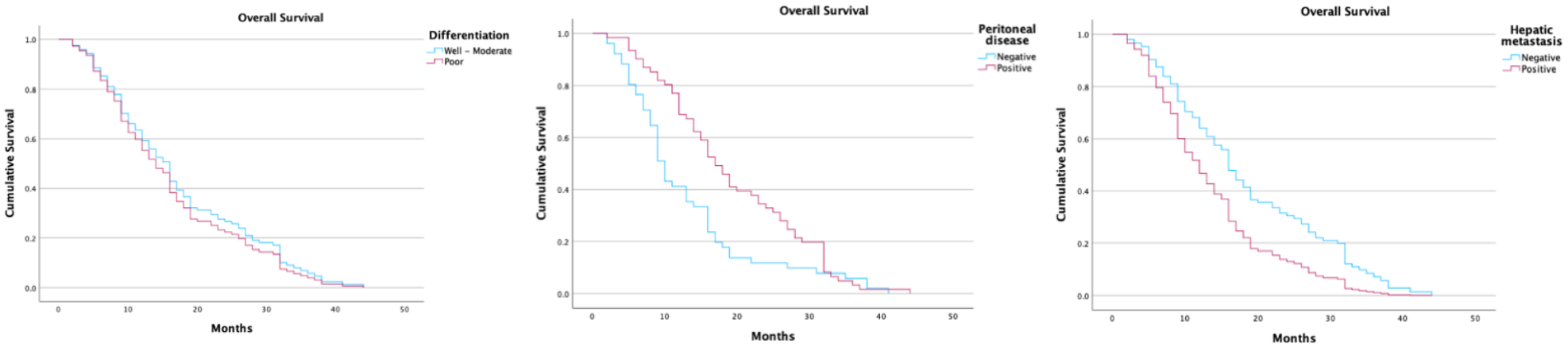


Figure 3. Overall survival of patients according to peritoneal and hepatic metastasis status (Log Rank p:0.008, p:0.004 respectively)

Table 2. Univariate and multivariate factors associated with overall survival

	Univariate	*p*	Multivariate	*p*
Age	1.007 (0.988-1.026)	0.488		
Age>65	1.301(0.876-1.933)	0.192		
Sex (M)	1.109 (0.706-1.742)	0.652		
Differentiation (poor)	1.133 (0.727-1.767)	0.577		
Number of Metastatic foci	1.272 (1.024-1.582)	0.03	1.292 (0.947-1.762)	0.106
Hepatic metastasis	1.714 (1.161-2.532)	0.007	1.744 (1.025-2.968)	0.04
Peritoneal disease	0.613 (0.418-0.897)	0.012	0.701 (0.454-1.089)	0.111
Ca19-9	1.0002 (1-1)	0.02	1 (1-1)	0.022
CEA	1 (1-1)	0.329		
Albumin (-)	2.272 (1.461-3.533)	<0.001	2.331 (1.230-4.424)	0.010
Ecog (2-3)	1.410 (0.861-2.309)	0.172		
CONUT (5-12)	1.967 (1.204-3.212)	0.007	1.328 (0.711-2.475)	0.373
Naples (3-4)	3.784 (2.501-5.726)	<0.001	2.983 (1.849-4.812)	<0.001

in metastatic GC [22]. In addition to albumin, cholesterol level also provides information about nutritional status, and low cholesterol levels are associated with a poor prognosis[23]. For these reasons, the nutritional status scores include albumin and cholesterol levels.

The right treatment options can be selected by accurately demonstrating the patient's immune and nutritional status. Studies have pointed out that laboratory parameters like low lymphocyte count and low serum albumin level are associated with poor prognosis of various tumours. Thus, integrating multiple parameters into a compound model has the potential to significantly improve the prognostic value [24, 25]. The scoring system, formed by combining nutritional and immune indicators, can effectively reflect patients' condition and estimate the prognosis with better accuracy. CONUT and NPS scores can be listed among these scores. The CONUT score is calculated using lymphocyte count, albumin and total cholesterol concentration. A high CONUT score represents a weak immune-nutritional state. 26147805. NPS is an index of serum albumin concentration, total cholesterol concentration, LMR, and NLR, and has proven to be an indicator of OS in various tumours [11, 26]. NPS and CONUT are among the most used scoring systems.

There are studies evaluating immune-nutritional scores such as NPS-CONUT scores for surgical success and long-term survival in patients with respectable tumours. However, there is scarce literature on the relationship between immune-nutritional scores with survival and which score is better in metastatic GC. NPS and CONUT are practical scores that can be easily calculated in outpatient conditions. In many ways, they represent the overall inflammatory burden and nutritional status of patients with metastatic GC. In our study, we showed that both NPS and CONUT can predict survival before first-line chemotherapy in metastatic GC patients when we evaluated them separately. Although both scores can be used in this sense, we have shown that NPS is superior in predicting prognosis in patients with metastatic GC. In our patient group, the presence of liver metastases and the number of metastatic foci were the other parameters related to survival. The relatively good prognosis of patients with peritoneal metastases may be because they are considered metastatic but do not have solid organ-liver metastases. On the other hand, among tumor markers, CA 19-9 also seem to be associated with prognosis per the literature. In multivariate regression analyses, CA19-9, serum albumin level, presence of liver metastases, and NPS score were found to be independently associated with prognosis, suggesting that this score is superior to CONUT in metastatic GC patients.

The contribution of immuno-nutritional scores in predicting the prognosis of metastatic GC and the superiority of NPS score over CONUT in this regard can be listed as the contribution of our study to the literature. Among its shortcomings, retrospective design and our inability to examine the prognostic importance of nutritional support can be listed. Another point is that our study group consisted of patients who received conventional first-line chemotherapy. This design prevents us from evaluating the prognostic significance of these scores in metastatic GC patients receiving immunotherapy.

In conclusion, CONUT and NPS, which evaluate the immuno-nutritional status calculated before first-line chemotherapy, predict poor prognosis in metastatic GC patients. The NPS seems superior to the CONUT in this respect.

REFERENCES

1. Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clin Gastroenterol Hepatol. 2020; 18(3): 534-542.
2. Asplund J, Kauppila JH, Mattsson F, Lagergren J. Survival Trends in Gastric Adenocarcinoma: A Population-Based Study in Sweden. Ann Surg Oncol. 2018; 25(9): 2693-2702.
3. Dassen AE, Lemmens VE, Van De Poll-Franse LV, Creemers GJ, Brenninkmeijer SJ, Lips DJ, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer. 2010; 46(6): 1101-1110.
4. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019; 14(1): 26-38.
5. Digklia A, Wagner AD. Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol. 2016; 22(8): 2403-2414.
6. Ramsey S, Lamb GW, Aitchison M, Graham J, Mcmillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer. 2007; 109(2): 205-212.
7. Forrest LM, Mcmillan DC, Mcardle CS, Angerson WJ, Dagg K, Scott HR. A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2005; 92(10): 1834-1836.
8. Mcmillan DC, Canna K, Mcardle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg. 2003; 90(2): 215-219.
9. Daitoku N, Miyamoto Y, Tokunaga R, Sakamoto Y, Hiyoshi Y, Iwatsuki M, et al. Controlling Nutritional Status (CONUT) Score Is a Prognostic Marker in Metastatic Colorectal Cancer Patients Receiving First-line Chemotherapy. Anticancer Res. 2018; 38(8): 4883-4888.
10. Dolan RD, Mcsorley ST, Horgan PG, Laird B, Mcmillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017; 116: 134-146.
11. Gulturk I, Yilmaz M, Tacar SY, Bakkaloglu OK, Sonmezoz GB, Erdal GS, et al. Naples prognostic score may predict overall survival in metastatic pancreatic cancer. Journal of Cancer Research and Therapeutics. 9000.
12. Galizia G, Auricchio A, De Vita F, Cardella F, Mabilia A, Basile N, et al. Inflammatory and nutritional status is a predictor of long-term outcome in patients undergoing surgery for gastric cancer. Validation of the Naples prognostic score. Ann Ital Chir. 2019; 90: 404-416.
13. Ignacio De Ulibarri J, Gonzalez-Madrono A, De Villar NG, Gonzalez P, Gonzalez B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp. 2005;20(1):38-45.
14. Zheng X, Li L, Yu C, Yang J, Zhao Y, Su C, et al. Establishment of a tumor immune microenvironment-based molecular classification system of breast cancer for immunotherapy. Aging (Albany NY). 2021;13(21):24313-24338.
15. Ramos M, Pereira MA, De Castria TB, Ribeiro RRE, Cardili L, De Mello ES, et al. Remnant gastric cancer: a neglected group with high potential for immunotherapy. J Cancer Res Clin Oncol. 2020; 146(12): 3373-3383.
16. Eberst G, Vernerey D, Laheurte C, Meurisse A, Kaulek V, Cuche L, et al. Prognostic value of CD4+ T lymphopenia in non-small cell lung Cancer. BMC Cancer. 2022; 22(1): 529.
17. Tatara T, Suzuki S, Kanaji S, Yamamoto M, Matsuda Y, Hasegawa H, et al. Lymphopenia predicts poor prognosis in older gastric cancer patients after curative gastrectomy. Geriatr Gerontol Int. 2019; 19(12): 1215-1219.
18. Xia X, Zhang Z, Zhu C, Ni B, Wang S, Yang S, et al. Neutrophil extracellular traps promote metastasis in gastric cancer patients with postoperative abdominal infectious complications. Nat Commun. 2022; 13(1): 1017.
19. Guan X, Lu Y, Zhu H, Yu S, Zhao W, Chi X, et al. The Crosstalk Between Cancer Cells and Neutrophils Enhances Hepatocellular Carcinoma Metastasis via Neutrophil Extracellular Traps-Associated Cathepsin G Component: A Potential Therapeutic Target. J Hepatocell Carcinoma. 2021; 8: 451-465.
20. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg. 2011; 35(4): 868-872.
21. Hardt J, Pilz L, Magdeburg J, Kienle P, Post S, Magdeburg R. Preoperative hypoalbuminemia is an independent risk factor for increased high-grade morbidity after elective rectal cancer resection. Int J Colorectal Dis. 2017; 32(10): 1439-1446.
22. Ma LX, Taylor K, Espin-Garcia O, Anconina R, Suzuki C, Allen MJ, et al. Prognostic significance of nutritional markers in metastatic gastric and esophageal adenocarcinoma. Cancer Med. 2021; 10(1): 199-207.
23. Hirano H, Ide H, Lu Y, Inoue Y, Okada H, Horie S. Impact of Pretreatment Total Cholesterol Level Is Associated With Metastasis of Prostate Cancer. Am J Mens Health. 2020; 14(2): 1557988320918788.
24. Schueneman AJ, Sugar EA, Uram J, Bigelow E, Herman JM, Edil BH, et al. Low total lymphocyte count is associated with poor survival in patients with resected pancreatic adenocarcinoma receiving a GM-CSF secreting pancreatic tumor vaccine. Ann Surg Oncol. 2013; 20 Suppl 3(0 3): S725-730.

25. Lien YC, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, et al. Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. J Gastrointest Surg. 2004; 8(8): 1041-1048.

26. Nakagawa N, Yamada S, Sonohara F, Takami H, Hayashi M, Kanda M, et al. Clinical Implications of Naples Prognostic Score in Patients with Resected Pancreatic Cancer. Ann Surg Oncol. 2020; 27(3): 887-895.

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Doi: 10.5505/aot.2023.80269

Original Article

Clinical Importance of the Hemoglobin, Albumin, Lymphocyte, Platelet Score in Metastatic Pancreatic Cancer

Metastatik Pankreas Kanserinde Hemoglobin, Albümin, Lenfosit, Trombosit Skorunun Klinik Önemi

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ABSTRACT

Introduction: Pancreatic adenocarcinoma is one of the deadliest cancers. Effective, simple and practical methods that can be used in daily life are still lacking to predict the prognosis of patients with advanced pancreatic cancer and a promising biomarker is needed to predict prognosis. Our study's objective was to demonstrate the correlation between the HALP score and prognosis in patients with metastatic pancreatic cancer.

Methods: Patients diagnosed with metastatic pancreatic cancer from 4 centers in Turkey between 2016 and 2022 were included. Demographic data, hemogram parameters, biochemistry values, as well as the treatments received were recorded. Survivals were also recorded

Results: There were 280 patients in our study. The median PFS was 7.53 months, while the median OS was 11.53 months for the whole population. Median PFS was 7.1 months for the HALP-Low group and 14.8 months for the HALP-High group. The HALP-Low group exhibited a significantly shorter median progression-free survival (PFS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$). Median OS was 10.57 months for the HALP-Low group and 18 months for the HALP-High group. The HALP-Low group demonstrated a significantly shorter median overall survival (OS) compared to the HALP-High group, with a statistically significant difference between the two groups ($p<0.001$)

Discussion and Conclusion: In conclusion, the HALP score is an inexpensive, practical, literature-contributing marker and, if validated by prospective studies, can be used in routine clinical practice to predict the prognosis of patients with metastatic pancreatic cancer.

Keywords: HALP score, Overall survival, Metastatic Pancreatic cancer, Progression-free survival

ÖZET

Giriş ve Amaç: Pankreas adenokarsinomu en ölümcül kanserlerden biridir. Metastatik pankreas kanserli hastaların prognozunu tahmin etmek için günlük hayatta kullanılabilecek etkili, basit ve pratik yöntemler halen eksiktir ve prognozu tahmin etmek için umut verici bir biyobelirteç gerekmektedir. Çalışmamızda metastatik pankreas kanserinde HALP skorunun prognoz ile ilişkisini göstermeyi amaçladık.

First Received: 25.07.2023, Accepted: 28.08.2023 doi: 10.5505/aot.2023.26779

Yöntem ve Gereçler: 2016-2022 yılları arasında Türkiye'de 4 merkezden metastatik pankreas kanseri tanısı alan hastalar dahil edildi. Demografik veriler, hemogram parametreleri, biyokimya değerleri ve alınan tedaviler kaydedildi. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) da kaydedildi.
Bulgular: Çalışmamızda 280 hasta vardı. Tüm popülasyon için medyan PFS 7,53 aydı, medyan OS ise 11,53 aydı. Medyan PFS, HALP-Düşük grup için 7,1 ay ve HALP-Yüksek grup için 14,8 aydı. HALP-Düşük grubun median PFS'si HALP-Yüksek gruba göre daha kısaydı ve gruplar arasında istatistiksel olarak anlamlı bir fark vardı (p: <0,001).
Tartışma ve Sonuç: Sonuç olarak, HALP skoru ucuz, pratik, literatüre katkıda bulunan bir belirteçtir ve prospektif çalışmalarla doğrulanırsa, metastatik pankreas kanseri olan hastaların prognozunu tahmin etmek için rutin klinik uygulamada kullanılabilir.

Anahtar Kelimeler: HALP skoru, Genel sağkalım, Metastatik Pankreas kanseri, Progresyonsuz sağkalım

Introduction

Pancreatic ductal adenocarcinoma (PC) is a highly lethal cancer, responsible for 496,000 new cases and 466,000 deaths in the United States in 2018. It ranks as the 7th leading cause of cancer-related deaths. PC is increasing in both sexes and the median age at diagnosis is around 40 years [1]. Although surgery is a curative treatment option, 80% of patients are metastatic or locally advanced at the time of diagnosis [2]. Although chemo-therapy, immunotherapies and targeted therapies are being developed, 5-year survival is around 5% [3,4]. There is currently a lack of effective, straightforward, and feasible methods for predicting the prognosis of individuals with advanced pancreatic cancer, despite the existence of proto-oncogenes like BRCA and PALB2, as well as some molecular tests such as tumor mutation burden and a promising biomarker is needed to predict prognosis. Developments in the field of cancer and inflammation and the lack of biomarkers in patients with PC have led to the need for many studies.

The link between nutritional status and inflammation and cancer progression has been known for many years. Chronic inflammation accelerates the neovascularization process by increasing cytokines and this contributes to tumor growth [5,6]. Nutritional status contributes to prognosis by affecting the immune system through cytokines [7,8]. Cancer-related anemia is highly prevalent. In the presence of anemia, hypoxia occurs at the cellular level. This leads to genomic and proteomic changes (e.g. increased growth factors for example vascular endothelial growth factor). Thus, it increases tumor growth and metastasis potential [9]. Platelets are involved in inflammation-mediated cancer development through growth factors, chemokines and proinflammatory cytokines. It is known that thrombocytosis increases the metastasis potential and plays a poor prognostic role in many malignancies [10,11].

Recent research has demonstrated that hemoglobin, albumin, lymphocyte, platelet score (HALP score) has significant relevance in forecasting the development of renal cancer, non-small cell lung cancer (NSCLCL), gastric cancer, and small cell lung cancer. (SCLC) [12,15]. As far as we know, there have been no studies demonstrating the correlation between HALP score and prognosis in metastatic PC.

Our study aims to establish the association between HALP score and prognosis in metastatic PC.

Materials and Methods

Patients diagnosed with metastatic pancreatic cancer at Mardin Training and Research Hospital, Aydın Adnan Menderes University Hospital, Manisa Celal Bayar University, and Aydın Atatürk State Hospital between 2016 and 2022 were included. Patient records and hospital databases were examined for this

study. The patients' age, ECOG performance status, gender, comorbidities, hemoglobin at the time of metastasis, thrombocyte, lymphocyte, albumin and the treatments they received were recorded.

Patients with another malignancy, younger than 18 years of age, known hematologic disease, autoimmune disease, inflammatory bowel disease, history of steroid or anticoagulant use, non-metastatic patients whose data could not be securely accessed were excluded. HALP score had been calculated as × lymphocyte (/L) x albumin (g/L) x hemoglobin (g/L) / platelet count (/L). The cut-off for HALP score was determined as 0.6 with the X-tile program.

Statistical analyses were conducted using R version 2.15.3 (R Core Team, 2013). The study data were summarized using various descriptive statistics, including the minimum, maximum, first quartile, third quartile, median, mean, standard deviation, frequency, and percentage. These measures were utilized to provide a comprehensive overview and description of the study data. The normality of the quantitative data was assessed through the Shapiro-Wilk test and graphical analysis to determine if it followed a normal distribution. These methods were used to examine the distributional characteristics of the data and assess its adherence to the assumptions of a normal distribution. The Dunn-Bonferroni test and Kruskal-Wallis test were employed to compare quantitative variables among more than two groups when the data did not exhibit a normal distribution. These statistical tests were used to examine potential differences or relationships between the groups, considering the non-normal distribution of the data. Qualitative data were compared using Fisher's exact test, Pearson chi-square test, and Fisher-Freeman-Halton exact test. These statistical tests were employed to assess potential associations or differences among categorical variables. For evaluating progression-free survival (PFS) and overall survival (OS), univariable and multivariable Cox regression analyses were performed. A significance level of $p<0.05$ was considered to determine statistical significance in the results.

This study was conducted and designed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. It received approval from the ethics committee of Diyarbakır Gazi Yaşargil Training and Research Hospital (Approval Date-No: 25.11.2022-2022/242). Informed consent was obtained from all patients Results

There were 280 patients in our study. The median age was 64.5 years (58, 72). 165 (58.9%) of our patients were male. ECOG performance scale was 0 or 1 in 182 (65%) of our patients. Most of our patients 230 (82.1%) were de-novo metastatic. Liver was the site of metastasis in 202 (72.1%) of our patients. The primary site of origin was the head of the pancreas in 184 (65.7%) of our patients. In metastatic 1st line chemotherapy, 59 (21.1%) patients received cisplatin + gemcitabine, 59 (21.1%) patients received single agent gemcitabine and 47 (16.8%) patients received FOLFIRINOX regimen. In our study, 254 (90.7%) patients were exited. No statistically significant differences were found concerning gender, ECOG performance status, and tumor localization.

Percentages between the group with a HALP score ≤ 0.6 (HALP-Low) and the group with a HALP score > 0.6 (HALP-High) ($p>0.05$). We observed a statistically significant difference between the HALP-Low group and the HALP-High group in terms of the proportion of patients receiving the 1st step chemotherapy ($p=0.002$).

The HALP-Low group had a higher percentage of patients receiving capecitabine. Detailed information on the general characteristics and demographics of the patients is provided in Table 1.

Table 1. Demographic and clinicopathological characteristics of the patients

	Total (n=280)	Low HALP score (≤0.6) (n=234)	High HALP score (>0.6) (n=46)	p
Age, year	64.5 (58, 72)	65 (59, 72)	63 (56, 71)	0.253
Gender				0.972
Female	115 (41.1)	96 (41)	19 (41.3)	
Male	165 (58.9)	138 (59)	27 (58.7)	
ECOG				0.761
0-1	182 (65)	153 (65.4)	29 (63)	
2-3	98 (35)	81 (34.6)	17 (37)	
Smoking (%)				0.788
No	151 (53.9)	126 (53.8)	25 (54.3)	
Active	121 (43.2)	102 (43.6)	19 (41.3)	
Former	8 (2.9)	6 (2.6)	2 (4.3)	
BMI				0.919
<20	44 (15.7)	37 (15.8)	7 (15.2)	
>20	236 (84.3)	197 (84.2)	39 (84.8)	
De-novo metastasis, n (%)				0.741
Yes	230 (82.1)	193 (82.5)	37 (80.4)	
No	50 (17.9)	41 (17.5)	9 (19.6)	
Liver metastasis				0.770
No	78 (27.9)	66 (28.2)	12 (26.1)	
Yes	202 (72.1)	168 (71.8)	34 (73.9)	
Lung metastasis				0.324
No	196 (70)	161 (68.8)	35 (76.1)	
Yes	84 (30)	73 (31.2)	11 (23.9)	
Periton metastasis				0.263
No	168 (60)	137 (58.5)	31 (67.4)	
Yes	112 (40)	97 (41.5)	15 (32.6)	
Others				0.543
No	222 (79.3)	184 (78.6)	38 (82.6)	
Yes	58 (20.7)	50 (21.4)	8 (17.4)	
First Line				0.002
FOLFOX	16 (5.7)	12 (5.1)	4 (8.7)	
FOLFIRINOX	47 (16.8)	39 (16.7)	8 (17.4)	
KAPOX	15 (5.4)	9 (3.8)	6 (13)	
Gemcitabine	59 (21.1)	49 (20.9)	10 (21.7)	
Gemcitabin+Capesitabin	25 (8.9)	24 (10.3)	1 (2.2)	
Gemcitabin+ Nab-paclitaxel	22 (7.9)	19 (8.1)	3 (6.5)	
Cisplatin+Gemcitabine	59 (21.1)	45 (19.2)	14 (30.4)	
Capesitabin	37 (13.2)	37 (15.8)	0 (0)	
Tumor location, n (%)				0.178
Head	184 (65.7)	159 (67.9)	25 (54.3)	
Body	55 (19.6)	42 (17.9)	13 (28.3)	
Tail	41 (14.6)	33 (14.1)	8 (17.4)	
Survival				0.401
Live	26 (9.3)	20 (8.5)	6 (13)	
Exitus	254 (90.7)	214 (91.5)	40 (87)	

HALP: Hemoglobin-Albumin-Lymphocyte-Platelet-Ratio

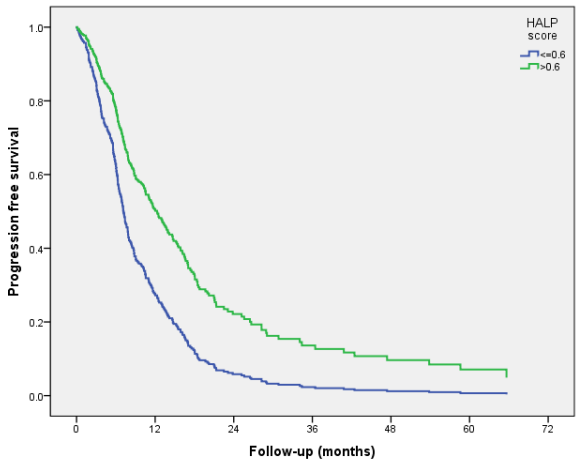

Figure-1: Progression free survival analysis functions

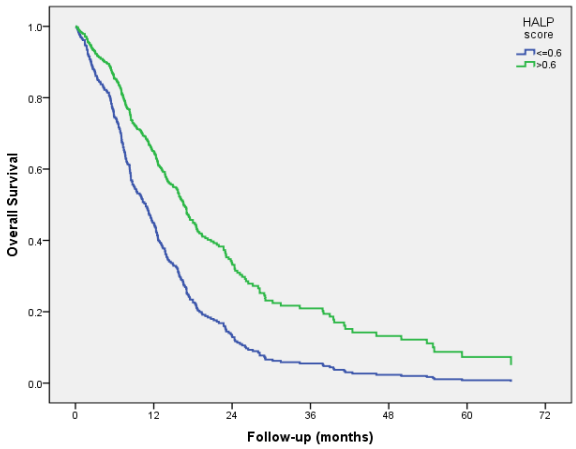

Figure-2: Overall survival analysis functions

For the whole population, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. Median PFS was 7.1 (95% CI: 6.37-7.83) months for the HALP-Low group and 14.8 (95% CI: 12.36-17.24) months for the HALP-High group. The HALP-High group exhibited a significantly longer median PFS compared to the HALP-Low group, with a p-value of less than 0.001 indicating statistical significance (Figure 1).

The HALP-Low group had a median overall survival (OS) of 10.57 months (95% CI: 8.66-12.47), while the HALP-High group had a median OS of 18 months (95% CI: 14.51-21.49). The HALP-Low group exhibited a shorter median OS compared to the HALP-High group, and this difference was statistically significant (p<0.001). (Figure 2).

There were no statistically significant differences observed between the HALP-Low group and the HALP-High group in terms of gender, ECOG performance status, and tumor localization percentages respectively (p-values: 0.972, 0.761, 0.178,). Median PFS was higher and statistically significant in patients with an ECOG performance score of 0-1 compared to those with an ECOG performance score of 2-3, 8.33 (95% CI: 7.16-9.51) and 6.77 (95% CI 5.68-7.85), respectively (p<0.001).

Furthermore, the median OS was higher and statistically significant in patients with ECOG performance score 0-1 compared to those with ECOG performance score 2-3, 13.3 (95% CI: 11.43- 15.17) and 7.9 (95% CI: 6.26, 9.54), respectively (p:0.001).

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). Univariate analyses of PFS and OS are shown in detail in Table 2.

Multivariate analysis was conducted to identify independent prognostic factors for progression-free survival (PFS) and overall survival (OS). The HALP-Low group had a lower PFS compared to the HALP-High group [HR (95% CI)=2.288 (1.587, 3.301), p<0.001]. Additionally, individuals with de-novo disease status had a lower PFS compared

Table 2: Univariate analysis of PFS and OS

	mOS (95%CI)	p-value	mPFS (95% CI)	p-value
Age, year	-	0.132	-	0.715
Gender				
Female	10.97 (9.01 – 12.93)	0.823	7.8 (6.52- 9.08)	0.863
Male	12.33 (10.32 -14.34)		7.3 (6.47- 8.13)	
ECOG-PS				
0-1	13.3 (11.39 - 15.21)		8.33 (7.16- 9.51)	
2-3	7.9 (6.34 - 9.46)	<0.001	6.77 (5.68- 7.85)	0.001
Smoking		0.989		0.679
Never	10.77 (9- 12.93)		7.63 (6.64- 8.62)	
Active	12.67 (10.64-14.83)	0.995	7.53 (6.26- 8.8)	0.406
Former	14.17 (0-28.81)	0.883	5.87 (0 - 19.73)	0.679
BMI				
<20	11.77 (6,04- 17.49)		7.3 (5.86- 8.74)	
>20	11.5 (9.92- 13.08)	0.362	7.63 (6.8 -8.47)	0.362
De-novo metastasis, n (%)				
Yes	10 (8.4 - 11.6)	<0.001	6.77 (6.12- 7.41)	<0.001
No	21.67 (15.41- 27.93)		16.43 (10.52-22.34)	
Liver metastasis				
No	11.53 (8.73- 14.34)		7.8 (6.18- 9.42)	
Yes	11.77 (10,02- 13.38)	0.215	7.4 (6.54- 8.26)	0.085
Lung metastasis				
No	11.53 (10,01- 13.06)		7.63 (6.68- 8.59)	
Yes	12.4 (7.51-17.29)	0.302	7.4 (5.65- 9.15)	0.592
Periton metastasis				
No	11.13 (8.9-13.33)		7.9 (6.41- 9.16)	
Yes	12 (10.2-13.8)	0.893	7.2 (6.44-7.96)	0.244
Others				
No	11.77 (10.16- 13.24)		7.4 (6.69- 8.11)	
Yes	11.3 (7.32-15.28)	0.942	8.5 (6.67- 10.33)	0.248
Tumor location, n (%)		0.446		0.144
Head	12 (10.97 – 13.03)		7.87 (6.78- 8.95)	
Body	10.1 (7.14- 13.06)	0.237	6.33 (5.26- 7.41)	0.057
Tail	10.3 (5.72- 14.88)	0.914	8.67 (5.05- 12.28)	0.820
HALP score				
Low (≤0.6)	10.57 (8.66-12.47)	<0.001	7.1 (6.37-7.83)	<0.001
High (>0.6)	18 (14.51- 21.49)		14.8 (12.36- 17.24)	

PFS: Progression-free survival , OS: Overall Survival, CI: Confidence interval, PS: performance status, BMI: Body mass index, n: number, HALP: Hemoglobin-Albumin-Lymphocyte-Platelet Ratio

to those with relapse [HR (95% CI) = 3.942 (2.747-5.656), p<0.001].

Multivariate analysis showed that OS was lower in the HALP-Low group than in the HALP-High group [HR (95% CI) = 2.076 (1.437, 2.998), p<0.001]. OS was lower in those with de-novo disease status than in those with relapse [HR (95% CI) = 3.205 (2.243-4.579), p<0.001].

Discussion

Many studies have been conducted to predict the prognosis of patients with metastatic PC and prognostic factors have been identified. Unfortunately, no markers have been found to be used in daily clinical practice. Many studies have shown that hemoglobin levels affect survival in patients with malignancy [16]. Albumin is a negative acute phase reactant synthesized in the liver. Hypo-

albuminemia may be caused by malnutrition, hypercatobolism caused by cancer cells and increased inflammation due to cytokine release and this plays a role in the survival of cancer patients. Lymphocytes inhibit apoptosis by secreting TNF alpha and interferon gamma and contribute to prolonged survival by preventing tumor migration and invasion [17,18]. Platelets increase angiogenesis, migration and vascular permeability through growth factors and therefore play an important role in cancer formation and prognosis. The Halp score, in which these parameters are used together, is one of the indices that is thought to play a prognostic role in the evaluation of nutrition and immune system. We decided to do this study, which we thought would play a prognostic role in metastatic cancer. To the best of our knowledge, this study represents the first investigation to assess the prognostic significance of the HALP score in metastatic PC.

In all our patients, median PFS was 7.3 (95% CI: 6.75-8.32) months and median OS was 11.53 (95% CI: 10.1-12.97) months. The general characteristics and median survival times of the patient population in our study were found to be compatible with the literature [19]. The HALP-Low group had a shorter median PFS compared to the HALP-High group, and this difference was statistically significant ($p<0.001$) In this study, high HALP score was found to be a good prognostic indicator and our study is compatible with the literature [12,14,15].

The literature contains numerous studies highlighting the prognostic significance of the HALP score. For instance, a study involving 582 patients with resectable pançreatic cancer demonstrated that a high HALP score prior to surgery was identified as a prognostic factor for survival [20]. According to a study involving 355 patients diagnosed with esophageal squamous cell carcinoma, a high HALP score before surgery was identified as an independent and favorable prognostic indicator [21]. In a separate study conducted by Topal et al., which included 110 colorectal cancer patients who underwent surgical procedures, it was observed that the prognostic significance of a low HALP score was diminished in the presence of tumor budding [22]. Again, in a study in which 591 patients with locally limited gastrointestinal stromal tumors were followed up post-operatively, low HALP score predicted short PFS [23].

Numerous publications also exist on this topic concerning locally advanced or metastatic stages. For instance, in a study conducted by Ekinci et al. involving 123 patients diagnosed with metastatic renal cell carcinoma, a low HALP score was associated with a poor prognosis [14]. A study in gastric cancer showed that a low HALP score numerically indicates a poor prognosis. The reason for the lack of statistical significance was thought to be the fact that the number of metastatic patients was 58 (12). Similarly, in a study conducted by Güç et al. involving 401 patients with NSCLC, it was noted that a low HALP score was associated with unfavorable survival outcomes [13]. Again, in a study including patients with limited and diffuse stage SCLC, low HALP score was found to be poor prognostic [15].

Patients with an ECOG performance score of 0-1 demonstrated a significantly higher median PFS compared to those with an ECOG performance score of 2-3, with durations of 8.33 months and 6.77 months, respectively ($p<0.001$). Additionally, patients with an ECOG performance score of 0-1 exhibited a significantly higher median OS compared to those with an ECOG performance score of 2-3, with durations of 13.3 months and 7.9 months, respectively (p: 0.001). Our study findings align with the existing literature, confirming the association between ECOG performance score and survival outcomes [24].

Median PFS was 6.77 (95% CI: 6.12-7.41) months with de-novo metastatic disease and 16.43 (95% CI: 10.52, 22.34) months with recurrent metastatic disease and was statistically significant (p:0.001). Median OS was 10 (95% CI: 8.36-11.64) months with de-novo metastatic disease and 21.67 (95% CI: 15.41-27.93) months with recurrent metastatic disease, which was statistically significant (p:0.001). In a study by Miotke et al. survival of recurrent patients was 10.8 months and OS of recurrent patients was 7.3 months and our study was found to be favorable with the literature [25].

The retrospective design of our study and the relatively limited sample size of the HALP-low group are acknowledged limitations. While we adopted a HALP score cut-off value of 0.6 based on previous literature, the optimal threshold is still undetermined. Another issue that should be mentioned at the same time was that our patient groups were heterogeneous. It included Denovo and metachronous metastatic patients. Therefore, more specific, prospective, well-designed studies with a larger patient population are needed to investigate this issue in more detail.

A high HALP score represents a cost-effective and practical marker that contributes to the existing literature. If validated by prospective studies, it could be utilized in clinical practice to prognosticate patients with metastatic prostate cancer. Furthermore, a high HALP score was identified as an independent predictor of unfavorable prognosis in patients with metastatic pancreatic cancer

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REFERENCES

1 - Sung, H., Ferlay, J., Siegel, R. L., et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.

2 - Siegel, R. L., Miller, K. D., & Jemal, A. et al. Cancer statistics, 2019. CA: a cancer journal for clinicians, 2019: 69(1), 7-34.

3- Shimizu, T., Taniguchi, K., Asakuma, et al. Lymphocyte–to–monocyte ratio and prognostic nutritional index predict poor prognosis in patients on chemotherapy for unresectable pancreatic cancer. Anticancer Research, 2019: 39(4), 2169-2176.

4- Medina-Jiménez, A. K., & Monroy-Torres, R. Repurposing Individualized Nutritional Intervention as a Therapeutic Component to Prevent the Adverse Effects of Radiotherapy in Patients with Cervical Cancer. Frontiers in Oncology, 2020: 10, 595351.

5- Wilde, L., Roche, M., Domingo-Vidal, M., et al. Metabolic coupling and the Reverse Warburg Effect in cancer: Implications for novel biomarker and anticancer agent development. Seminars in Oncology 2017: 44; 198-203

6- Chen, W., Wei, T., Li, Z., et al. Association of the preoperative inflammation-based scores with TNM stage and recurrence in patients with papillary thyroid carcinoma: a retrospective, multicenter analysis. Cancer Management and Research, 2020: 12, 1809.

7- Ravasco, P, Nutrition in cancer patients. Journal of Clinical Medicine, 2019: 8(8), 1211.

8- Ekinci, F., Sarı, D., Çelik, C., Dirican, A., Erdoğan, A. P., Gökse, G. Can Albumin Bilirubin Ratio and Inflammatory Prognostic Index Be A New Marker Determining Survival in Metastatic Pancreatic Cancer?. The Gulf Journal of Oncology, 2021: 1(36), 45-52.

9- Sounni, N. E., & Noel, A. Targeting the tumor microenvironment for cancer therapy. Clinical Chemistry, 2013:.59(1), 85-93.

10-Baldane, S., Ipekci, S. H., Sozen, M., & Kebapcilar, L. Mean platelet volume could be a possible biomarker for papillary thyroid carcinomas. Asian Pacific Journal of Cancer Prevention, 2015: 16(7), 2671-2674.

11- Franco, A. T., Corken, A., Ware, J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood, 2015: 126(5), 582-588.

12- Sargin, Z. G., Dusunceli, I. The Effect of HALP Score on the Prognosis of Gastric Adenocarcinoma. J Coll Physicians Surg Pak 2022: 64(104), 51.

13- Güç, Z. G., Alacacıoğlu, A., Kalender, M. E., et al. HALP score and GNRI: Simple and easily accessible indexes for predicting prognosis in advanced stage NSCLC patients. The İzmir oncology group (IZOG) study. Frontiers in Nutrition, 2022: 9; 905292

14- Ekinci, F., Balcik, O. Y., Oktay, E., & Erdogan, A. P. HALP Score as a New Prognostic Index in Metastatic Renal Cell

Cancer. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2022: 32(3), 313-318.
15- Shen, X. B., Zhang, Y. X., Wang, W., & Pan, Y. Y. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with small cell lung cancer before first-line treatment with etoposide and progression-free survival. Medical science monitor: international medical Journal of Experimental and Clinical Research 2019:. 25, 5630
16- Belcher, D. A., Ju, J. A., Baek, J. H., et al. The quaternary state of polymerized human hemoglobin regulates oxygenation of breast cancer solid tumors: A theoretical and experimental study. PLoS One, .2018: 13(2), e0191275
17 - Lucijanic, M., Veletic, I., Rahelic, D., et al. Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. Wiener klinische Wochenschrift, 2018: 130(3), 126-133.
18- Greten, F. R., & Grivennikov, S. I. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity, 2019: 51(1), 27-41
19 -Ettrich, T. J., Seufferlein, T. Systemic therapy for metastatic pancreatic cancer. Current Treatment Options in Oncology, 2021: 22(11), 1-12.
20-. Xu, S. S., Li, S., Xu, H. X., Li, et al. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. World Journal of Gastroenterology, 2020: 26(8), 828
21- Feng, J. F., Wang, L., & Yang, X. et al. The preoperative hemoglobin, albumin, lymphocyte and platelet (HALP) score is a useful predictor in patients with resectable esophageal squamous cell carcinoma. Bosnian Journal of Basic Medical Sciences, 2021: 21(6), 773.
22 - Topal, U., Guler, S., Teke, Z., Karakose, E., Kurtulus, I., Bektas, H. Diagnostic Value of Preoperative Haemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score in Predicting Tumour Budding in Colorectal Cancer. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP, 2022: 32(6), 751-757.
23- Zhao, Z., Yin, X. N., Wang, J., Chen, X., Cai, Z. L., & Zhang, B. Prognostic significance of hemoglobin, albumin, lymphocyte, platelet in gastrointestinal stromal tumors: A propensity matched retrospective cohort study. World Journal of Gastroenterology, 2022. 28(27), 3476-3487.
24 - Ekinci, F., Erdogan, A. P., Yildirim, S., Ozveren, A. Options in First Line Management of Metastatic Pancreatic Cancer and the Determinative Role of ECOG Performance Status. Eurasian Journal of Medical Investigation. 2021: 5; 500-507.
25 - Miotke, L., Nevala-Plagemann, C., Ying, J., Florou, V., Haaland, B., & Garrido-Laguna, I. Treatment outcomes in recurrent versus de novo metastatic pancreatic adeno-carcinoma: a real world study. BMC Cancer, 2022: 22(1), 1-8..

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Doi: 10.5505/aot.2023.26779

Original Article

Systemic Immune-Inflammation Index and Hodgkin Lymphoma: An Underexplored Relationship

Sistemik İmmün-İnflamasyon İndeksi ve Hodgkin Lenfoma: Yeterince Keşfedilmemiş Bir İlişki

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ABSTRACT

Introduction: Tumor-associated inflammation is an important feature of tumor development and progression. We aimed to investigate whether the clinicopathological and prognostic characteristics of patients with classical Hodgkin lymphoma (cHL) were associated with systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).
Materials and methods: This was a retrospective cohort study conducted between January 2012 and December 2021. A total of 77 patients with newly diagnosed cHL were included in the study.
Results: The median age of the patients was 37 (24-49) years. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR. Female patients (p=0.005), those with B symptoms (p=0.014) and subjects with extranodal involvement (p=0.011) had significantly higher PLR. Also, the SII of patients with B symptoms was significantly higher compared to those without (p=0.009). There were significant but weak correlations between international prognostic score-7 and SII (r=0.271, p=0.017), PLR (r=0.294, p=0.010) and NLR (r=0.378, p=0.001).
Discussion: SII was associated with B symptoms, but was not prognostic for cHL. PLR and NLR were also unassociated with prognosis in patients with cHL. However, considering the exceedingly limited data on this topic, further studies to assess inflammation indices are necessary.

Keywords: Hodgkin lymphoma, prognosis, inflammation, biomarkers, neutrophil, lymphocyte, platelet

ÖZET

Giriş: Tümörle ilişkili inflamasyon, tümör gelişimi ve ilerlemesinin önemli bir özelliğidir. Klasik Hodgkin lenfoma (kHL) hastalarının klinikopatolojik ve prognostik özelliklerinin sistemik immün-inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranı (PLO) ile ilişkili olup olmadığını araştırmayı amaçladık.
Gereç ve yöntemler: Bu, Ocak 2012 ile Aralık 2021 tarihleri arasında yürütülen retrospektif bir kohort çalışmasıdır. Çalışmaya yeni tanı almış toplam 77 kHL hastası dahil edildi.
Bulgular: Hastaların ortanca yaşı 37 (24-49) idi. Evre IV hastalığı (p=0,036), B semptomları (p=0,005) ve ekstranodal tutulumu (p=0,012) olan hastalarda NLO anlamlı olarak daha yüksekti. Kadın hastalarda (p=0,005), B semptomu olanlarda (p=0,014) ve ekstranodal tutulumu olanlarda (p=0,011) PLR anlamlı olarak daha yüksekti. Ayrıca B semptomu olan hastaların olmayanlara göre SII değeri anlamlı olarak daha yüksekti (p=0,009). Uluslararası prognostik skor-7 ile SII (r=0,271, p=0,017), PLO (r=0,294, p=0,010) ve NLO (r=0,378, p=0,001) arasında anlamlı ancak zayıf düzeyde korelasyon vardı.
Tartışma: SII, B semptomları ile ilişkili bulundu, ancak kHL için prognostik değildi. Ayrıca PLO ve NLO da kHL'li hastalarda prognozla ilişkili değildi. Ancak bu konudaki verilerin son derece sınırlı olduğu düşünüldüğünde, inflamasyon indekslerinin değerlendirilmesi için daha fazla çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Hodgkin lenfoma, prognoz, inflamasyon, biyobelirteç, nötrofil, lenfosit trombosit

First Received: 09.05.2023, Accepted: 26.06.2023 doi: 10.5505/aot.2023.62582

Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas [1] and has an annual incidence of 2–3 cases per 100 000 people [2]. It is characterized by B lymphocyte-derived malignant cells and a general inflammatory microenvironment [3]. Although genetic and environmental factors and various viral infections contribute to pathophysiology [3, 4], it is still unclear what causes normal B lymphocytes to turn into malignant, biologically active tumor cells [3].

HL is histopathologically classified as classical HL (cHL) and nodular lymphocyte-predominant HL. Patients with cHL constitute 95% of all cases [3]. Today, up to 90% of patients with cHL can be cured [4]; however, 5-10% of cases develop primary resistant disease [1], and approximately 50% of patients with relapse or resistance die from progressive disease [1, 3]. Defined prognostic factors for early stage HL are high erythrocyte sedimentation rate (ESR), multiple nodular involvement, extra-nodal involvement, being aged >50 years, and presence of massive spleen disease, bulky disease, and B symptoms [5-7]. International prognostic scores (IPS-7 and IPS-3) are used to assess patients with advanced cHL [8]; however, many of the parameters required to obtain scores are generally difficult to clarify and require detailed investigation. As such, there is a lack of generally accepted, simple and inexpensive prognostic markers that may be applicable to cHL prognostication, including those with early stage cHL, and it is evident that such markers could facilitate individualized treatment for patients with poor prognosis.

Tumor-associated inflammation is an important feature of tumor development and progression [9, 10]. Several studies have reported that increased systemic inflammatory response may predict worse survival and prognosis for various neoplasms including lymphomas [11-13]. The literature on this topic has assessed the prognostic potential of various inflammatory markers in lymphoma, such as neutrophil-to-lymphocyte ratio (NLR) [12, 14], platelet-to-lymphocyte ratio (PLR) [12, 15] and systemic immune inflammation index (SII) [1, 11, 16]. The SII, which is based on peripheral blood neutrophil, platelet, and lymphocyte counts, has been shown to predict prognosis and/or severity in various cancer types including lymphomas [1, 16]. There have been many attempts to investigate the relationship between non-Hodgkin lymphoma (nHL) and SII [11, 16, 17]; however, to our knowledge, only one such study exists for HL [1].

Therefore, in this study, we aimed to investigate whether clinicopathological and/or prognostic parameters in patients with cHL were associated with SII, NLR and PLR values.

Material and Method

Study design and ethical considerations

This retrospective study was carried out in the Hematology department of our hospital. The protocol of this study was approved by the local ethics committee. It has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Study population

A total of 77 patients with new-onset cHL who were treated and followed up for cHL at our clinic, between January 2012 and December 2021, were included in the study. Patients younger than 18 years of age, those with known active infection, rheumatic or immunological disease at the time of blood sampling, patients with concomitant or previously treated malignancy, subjects with any known comorbid disease, patients with missing data, and those with no follow-up information were excluded from the study.

Data collection

All data about patients including age and sex information, performance status, pathology results, HL-related information, laboratory results, and follow-up data were retro-

spectively collected from hospital computer database.

Patient management and examinations

All steps of cHL management, including diagnosis, treatment and follow-up, were carried out in accordance with the current European Society for Medical Oncology Guidelines (www.esmo.org/ Guidelines/ Haematological-Malignancies) and the National Comprehensive Cancer Network, USA, Cinical Practice Guidelines (www.nccn.org /professionals/ physician_gls/ default.aspx).

The pretreatment information including B symptoms, performance score, pathological subtype, Ann Arbor stage, EBV positivity, bulky mass/mediastinal mass, diagnosis date and extranodal involvement positivity and IPS-7 score, treatment, and post-treatment data including refractory/recurrent disease and mortality were collected.

Performance status (PS) was determined in accordance with the Eastern Cooperative Oncology Group (ECOG) criteria [18]. The IPS-7 score was calculated as previously described [8]. Refractory disease was defined as a condition that either does not respond to treatment or achieves remission with treatment but relapses within six months. Relaps was defined as recurrent cHL after a documented complete remission that lasted at least six months after the first line treatment [19, 20].

Definitions for analyses

Patients with relapsed disease and/or death were defined as having a poor prognosis. However, disease (refractory/recurrent or death)-free-survival (DFS) was calculated using data from patients with poor prognosis (refractory/recurrent or death). When calculating DFS, the time between the diagnosis date and refractory/recurrent determining date or death date or data collection starting date was used. The follow-up time was calculated as the duration from the diagnosis date to data collection starting date or mortality.

Laboratory measurements and related tools

All laboratory analyses were performed in the Biochemistry department of our hospital using calibrated standard measuring devices and according to the manufacturer's recommendations. The results of the following laboratory findings, which were studied from blood samples obtained at the time of diagnosis and before any treatment, were included in the study: aspartate amino-transferase (AST), alanine amino-transferase (ALT), albumin, ESR, lactate dehydrogenase (LDH), C-reactive protein (CRP), and hemogram.

The NLR, PLR and SII were calculated using absolute neutrophil, lymphocyte, platelet counts. SII was calculated by using the following formula: SII ($\times 10^3$) = Absolute neutrophil count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [1].

Glomerular filtration rate (GFR) was calculated automatically using the short Modification of Diet in Renal Disease formula from the Turkish Society of Nephrology's internet application called “formula and calculations” (https://nefroloji.org.tr/tr/ formul-ve-hesaplamalar).

Statistical analysis

The classical $p<0.05$ threshold was accepted to show statistical significance. All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Between-group analyses were performed with the Mann-Whitney U test or Kruskal-Wallis test depending on normality of distribution. Pairwise comparisons were adjusted by the Bonferroni correction. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. DFS was calculated with the Kaplan-Meier method by using time between remission and recurrence or death. Cox regression analyses were performed to determine significant factors independently associated with poor prognosis.

Variables were analyzed with the univariable cox regression analysis and statistically significant variables were included into the multivariable cox regression model.

Results

The median age of the patients was 37 (24-49) years, and 62.34% (n=48) of them were males. Mean follow-up time was 48.74±26.46 (range 9-118) months. One patient died of ischemic heart disease 93 months after diagnosis. Patients' disease characteristics and laboratory measurements are depicted in Table 1 and Table 2.

The relationships between NLR, PLR and SII and the characteristics of patients with cHL are presented in Table 3. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR than patients without these characteristics. The PLR values of female patients (p=0.005), patients with B symptoms (p=0.014) and those with extra-nodal involvement (p=0.011) were significantly higher than comparative groups. The SII values of patients with B symptoms were significantly higher than those without (p=0.009).

Correlations between NLR, PLR, SII and other continuous variables are presented in Table 4. Significant correlations were found between NLR and age (r=-0.226, p=0.048), IPS-7 score (r=0.378, p=0.001), albumin (r=-0.280, p=0.014), ESR (r=0.416, p<0.001), CRP (r=0.452, p<0.001), hemoglobin (r=-0.387, p=0.001) and hematocrit (r=-0.387, p<0.001) levels. There were significant correlations between PLR and IPS-7 score (r=0.294, p =0.010), albumin (r=-0.264, p=0.020), ESR (r=0.446, p<0.001), CRP (r=0.541, p<0.001), hemoglobin (r=-0.519, p<0.001), hematocrit (r=-0.515, p<0.001) levels and mean corpuscular volume (MCV) (r=-0.367, p=0.001) values. Also, significant correlations were found between SII and age (r =-0.278, p=0.014), IPS-7 score (r=0.271, p=0.017), GFR (r=0.252, p=0.027), AST (r=-0.300, p=0.008), ALT (r=0.263, p=0.021), ESR (r=0.390, p<0.001), CRP (r=0.519, p<0.001), hemoglobin (r=-0.369, p=0.001),

Table 1. Summary of patients and disease characteristics

Age at diagnosis	37 (24 - 49)
Sex	
Male	48 (62.34%)
Female	29 (37.66%)
ECOG performance score	
0	60 (77.92%)
1	16 (20.78%)
2	1 (1.30%)
Histological subtype	
Nodular sclerosis	39 (50.65%)
Mixed cellularity	32 (41.56%)
Lymphocyte-depleted	1 (1.30%)
Lymphocyte-rich	5 (6.49%)
Other	0 (0.00%)
EBV	
Negative	21 (27.27%)
Positive	25 (32.47%)
Unknown	31 (40.26%)
Stage	
Stage I	3 (3.90%)
Stage II	29 (37.66%)
Stage III	25 (32.47%)
Stage IV	20 (25.97%)
Bulky disease	14 (18.18%)
B symptoms	35 (45.45%)
IPS-7	2 (2 - 3)
Mediastinal mass	35 (45.45%)
Extranodal involvement	16 (20.78%)
Chemotherapy	
ABVD	72 (93.51%)
BEACOPP	1 (1.30%)
GEMOX	0 (0.00%)
Brentuximab	4 (5.19%)
Nivolumab	0 (0.00%)
Radiotherapy	19 (24.68%)
Refractory/Recurrent disease	18 (23.38%)
Autologous stem cell transplantation	18 (23.38%)
Mortality	1 (1.30%)
Follow-up time, months	48.74 ± 26.46

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables
Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, IPS-7: International prognostic scores-7

Table 2. Summary of laboratory measurements

GFR (mL/min/1.73 m^2)	115.61 ± 18.21
AST (IU/L)	18 (16 - 28)
ALT(IU/L)	17 (12.6 - 33)
Albumin (g/dL)	3.96 ± 0.66
ESR (mm/h)	46 (11 - 67)
LDH (mg/dL)	207 (179 - 270)
CRP (mg/L)	12 (2.5 - 72)
Hemoglobin (g/dL)	11.74 ± 2.62
Hematocrit (%)	36.14 ± 6.74
MCV (fl)	81.13 ± 6.89
WBC ($x10^3$)	8.32 (4.96 - 15.47)
Neutrophil ($x10^3$)	5.28 (3.20 - 11.92)
Lymphocyte ($x10^3$)	1.75 ± 0.82
Monocyte ($x10^3$)	0.78 ± 0.47
Eosinophil ($x10^3$)	0.18 (0.08 - 0.34)
Platelet ($x10^3$)	357.53 ± 168.95
NLR	4.06 (1.99 - 6.84)
PLR	180.46 (142.57 - 321.43)
SII ($x10^3$)	1045.39 (515.46 - 2598.73)

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

hematocrit (r=-0.369, p=0.001) levels and MCV (r=-0.257, p=0.024) values.

DFS was 73.54 ± 7.14 (95% CI: 59.54 - 87.54) months (Figure 1). Univariable cox regression analysis revealed that stage at diagnosis and Bulky disease were the only factors independently associated with poor prognosis. Multivariable cox regression revealed that stage at diagnosis was the only factor independently associated with poor prognosis. Patients with stage III & IV cHL at diagnosis had a 4.270-fold higher risk for refractory/ recurrent disease or death compared to patients with stage I & II cHL at diagnosis (HR: 4.270, 95% CI: 1.165 - 15.655, p=0.029, Figure 2) (Table 5).

Discussion

The main findings of the present study were as follows: Firstly, there were significant associations between SII and B symptoms, between NLR and stage IV disease, B symptoms and extranodal involvement, and between PLR and female sex. Secondly, SII, NLR and PLR were not found to be significant markers in predicting poor prognosis. Finally, only Stage III & IV disease and Bulky disease were associated with poor prognosis in the present study [7].

SII is assumed to reflect systemic inflammation in a balanced way, and has been claimed to be a stronger prognostic marker in some malignancies –compared to other systemic inflammation markers such as NLR, PLR and lymphocyte-to-monocyte ratio [1, 17, 21]. However, the relationship between SII and the clinicopathological and prognostic features of HL has not been adequately studied. In the present study, SII was only associated with the presence of B symptoms. There was also a weak correlation between SII and IPS-7 score. Although the presence of B symptoms and a high IPS-7 score are predictors of poor prognosis in HL, no strong relationship was found between SII and these factors of poor prognosis in our study. Mirilli and colleagues showed that SII was an independent predictive factor for both overall survival (OS) and progression free survival (PFS) in HL patients. They also found SII to be a more powerful indicator than other scores and inflammatory parameters including NLR, prognostic nutritional index and B2 microglobulin, as demonstrated by its predictive sensitivity of 73% and specificity of 73% [1]. To our knowledge, there have been no other studies investigating the role of SII in HL, whereas there has been research in patients with nHL [16, 22-24]. In the light of available data, although SII seems to have a prognostic role for nHL, it seems that more comprehensive studies are needed to ascertain its prognostic role in cHL.

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Table 3. Inflammation indices with regard to patient characteristics

	NLR	p	PLR	p	SII	p
Sex						
Male	3.40 (1.92 - 6.79)	0.223	155.02 (133.80 - 271.51)	**0.005**	950.60 (445.10 - 2890.10)	0.185
Female	4.88 (2.16 - 7.07)		227.92 (168.31 - 391.20)		1499.18 (794.92 - 2548.65)	
ECOG performance score						
0	4.14 (1.96 - 7.17)	0.778	171.24 (143.14 - 329.73)	0.615	963.64 (495.73 - 3281.13)	0.893
1 & 2	3.42 (2.54 - 6.57)		218.95 (141.00 - 321.43)		1212.39 (809.34 - 2246.51)	
Histological subtype						
Nodular sclerosis	6.02 (1.99 - 7.90)		195.00 (154.49 - 349.60)		2246.51 (476.77 - 3641.94)	
Mixed cellularity	3.30 (2.05 - 6.06)	0.195	163.62 (140.68 - 315.72)	0.355	902.81 (529.50 - 1425.97)	0.194
Other	2.41 (1.66 - 4.64)		157.32 (136.56 - 218.95)		797.19 (286.51 - 1928.93)	
EBV						
Negative	4.88 (1.66 - 7.07)	0.275	212.03 (158.48 - 310.00)	0.434	1352.75 (448.98 - 3454.05)	0.700
Positive	5.64 (3.11 - 10.42)		280.00 (150.79 - 418.02)		1204.61 (583.10 - 2598.73)	
Stage						
Stage I & II	2.75 (1.75 - 6.63) [a]		160.58 (138.45 - 229.60)		827.90 (402.35 - 2238.79)	
Stage III	4.47 (2.19 - 6.08) [ab]	**0.036**	181.08 (143.70 - 391.20)	0.115	1357.43 (562.49 - 2492.16)	0.118
Stage IV	6.80 (3.27 - 9.15) [b]		214.67 (159.77 - 347.31)		1425.97 (905.88 - 4232.40)	
Bulky disease						
No	3.55 (1.94 - 6.84)	0.345	170.31 (140.91 - 280.00)	0.107	941.92 (476.77 - 2548.65)	0.316
Yes	6.29 (3.19 - 6.84)		306.25 (158.48 - 391.20)		1483.56 (861.43 - 4143.38)	

Table 1 continued next page

B symptom						
No	2.99 (1.58 - 6.08)	**0.005**	155.66 (136.56 - 280.00)	**0.014**	640.06 (395.79 - 2492.16)	**0.009**
Yes	4.88 (2.62 - 8.12)		217.30 (168.75 - 391.20)		1274.81 (867.31 - 3380.79)	
Mediastinal mass						
No	3.25 (1.94 - 6.31)	0.111	157.20 (136.56 - 231.28)	**0.011**	940.11 (476.77 - 2492.16)	0.260
Yes	4.88 (2.43 - 9.37)		217.30 (163.55 - 418.02)		1499.18 (543.54 - 3641.94)	
Extranodal involvement						
No	3.34 (1.94 - 6.31)	**0.012**	170.31 (141.00 - 238.00)	0.058	938.30 (476.77 - 2492.16)	0.092
Yes	6.96 (5.03 - 10.29)		306.25 (157.98 - 385.94)		1479.67 (905.88 - 4963.06)	
R/R or Death						
No	3.78 (1.94 - 7.07)	0.911	180.77 (154.19 - 321.43)	0.408	940.11 (514.69 - 2548.65)	0.339
Yes	5.64 (2.19 - 6.63)		153.11 (126.87 - 396.88)		1499.18 (583.10 - 2689.67)	

Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. Same letters denote the lack of statistically significant difference between groups. The letters in the table represent pairwise comparison results. Each letter provides contextual information regarding the comparative groups and are coded with an approach that reduces clutter. For example: The lettering “a b b” indicates that the first measurement/group is different from the others, and there is no difference between the second and third measurements/groups. The lettering “a ab b” indicates that the first measurement/group and the third measurement/group are different, and the second measurement/group is similar to both other measurements/groups
Abbreviations: EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, R/R: Refractory/Recurrent, SII: Systemic immune inflammation index.

Table 4. Relationships between inflammation indices and other continuous variables

		NLR	PLR	SII
Age at diagnosis	r	**-0.226**	-0.142	**-0.278**
	p	**0.048**	0.219	**0.014**
IPS-7	r	**0.378**	**0.294**	**0.271**
	p	**0.001**	**0.010**	**0.017**
GFR (mL/min/1.73 m2)	r	0.192	0.150	**0.252**
	p	0.095	0.192	**0.027**
AST (IU/L)	r	-0.172	-0.068	**-0.300**
	p	0.135	0.555	**0.008**
ALT (IU/L)	r	-0.155	-0.123	**-0.263**
	p	0.178	0.287	**0.021**
Albumin (g/dL)	r	**-0.280**	**-0.264**	-0.221
	p	**0.014**	**0.020**	0.054
ESR (mm/h)	r	**0.416**	**0.446**	**0.390**
	p	**<0.001**	**<0.001**	**<0.001**
LDH (mg/dL)	r	0.009	-0.105	-0.024
	p	0.939	0.365	0.835
CRP (mg/L)	r	**0.452**	**0.541**	**0.519**
	p	**<0.001**	**<0.001**	**<0.001**
Hemoglobin (g/dL)	r	**-0.387**	**-0.519**	**-0.369**
	p	**0.001**	**<0.001**	**0.001**
Hematocrit (%)	r	**-0.387**	**-0.515**	**-0.369**
	p	**<0.001**	**<0.001**	**0.001**
MCV (fl)	r	-0.193	**-0.367**	**-0.257**
	p	0.093	**0.001**	**0.024**

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, r: Spearman correlation coefficient

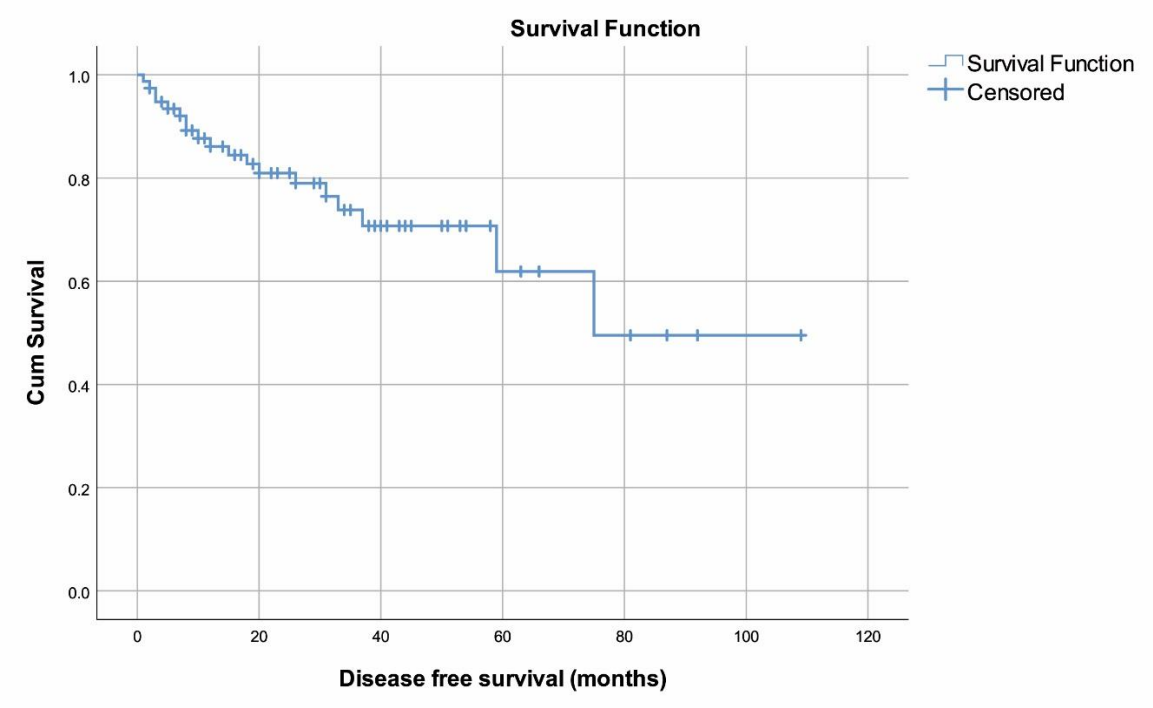

Figure 1. Disease free survival plot

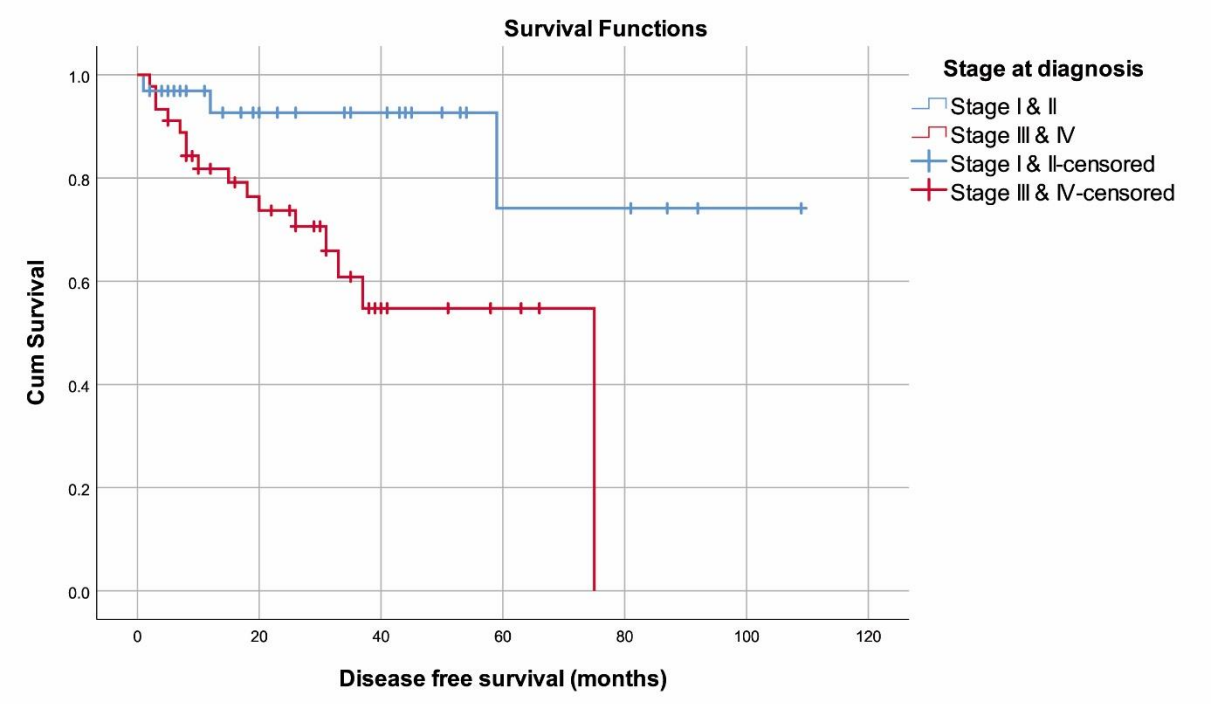

Figure 2. Disease free survival plot with regard to stage

Table 5. Association between variables and poor prognosis (refractory/recurrent disease or death), Cox Regression

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis	0.981 (0.948 - 1.014)	0.255		
Sex (based female)	0.538 (0.192 - 1.505)	0.237		
ECOG performance score (based ECOG≥1)	1.328 (0.472 - 3.738)	0.591		
Histological subtype (based mixed cellularity)	1.440 (0.577 - 3.590)	0.434		
EBV (based positive)	2.453 (0.651 - 9.252)	0.185		
Stage (based stage III & IV)	4.970 (1.407 - 17.564)	**0.013**	4.270 (1.165 - 15.655)	**0.029**
Bulky disease (based present)	2.986 (1.098 - 8.119)	**0.032**	2.004 (0.722 - 5.557)	0.182
B symptom (based present)	1.662 (0.674 - 4.100)	0.270		
IPS-7	1.027 (0.725 - 1.454)	0.882		
Mediastinal mass (based present)	1.526 (0.594 - 3.924)	0.380		
Extranodal involvement (based present)	1.982 (0.693 - 5.671)	0.202		
Chemotherapy (based ABVD)	0.773 (0.101 - 5.894)	0.803		
Radiotherapy (based present)	0.507 (0.147 - 1.755)	0.284		
GFR (mL/min/1.73 m2)	1.015 (0.991 - 1.039)	0.231		
AST (IU/L)	0.987 (0.953 - 1.023)	0.480		
ALT (IU/L)	0.990 (0.965 - 1.016)	0.445		
Albumin (g/dL)	1.230 (0.598 - 2.529)	0.574		
ESR (mm/h)	1.003 (0.989 - 1.018)	0.655		
LDH (mg/dL)	1.000 (0.997 - 1.003)	0.947		
CRP (mg/L)	1.002 (0.995 - 1.010)	0.583		
Hemoglobin (g/dL)	0.951 (0.802 - 1.128)	0.567		
Hematocrit (%)	0.984 (0.922 - 1.052)	0.642		
MCV (fl)	1.078 (0.994 - 1.168)	0.070		
WBC ($x10^3$)	1.045 (0.986 - 1.108)	0.141		
Neutrophil ($x10^3$)	1.047 (0.977 - 1.123)	0.193		
Lymphocyte ($x10^3$)	1.628 (0.918 - 2.885)	0.095		
Monocyte ($x10^3$)	1.681 (0.717 - 3.939)	0.232		
Eosinophil ($x10^3$)	1.327 (0.546 - 3.228)	0.533		
Platelet ($x10^3$)	1.002 (0.999 - 1.004)	0.197		
NLR	0.990 (0.913 - 1.074)	0.811		
PLR	0.999 (0.997 - 1.002)	0.656		
SII ($x10^3$)	1.000 (1.000 - 1.000)	0.917		

Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CI: Confidence interval, CRP: C-reactive protein, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, HR: Hazard ratio, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

It is known that platelets play an important role in the spread and growth of tumors [25] and platelet related markers are suggested to be prognostic factors for solid tumors [26, 27]It has also been shown that platelets play a critical role in the spread of Hodgkin-Reed Sternberg cells, especially in the spleen [28]. In the current study, a significant association was found between PLR and B symptoms and mediastinal mass. There was also a weak correlation between PLR and IPS-7 score. However, PLR was not found to be a significant marker for cHL prognosis. Reddy et al. showed that 2-year PFS was 84.3% for early cHL patients with a PLR of ≥266.2, which was significantly lower compared to the 96.1% 2-year PFS of patients with a PLR of <266.2. PLR remained a significant, independent prognostic factor. Also, high PLR (≥266.2) was also associated with advanced Ann-Arbor stage, B symptoms, and Bulky disease [12]. In another study high PLR was shown to be associated with lower likelihood of complete treatment response in patients with HL, and high PLR was independently associated with shorter PFS [15]. In contrast, similar to our findings, PLR was not found to be a prognostic factor for HL in other studies [29]. PLR seems to have the potential to be a prognostic marker for HL but available evidence needs to be supported by randomized controlled trials.

NLR has also been used for the prognostication of many types of

malignancies, including lymphomas [1, 6, 12]. Our results showed that NLR was associated with Stage IV disease, B symptoms, and extranodal involvement. Also, there was a weak correlation between NLR and IPS-7 score, but NLR was not a reliable predictor for poor cHL prognosis. In a comprehensive retrospective study, it was reported that 2-year PFS for early cHL patients with an NLR of ≥6.4 was 82.2% versus 95.7% among those with an NLR of <6.4. Similar to high PLR, having high NLR (≥6.4) was also associated with advanced Ann-Arbor stage, B symptoms and Bulky disease [12]. In another study in pediatric HL patients, it was reported that patients with an NLR of >3.5 had significantly higher stage and greater frequency of Bulky disease and B symptoms [14]. High NLR values have also been associated with disease stage, early-stage risk scoring, and response to treatment [6]. We did not find any notable association between prognostic characteristics and NLR in the present study, which has been reported before in patients with HL [29].

As a general comment, unfortunately, current prognostic models have not shown satisfactory success in early detection of HL patients at high risk of shortened survival [30]. For example, IPS has little clinical benefit, because only 19% of patients with scores of 4 and 5 are found to have a less than 50% probability of 7-year PFS [31, 32]. IPS calculation is usually preferred for high-stage HLs. Considering these disadvantages, it is undoubtedly crucial to obtain further data to assess the roles of inflammation markers such as NLR, PLR and SII in cHL, particularly since these markers are readily-available, easy to access and low cost.

Despite being one of the first studies to assess these markers in patients with cHL, the limitations of the present study must be considered when interpreting the results. This is a single-center retrospective study with a relatively small sample size, and thus, there were a low number of deaths in the study group which made OS-related analyses impossible. In addition, the number of recurrences may be considered insufficient, which may impact the results concerning DFS. Although factors thought to affect the inflammatory markers were assessed to exclude patients, some relevant data of patients may not have been recorded in the database. The follow-up period of the patients who were diagnosed towards the end of the study may have been short. The patients included in the study were diagnosed between 2012 and 2021, and changes or advances in patient management may have affected the findings. As the number of similar studies was limited (especially for SII), there were inadequacies in comparative analyses with the literature.

Conclusion

SII was associated with B symptoms, NLR with Stage IV disease, and PLR with B symptoms and mediastinal mass. There were weak correlations between all three markers and IPS-7; however, none of the inflammation indices were found to be prognostic for cHL. Taken together with the limited literature, it is evident that current data is insufficient for the use of pretreatment SII, NLR, and PLR in the prognostication of cHL disease

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REFERENCES

1. Mirili C, Paydas S, Kapukaya TK, Yılmaz A. Systemic immune-inflammation index predicting survival outcome in patients with classical Hodgkin lymphoma. Biomark Med. 2019; 13(18): 1565-75.
2. Yung L, Linch D. Hodgkin's lymphoma. Lancet. 2003; 361(9361): 943-51.
3. Momotow J, Borchmann S, Eichenauer DA, Engert A, Sasse S. Hodgkin Lymphoma-Review on Pathogenesis, Diagnosis, Current and Future Treatment Approaches for Adult Patients. J Clin Med. 2021; 10(5): 1125.
4. Brice P, De Kerviler E, Friedberg JW. Classical Hodgkin lymphoma. Lancet. 2021; 398(10310): 1518-27.
5. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016; 91(4): 434-42.
6. Dogan A, Demircioglu S. Assessment of the Neutrophil-Lymphocyte Ratio in Classic Hodgkin Lymphoma Patients. Pak J Med Sci. 2019; 35(5): 1270-5.
7. Kumar A, Burger IA, Zhang Z, Drill EN, Migliacci JC, Ng A, et al. Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes. Haematologica. 2016; 101(10): 1237-43.
8. Diefenbach CS, Li H, Hong F, Gordon LI, Fisher RI, Bartlett NL, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. Br J Haematol. 2015; 171(4): 530-8.
9. Chu Y, Liu Y, Jiang Y, Ge X, Yuan D, Ding M, et al. Prognosis and complications of patients with primary gastrointestinal diffuse large B-cell lymphoma: Development and validation of the systemic inflammation response index-covered score. Cancer Med. 2023; 00:1–13.
10. Samadi A, Sabuncuoglu S, Samadi M, Isikhan SY, Chirumbolo S, Peana M, et al. A comprehensive review on oxysterols and related diseases. Curr Med Chem. 2021; 28(1): 110-36.
11. Luo Q, Yang C, Fu C, Wu W, Wei Y, Zou L. Prognostic Role of Blood Markers in Primary Central Nervous System Lymphoma Patients Treated With High-Dose Methotrexate-Based Therapy. Front Oncol. 2021; 11: 639644.
12. Reddy JP, Hernandez M, Gunther JR, Dabaja BS, Martin GV, Jiang W, et al. Pre-treatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are prognostic of progression in early stage classical Hodgkin lymphoma. Br J Haematol. 2018; 180(4): 545-9.
13. Tao Y, He X, Qin Y, Liu P, Zhou S, Yang J, et al. Low platelet/platelet distribution width and high platelet/lymphocyte ratio are adverse prognostic factors in patients with newly diagnosed advanced Hodgkin lymphoma. Leuk Lymphoma. 2021; 62(13): 3119-29.
14. Jan S, Mustafa O, Elgaml A, Ahmad N, Abbas A, Althubaiti S. Neutrophil-to-Lymphocyte Ratio and Ferritin as Measurable Tools for Disease Burden and B Symptoms in Pediatric Patients With Hodgkin Lymphoma. J Pediatr Hematol Oncol. 2022; 44(2): e567-e71.
15. Tao Y, Zhou Y, Chen H, Qin Y, He X, Liu P, et al. Prognostic role of red blood cell distribution width and platelet/lymphocyte ratio in early-stage classical Hodgkin lymphoma. Future Oncol. 2022; 18(15): 1817-27.
16. Wang Z, Zhang J, Luo S, Zhao X. Prognostic Significance of Systemic Immune-Inflammation Index in Patients With Diffuse Large B-Cell Lymphoma. Front Oncol. 2021; 11: 655259.
17. Yang J, Guo X, Hao J, Dong Y, Zhang T, Ma X. The Prognostic Value of Blood-Based Biomarkers in Patients With Testicular Diffuse Large B-Cell Lymphoma. Front Oncol. 2019; 9: 1392.
18. Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. Cancer. 1990; 65(8): 1864-6.
19. Tarella C, Cuttica A, Vitolo U, Liberati M, Di Nicola M, Cortelazzo S, et al. High-dose sequential chemotherapy and peripheral blood progenitor cell autografting in patients with refractory and/or recurrent Hodgkin lymphoma: a multicenter study of the intergruppo Italiano Linfomi showing prolonged disease free survival in patients treated at first recurrence. Cancer. 2003; 97(11): 2748-59.
20. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. Crit Rev Oncol Hematol. 2013; 85(2): 216-37.
21. Fu X, Li T, Dai Y, Li J. Preoperative systemic inflammation score (SIS) is superior to neutrophil to lymphocyte ratio (NLR) as a predicting indicator in patients with esophageal squamous cell carcinoma. BMC Cancer. 2019; 19(1): 721.
22. Wu XB, Hou SL, Liu H. Systemic immune inflammation index, ratio of lymphocytes to monocytes, lactate dehydrogenase and prognosis of diffuse large B-cell lymphoma patients. World J Clin Cases. 2021; 9(32): 9825-34.
23. Wu J, Zhu H, Zhang Q, Sun Y, He X, Liao J, et al. Nomogram based on the systemic immune-inflammation

index for predicting the prognosis of diffuse large B-cell lymphoma. Asia Pac J Clin Oncol. 2023; 19(2): e138-e48.
24. Feng Y, Liu Y, Zhong M, Wang L. Complete blood count score model predicts ınferior prognosis in primary central nervous system lymphoma. Front Oncol. 2021; 11: 618694.
25. Nash GF, Turner LF, Scully MF, Kakkar AK. Platelets and cancer. Lancet Oncol. 2002; 3(7): 425-30.
26. Sahin F, Yildiz P. Serum platelet, MPV, PCT and PDW values, neutrophil to lymphocyte and platelet to lymphocyte ratios in lung cancer diagnosis. Eur Respiratory Soc; 2015; 46: PA4279
27. Aksoy EK, Kantarcı S, Torgutalp M, Akpınar MY, Sapmaz FP, Yalçın G, et al. The importance of complete blood count parameters in the screening of gastric cancer. Prz Gastroenterol. 2019; 14(3): 183-7.
28. Ohana OM, Ozer J, Prinsloo I, Benharroch D, Gopas J. Hodgkin lymphoma cell lines bind to platelets. Incubation with platelets induces CD15 and P-selectin dependent adhesion of the cell lines to Human Umbilical Vein Endothelial cells (HUVEC). Cancer Biol Ther. 2015; 16(11): 1651-9.
29. Ertan K, Dogru A, Kara B, Koksal Y. Impact on the survival of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and monocyte-lymphocyte ratio on prognosis in children with Hodgkin lymphoma. Saudi Med J. 2022; 43(5): 451-7.
30. Romano A, Parrinello NL, Vetro C, Chiarenza A, Cerchione C, Ippolito M, et al. Prognostic meaning of neutrophil to lymphocyte ratio (NLR) and lymphocyte to monocyte ration (LMR) in newly diagnosed Hodgkin lymphoma patients treated upfront with a PET-2 based strategy. Ann Hematol. 2018; 97(6): 1009-18.
31. Hasenclever D. The disappearance of prognostic factors in Hodgkin's disease. Ann Oncol. 2002; 13 Suppl 1: 75-8.
32. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998; 339(21): 1506-14..

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Doi: 10.5505/aot.2023.62582

Case Report

Anaplastic Multiple Myeloma: A Report of a Rare Case with CD38 and CD117 Positivity

Anaplastik Multipl Miyelom: CD38 ve CD117 Pozitifliği Olan Nadir Bir Olgu Sunumu

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ABSTRACT

Anaplastic multiple myeloma (AMM), which comprises anaplastic multiple myeloma and anaplastic plasmacytoma, is a rare illness that aggressively advances as a morphological subtype of multiple myeloma (MM). It has a poor prognosis and is believed to be particularly resistant to treatment. In this case report, we presented a 66-year-old woman diagnosed with AMM. The anaplastic morphology of MM may pose a diagnostic challenge. The need for a multidisciplinary approach to detect hematological neoplasms is highlighted in this example. For AMM instances, prompt radiographic, flowcytometry, and histological examination may assist guide effective treatment strategies.

Keywords: Anaplastic myeloma, multiple myeloma, monoclonal antibody

ÖZET

Anaplastik multipl miyelom ve anaplastik plazmasitoma içeren anaplastik multipl miyelom (AMM), multipl miyelomun (MM) morfolojik bir alt tip olarak agresif bir şekilde ilerleyen nadir bir hastalıktır. Kötü bir prognoza sahiptir ve tedaviye özellikle dirençli olduğuna inanılmaktadır. Bu olgu sunumunda AMM tanısı alan 66 yaşında bir kadın hastayı sunduk. MM'nin anaplastik morfolojisi tanısal bir zorluk teşkil edebilir. Bu örnekte hematolojik neoplazmları tespit etmek için multidisipliner bir yaklaşıma olan ihtiyaç vurgulanmıştır. AMM vakaları için hızlı radyografik, akım sitometri ve histolojik inceleme, etkili tedavi stratejilerini yönlendirmeye yardımcı olabilir.

Anahtar kelimeler: Anaplastik myelom, multiple myelom, monoklonal antikor

Introduction

Anaplastic multiple myeloma (AMM), which comprises anaplastic multiple myeloma and anaplastic plasmacytoma, is a rare illness that aggressively advances as a morphological subtype of multiple myeloma (MM). In newly-diagnosed instances of MM aberrant morphology and asynchronous immuno-phenotypic expression of plasma cells might be detected, leading to error in the initial diagnosis. It has a poor prognosis and is believed to be particularly resistant to treatment [1]. All ethnic groups and both sexes are impacted by AMM. AMM is far more common in younger patients than traditional multiple myeloma (median age of 69 years old), with a median age of 57.02 years [2, 3]. Because of its rarity, the clinical and pathological aspects of AMM have not been thoroughly understood yet. AMM

First Received: 09.02.2023, Accepted: 28.03.2023 doi: 10.5505/aot.2023.43925

patients are often young, with anemia or pancytopenia, dramatically reduced Ig, IgA isotype blood levels, and quickly developing extramedullary diseases [4]. Even in the presence of clinical, radiographic, and biochemical indications of the disease, a bone marrow test is necessary for the diagnosis of AMM. Using immunophenotyping, the bone marrow is evaluated both qualitatively and quantitatively. Myeloma cells are divided into 4 kinds based on their cytomorphology: mature, immature, pleomorphic, and plasmablastic [5]. AMM cells are atypical plasmacytoid differentiated cells that are widely dispersed. They have the following morphological characteristics: More than one big and irregular nucleolus; nucleoli with numerous distributed vacuoles; pleomorphic cells with significantly enriched cytoplasm [6]. Conventional chemotherapy and radiation are ineffective in the majority of AMM patients [1]. Immunotherapy, such as chimeric antigen receptor T cell immunotherapy, monoclonal antibodies, and potentially hematopoietic stem cell transplantation, might give these patients hope [1]. Chemotherapy has not been very effective in the past against this illness. It has been proposed that this aggressive phase may be the consequence of clonal evolution of the initial malignant cell rather than the emergence of a brand-new neoplasia on its own [7]. In this case report, we presented a 66-year-old woman diagnosed with AMM.

Case report

A 66-year-old female was admitted to the hematology clinic with increased fatiguability and night sweats. Physical examination revealed splenomegaly but was otherwise unremarkable. Hemogram revealed anemia (Hemoglobin = 9.1 g/dL), and thrombocytopenia (Platelet count = 74 × 10^6/L). Biochemical tests resulted in total protein: 105 g/L, albumin level of 35 g/L, creatinine 0.9 mg/dL, LDH 250 U/L. Roll formation was observed in erythrocytes in peripheral blood smear as depicted in Figure 1 (A). High lambda (207 mg/L) compared to kappa (10.8 mg/L) with a ratio of 19.1 verified the lambda light chain limitation in neoplastic cells by free light chain test. IgG isotype blood level was 64.12 g/L (7-16 g/L). Hypercellular particles with decreased trilineage hematopoiesis were seen on bone marrow aspiration. The aspirate smear of bone marrow was densely infiltrated with cohesive clusters/sheets of extremely pleomorphic neoplastic cells, many of which had anaplastic shape. There are numerous big atypical pleomorphic cells with a high nucleo-cytoplasmic ratio, basophilic cytoplasm, and a central eccentric nucleus with an uneven nuclear border as depicted in Figure 1 (B). Flowcytometric evaluation of bone marrow showed a CD45 negative cell population expressing CD38, CD117, and lambda on their surface without CD138 and CD56 expressions. (Figure 2). These cells were plasma cells and negative for surface expressions of CD19, CD20, CD22, and CD23, and also negative for intracytoplasmic CD79a. Positron emission tomography was reported as pleural nodular thickening, spleen 25 cm, diffusely increased involvement, multiple soft tissue lesions in the pelvic region, and multiple foci of involvement in bone structures and bone marrow as depicted in Figure 3 (maximum SUVmax value: 13.6). Based on the morphological and immuno-phenotypic findings, the patient was diagnosed with AMM. The patient is now being treated with bortezomib, lenalidomide, and dexamethasone, and is being followed up. After chemotherapy, autologous stem cell transplantation treatment is planned.

Discussion

AMM is a kind of plasma cell myeloma that has a very aggressive clinical course and a poor prognosis. One of the most frequent signs of AMM was anemia, and 9.6% of patients had thrombocytopenia when they were diagnosed, which is probably due to the

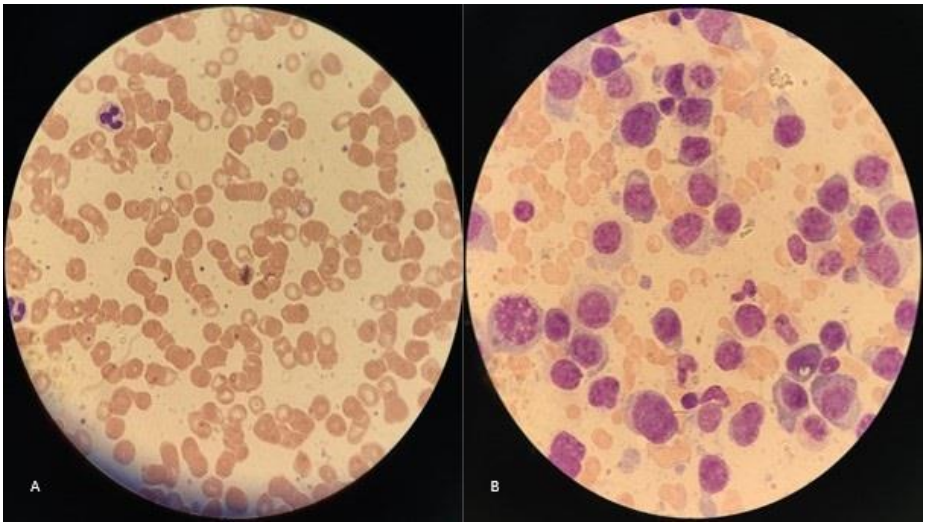

Figure 1. (A) Roll formation was observed in erythrocytes in peripheral blood smear, (B) Numerous big atypical pleomorphic cells with a high nucleocytoplasmic ratio, basophilic cytoplasm, and a central eccentric nucleus with an uneven nuclear border were seen in bone marrow aspiration.

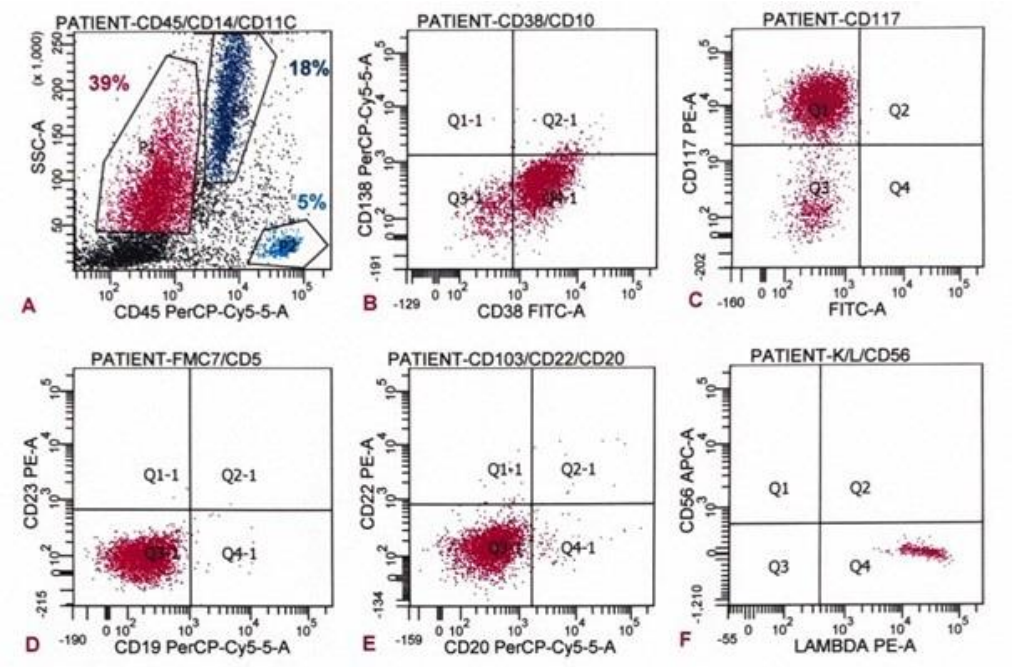

Figure 2. Flowcytometry showed (A) plasma cells account for 39%; were negative for CD45; (B) positive for CD38, negative for 138; (C) positive for CD117, (D) negative for CD19 and CD23; (E) negative for CD20 and CD22; (F) negative for CD56 and positive for lambda chain (FACS Canto, Becton Dickenson).

disease's aggressiveness and the significant anaplastic plasma cell infiltration of the bone marrow [3, 8]. Because of their unusual form, they might be difficult to diagnose. By morphology, they might seem like high-grade lymphoma or non-hematopoietic cancer. Anaplastic morphology can be detected in the early stages of myeloma or as the disease progresses. Infiltration of the extramedullary space is prevalent [9]. For the proper diagnosis, a combination of clinical symptoms, morphology, biochemical data, and immunophenotype are required. We reported a 66-year-old woman diagnosed with AMM in this case report. After further examination, multiple extramedullary infiltrates were detected in the patient. AM cells resemble "immunoblasts" at times, and

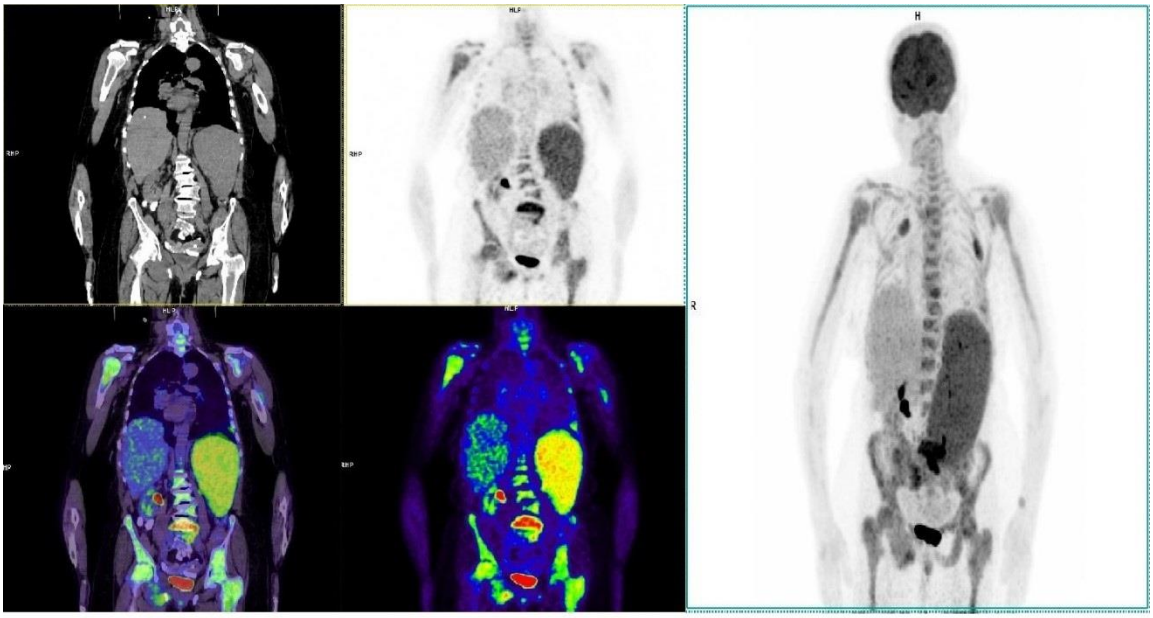

Figure 3. FDG uptake of tumor tissue in the skeletal system, spleen, bilateral pleura, and the lesion adjacent to L5 vertebra anterior in the coronal plane and MIP images observed in 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT)

they're frequently mistaken as other low-differentiated malignancies such as malignant melanoma, Burkitt lymphoma, and sarcoma. As a result, immunohistochemistry and flow-cytometry play a crucial role in differential diagnosis. AM cells typically express CD38, CD138, and MUM1 with little light chain expression, while lymphocyte markers CD20, CD19, and CD3 are absent [1]. This is in line with our findings. AM cells may also express CD56 and CD117 on their surface. Vinho Do et al. reported a case of AMM. In this case, flow cytometric analysis was positive in an expanded panel of CD138, CD56, and CD117 together with the kappa light chain. They reported that plasma cells account for 81.0% and those cells are negative for CD45, positive for CD138, negative for CD38, and positive for CD117 [10]. After this case report reported by Vinho Do et al. in the literature, flowcytometric analysis of the bone marrow showed CD117 positivity in our case.1q21 amplification [13], 17p (p53) deletion, t(4;14), and/or chromosomal 13 abnormalities are all prevalent [11]. Conventional chemotherapy and radiation are ineffective in the majority of AMM patients. As a result, combining stronger chemotherapies with new drugs may increase response. According to one case series, 66.7% of patients receiving VRD (Bortezomib, Lenalidomide, and Dexa-methasone) and VCD (Bortezomib, Cyclophosphamide, and Dexamethasone) conventional myeloma treatment regimens had an inadequate response. In two patients, VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) regimen was used along with VRD prior to hematopoietic stem cell transplantation consolidation and was able to achieve remission for over 2 years [3]. Immunotherapy, such as chimeric antigen receptor T cell immunotherapy, monoclonal antibodies, and potentially hematopoietic stem cell transplantation, may offer these patients fresh therapeutic hope [1]. We applied bortezomib (1.3 mg/m^2), lenalidomide (25 mg), and dexamethasone (40 mg) chemotherapeutic in this case we presented. In conclusion, the anaplastic morphology of MM

may pose a diagnostic challenge. The need for a multidisciplinary approach to detect hematological neoplasms is highlighted in this example. For AMM instances, prompt radiographic, flow cytometry, and histological examination may assist the diagnosis

REFERENCES

1. Huang J-X, Meng F-J, Feng X-Q, Lyu X, Wang X. Clinical and histopathological analyses of anaplastic myeloma. Chinese Medical Journal. 2020; 133(13): 1614-6.
2. Dimopoulos MA, Stewart AK, Masszi T, Špička I, Oriol A, Hájek R, et al. Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age: secondary analysis from the phase 3 ASPIRE study. British Journal of Haematology. 2017; 177(3): 404-13.
3. Wu J, Chu E, Chase CC, Choi T, Gasparetto C, Young K, et al. Anaplastic Multiple Myeloma: Case Series and Literature Review. Asploro Journal of Biomedical and Clinical Case Reports. 2022; 5(1): 1-11.
4. Jain BB, Majumdar A, Chowdhary KM. Plasmablastic lymphoma versus anaplastic myeloma in a human immunodeficiency virus negative male: a diagnostic quandary. Archives of Iranian Medicine. 2013; 16(10): 608-610.
5. Fujino M. The histopathology of myeloma in the bone marrow. Journal of Clinical and Experimental Hematopathology. 2018; 58(2): 61-7.
6. Elsabah H, Soliman DS, Ibrahim F, Al-Sabbagh A, Yassin M, Moustafa A, et al. Plasma cell myeloma with an aggressive clinical course and anaplastic morphology in a 22-year-old patient: a case report and review of literature. The American Journal of Case Reports. 2020; 21: e920489-1.
7. Sakthisankari S, Kumar PN, Syed T. Anaplastic multiple myeloma-a morphological challenge–A case series. Indian Journal of Medical and Paediatric Oncology. 2020; 41(03): 430-3.
8. Taccone FS, Bouko Y, Robin V. Exceptional association of diffuse anaplastic myeloma with microangiopathic anemia. European Journal of Internal Medicine. 2007; 18(8): 607.
9. Ichikawa S, Fukuhara N, Hatta S, Himuro M, Nasu K, Ono K, et al. Anaplastic multiple myeloma: possible limitations of conventional chemotherapy for long-term remission. Journal of Clinical and Experimental Hematopathology. 2018; 58(1): 39-42.
10. Do ATV. CD38–Negative Anaplastic Plasma Cell Myeloma: A Rare Case Report. Cureus. 2022;14(1).
11. Sethi S, Miller I. Plasma cell myeloma with anaplastic transformation. Blood, 2016; 128(16): 2106.

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Doi: 10.5505/aot.2023.43925

Case Report

A Case of Diffuse Large B Cell Lymphoma with Unusual Extranodal Breast, Brain İnvolvement And Autoimmune Hemolytic Anemia: Clinical and Radiological Presentations

Ekstranodal Meme, Beyin Tutulumu ve Otoimmun Hemolitik Anemisi Olan Alışılmadık Bir Diffüz Büyük B Hücreli Lenfoma Olgusu: Klinik ve Radyolojik Prezentasyonlar

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ABSTRACT

Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all non-Hodgkin lymphomas. Extranodal breast involvement of DLBCL is very rare. We present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms. A 54-year-old female patient was admitted to the emergency department with complaints of weakness and palpitations. Hemolytic anemia was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There were an increased fluorodexiglucose uptake detected in the middle and upper quadrant of the left breast in positron emission to-mography–computed tomography. She had impaired consciousness, her speech was dysarth-ric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. Cranial magnetic resonance imaging revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient, and had an expansile feature that restricted the diffusion. In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infil-tration was observed. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings im-proved and regressed completely after one course of therapy. This patient makes a signifi-cant contribution to the literature in terms of referring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of autoim-mune hemolytic anemia etiology and treatment preference.

Keywords: Diffuse large B cell lymphoma, extranodal involvement, hemolytic anemia, prognosis

ÖZET

Diffüz büyük B hücreli lenfoma (DBBHL), tüm Hodgkin dışı lenfomaların %30-40'ını oluşturan büyük ve transforme B hücrelerinden oluşan heterojen bir tümör grubudur. DBBHL'nin ekstranodal meme tutulumu oldukça nadirdir. Coombs pozitif hemolitik anemi ve nörolojik semptomlarla başvuran, meme

First Received: 19.02.2023, Accepted: 13.04.2023 doi: 10.5505/aot.2023.14890

kaynaklı bir DBBHL olgusunu sunmaktayız. Elli dört yaşında kadın hasta acil servise halsizlik ve çarpıntı şikayetleri ile başvurdu. Periferik kan yaymasında atipik hücre görülmeyen hastada hemolitik anemi düşünüldü. Pozitron emisyon tomografi-bilgisayarlı tomografide sol meme orta ve üst kadranda florodeksiglikoz tutulumunda artış saptandı. Bilinci bozuk, konuşması dizartrik, oryantasyon kısıtlı, kas kuvveti ve duyu ise muayenesi doğaldı, patolojik refleksi yoktu. Kranial manyetik rezonans görüntülemede pons seviyesinde difüzyonu kısıtlayan ekspansil özellikte T2 ve FLAIR hiperintens lezyon saptandı. Meme ilişkili kitlenin tru-cut biyopsisinde CD20(+), PAX5(+), CD3(-), CD5(-) büyük B hücreli lenfoma infiltrasyonu görüldü. Bir kür R-CHOP ve MTX tedavisi sonrası hastanın transfüzyon ihtiyacı geriledi. Nörolojik semptomları ve radyolojik bulguları bir kür tedaviden sonra tamamen düzeldi. Bu hasta, nörolojik semptomlarla başvurması, otoimmun hemolitik anemi etiyolojisinin araştırılması sırasında meme ilişkili kitleden DBBHL tanısı alması ve tedavi tercihi açısından literatüre önemli bir katkı sağlamaktadır.

Anahtar Kelimeler: Diffüz büyük B hücreli lenfoma, ekstranodal tutulum, hemolitik anemi, prognoz

Introduction

Non-Hodgkin lymphoma (NHL) ranks first among all hematological malignancies. Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all NHL [1]. Its incidence increases with age, and the median age at diagnosis is 64 years old. It is more common in men and 55% of the patients are male [2, 3]. It can occur de novo or histologically transformed from indolent lymphomas. The disease typically pre-sents as a rapidly growing nodal or extranodal mass associated with systemic symptoms [4].

One of the most common extranodal involvement sites for DLBCL is central nervous system (CNS) involvement. Extra-nodal breast involvement of DLBCL is very rare. It accounts for 0.5% of all NHLs and 2% of extranodal lymphomas [5]. However, even if lymphoma is the most common hematological malignancy affecting the breast, it accounts for only about 0.04% to 0.7% of all breast cancer cases, and this rare involvement appears to be associated with very few lym-phoid tissues in the breast. It is often confused with breast-derived solid malignancies due to both clinical and imaging findings [6].

CNS involvement is seen in one third of NHL patients. Involvement can be considered as leptomeningeal, epidural and intra-parenchymal metastasis. CNS involvement of lymphomas may present in many different clinics. The most common neurological complication of NHL is leptomeningeal disease that develops due to lymphoma infiltration of the leptomeninges. It can manifest with different symptoms and signs such as headache, nausea, communicating hydrocephalus, cranial neuropathy (for example, hearing loss, imbalance, dizziness, dysphagia, and hoarseness), limb weakness, paresthesia and pain. On magnetic resonance imaging (MRI), focal and diffuse leptomeningeal contrast involvement, sub-arachnoid nodule or enlargement of the intradural filum terminale can be seen [7]. Primary CNS lymphomas mostly present with single and all paren-chymal lesions, systemic involvement is not expected due to the blood brain barrier; second-ary CNS lymphomas are mostly characterized by leptomeningeal involvement and multiple parenchymal lesions can be detected [8].

In autoimmune hemolytic anemia (AIHA), autoantibodies are produced in abnormal amounts as a result of hyperfunction of B lymphocytes and complement are absorbed by erythro-cytes. As a result, it is destroyed rapidly after antigen-antibody reaction. While there is no role of any disease in primary AIHA etiology, secondary AIHA causes include lymphoproliferative dis-eases, viruses

such as Ebstein-barr virus, measles or cytomegalovirus, leukemias, thymoma and colon cancers. The incidence of AIHA / NHL is extremely rare [9].

In this case presentation, we present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms.

Case Presentation

A 54-year-old female patient was admitted to the emergency department with complaints of weakness, shortness of breath and palpitations. In the systemic examination of the patient, whose medical history was unremarkable, her body temperature was 38.6 C, blood pressure 120/86 mmHg, heart rate 96 / min and respiratory rate was 16 / min. In her neurological exami-nation, she had impaired consciousness, her speech was dysarthric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. In the extended biochemical analysis of the patient, hemoglobin was 5.3 gr/dl, leukocyte: 5510/mm^3, neutrophil: 3710/mm^3, thrombo-cyte: 140,000 / mm^3, lactate dehydrogenase (LDH): 1588 IU / L, haptoglobulin: 1 mg / dl (normal range: 30-200 mg / dl), total bilirubin: 1.26 mg /dl, indirect bilirubin: 0.86 mg / dl, and corrected reticulocyte resulted in 5.9%. Direct and indirect coombs tests were resulted as positive; AIHA was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There was no focus for infec-tion that could cause fever, and there was no growth in the blood and urine cultures.

The antinuclear antibody test (ANA) and extractable nuclear antigen (ENA) profile (RNP, Sm, SS-A, SS-B, Scl-70, Jo-1, anti-histone, anti-nucleosome) for possible underlying collagen tissue and lympho-proliferative diseases were found to be negative. In thoracic and abdominal computed tomography (CT), the spleen as 137 mm in size, reactive lymphadenopathies in the paraaortic and bilateral inguinal areas, and thickening of the skin and subcutaneous areas in both breast tissues were detected. There were also an increased fluorodexiglucose (FDG) uptake detect-ed in the middle (sudmax: 7.8) and upper quadrant (sudmax: 8.4) of the left breast in positron emission tomography–computed tomography (PET / CT) (Figure 1), and 6 cm heterogeneous contrast enhancement evaluated as breast imaging reporting and data system (BI-RADS) 4A in breast magnetic resonance (MRI) (Figure 2).

A bone marrow biopsy was performed by investigating the etiology of anemia. As a result of biopsy, megakaryocytes without significant clustering and dysplasia were interpreted as hypercellular bone marrow with mild reticulin fiber increase and no blast increase.

Cranial MRI revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient (ADC), and had an expansile feature that restricted the diffusion (Figure 3.A). In addition, a non-contrast appearance was observed, consistent with leptomeningeal thickening (Figure 4.A). Glucose was 78 mg / dL and protein was 18 g/L in the CSF sampling performed on the patient, and no cells were observed in direct examination. CSF flow examination was normal.

In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infiltration was observed (Figure 5a. and 5b) In the second bone marrow biopsy performed for possible infiltration of lymphoma, large b-cell lymphoid infiltration in the interstitial pattern, showing strong CD20 and weak CD5 expression was also revealed (Figure 6). No cytogenetic or molecular features were revealed in the fluorescence in situ

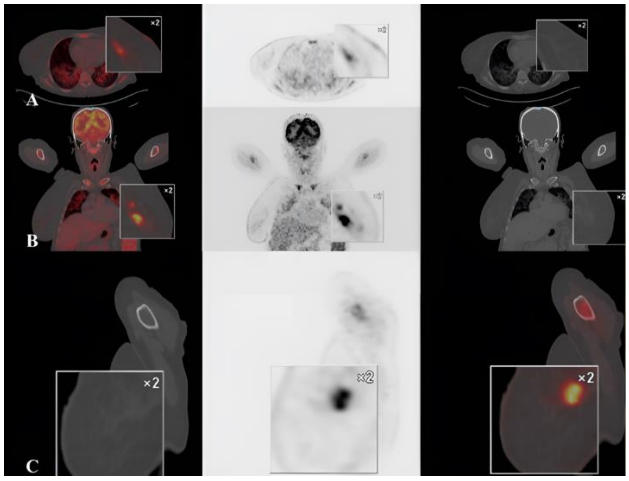

Figure 1.: Positron emission tomography–computed tomography (PET / CT) sections of patient: A. Axial (transverse), B. Coronal, C. Sagittal planes

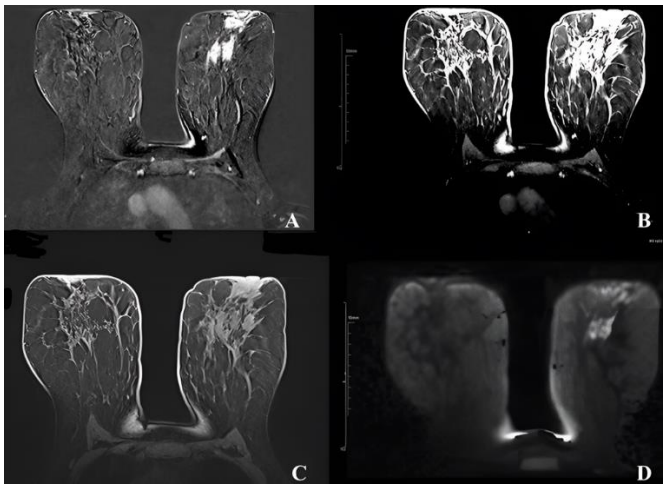

Figure 2.: Magnetic resonance (MRI) sections of breast associated mass: A. T1-weighted dynamic contrast-enhanced, B. Contrast-enhanced T1-weighted fat-suppressed subtraction, C. T1-weighted fat-saturated pre-contrast, D. Diffusion-weighted (DWI)

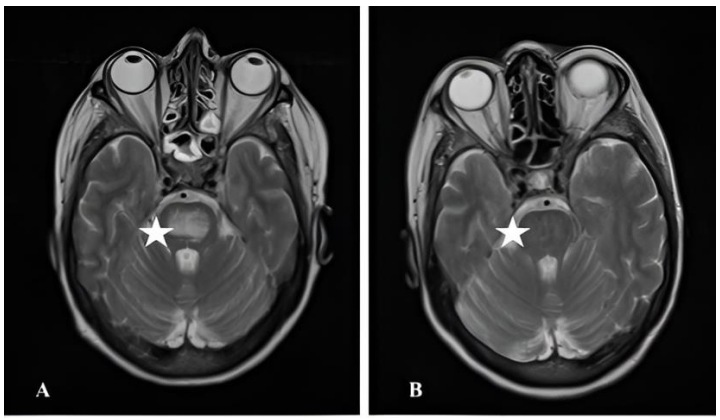

Figure 3: Hyperintense lesion on axial T2W MRI at pontin level. A.: Initial diagnosis, B.: After one course of therapy

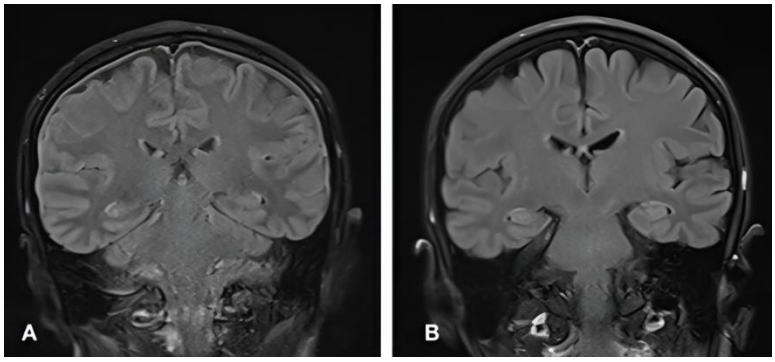

Figure 4: Leptomeningeal thickening on MRI. A.: Initial diagnosis, B.: After one course of therapy

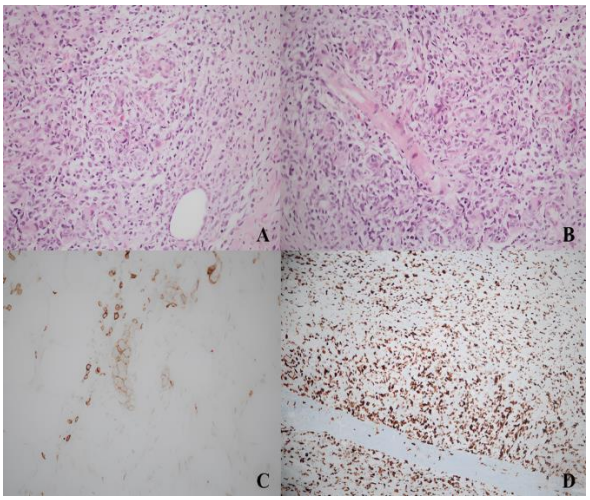

Figure 5a: Tru-cut biopsy sections of the breast associated mass: A. and B. Hematoxylin & eosin staining, C. CD-5 antibody staining, D. KI-67 staining

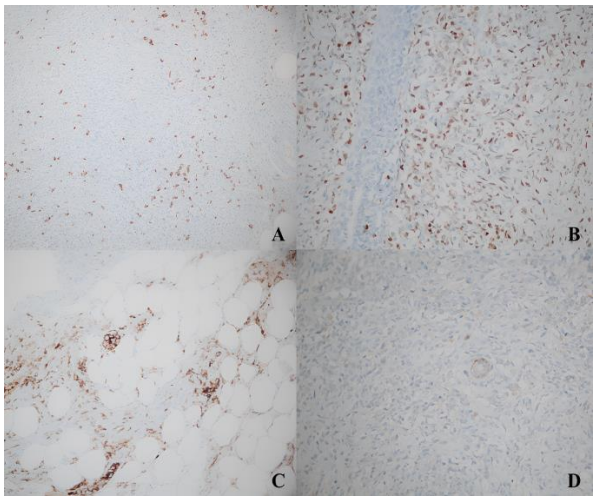

Figure 5b: Tru-cut biopsy sections of the breast associated mass: A. CD-3 staining, B. MUM-1 staining, C. CD-20 staining, D. CD-10 staining

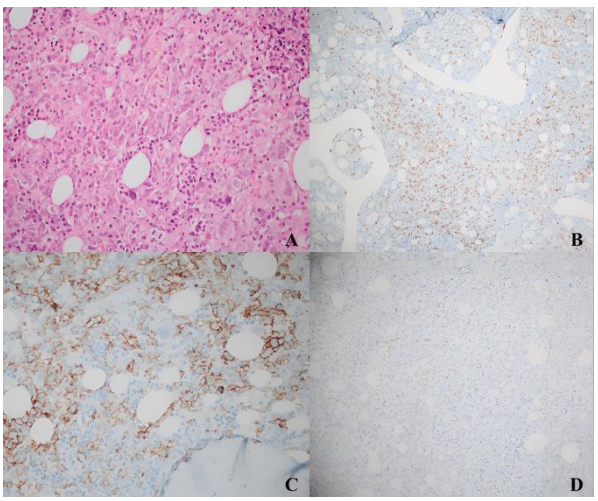

Figure 6: Bone marrow biopsy sections: A. Hematoxylin & eosin staining, B. MUM-1 staining, C. CD-20 staining, D. CD-34 staining

hybridization (FISH) analysis performed on both biopsy specimen and bone marrow samples.

Neurological clinical findings of the patient were considered as a result of neurological involvement of DLBCL. Methylprednisolone at a dose of 1 mg/kg was initiated due to hemolytic anemia and a treatment plan was made such as follows: Rituximab 375 mg/ m^2, cyclophosphamide 750 mg/m2, adriamycin 50 mg/m^2, vincristine 1,4 mg/m^2, prednisolone 100 mg (R-CHOP) every 21 days and on the 14th day, methotrexate (MTX) 3 gr/m^2, every 21 days. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings improved and regressed completely after one course of therapy (Figure 3.B., Figure 4.B.).

Discussion

Our case contributes significantly to the literature with its three features: AIHA, DLBCL diagnosed by a biopsy from breast associated mass, and CNS involvement associated or parane-oplastic neurological symptoms.

The incidence of AIHA and NHL is extremely rare. In a study by Ji-cheng Zhou et al., a total of 2204 NHL patients and 204 AIHA patients were screened between 2009 and 2018. AIHA and NHL association was observed in 20 of them. AIHA was detected in 0.91% of NHL patients, while NHL was detected in 9.8% of AIHA patients. Fourteen of the cases were male, 6 were fe-male and, the median age was 60 years old. All patients were stage 3-4 NHL. Lymphoma subtype with the highest incidence of AIHA was angioimmunoblastic t-cell lymphoma (AITL) with 7.31%, while marginal zone b-cell lymphoma was 6.25%, B cell lymphoma 4.25%, chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) 2.5% and mantle cell lymphoma 2.3% [9]. In another study, an AIHA serie was reported in patients diagnosed with splenic marginal zone lymphoma [10]. A total of 13 patients were complicated with AIHA in total and all patients died during follow-up. Patients with AIHA were found to have significantly ($p < 0.001$) shorter survival than those without AIHA [10]. In a study from 2000, a total of 16 patients with a diagnosis of NHL were found to be complicated with AIHA [11]. The treatment response for NHL was found to be significantly lower in this group, patients with NHL who did not develop AIHA had longer overall and median survival compared to the NHL/AIHA subgroup [11]. In another French multicenter retrospective cohort, all autoimmune manifestations were revealed in patients diagnosed with lymphoma and they were defined frequently together with CLL and DLBCL, while AIHA was the most common cause of autoimmune cytopenias [12]. The presence of autoimmune phenomena was associated with lower survival compared to non-autoimmune feature group when examining entire cohort. In general, it has been shown that the presence of AIHA or any autoimmune phe-nomenon has negative effects on treatment response and survival in patients diagnosed with lym-phoma. Although AIHA/ NHL coexisting is a rare condition, AIHA was detected as the first sign of the disease in our NHL patient.

Clinically, primary breast lymphomas manifest as painless palpable masses. Its distinction from other carcinomas is not clear radiologically. More than 95% of the primary breast lymphoma cases are B cell non hodgkin lymphomas, and 60% to 85% of them are DLBCL. Follicular lym-phoma, mucosa-associated lymphoma or marginal zone lymphoma are seen less common. Since these lymphomas are rare, there is no common approach to treatment. However, current treat-ments such as chemotherapy, immunotherapy and radiotherapy provide well designed disease con-trol in these patients. Average life

expectancy in 80% of the patients is 5 years [13].

It is difficult to differentiate breast lymphomas from benign and malignant breast diseases radiologically and clinically. However, differentiation of breast lymphomas from other malignan-cies (such as invasive breast cancer, inflammatory breast cancer or metastasis) is very important in terms of treatment preference. It is very important to know whether there is a systemic in-volvement. If the patient has systemic lymphoma, the risk of lymphoma involvement of breast increases.6 There was no finding in favor of systemic involvement in the different imaging results of our patient; the presence of only breast involvement was the most important clinical challenge.

Although DLBCL and neurological involvement has been widely reported, it is a difficult condition to diagnose. It often occurs as leptomeningeal involvement, intracranial and spinal me-tastasis, lymphomatosis cerebri and peripheral nervous system involvement causes different radi-ological appearances associated with these conditions.[7] Abe et al. evaluated cranial MRIs of 33 patients with intravascular DLBCL and found hyperintense lesions in the pons as the most com-mon finding (n = 19 (57.6%); leptomeningeal thickening was observed in 12.1% of cases [14]. Kawata et al. presented also a DLBCL case with central pontine myelinosis [15]. In our case, a lesion in pons and leptomeningeal thickening were observed together. However, flow cytometry and pathology of the patient's CSF sampling did not show any findings compatible with the DLBCL involvement. Also, sodium values measured in terms of central pontine myelinosis were normal during the clinical follow-up. High-dose systemic methotrexate ($3mg/m^2$) treatment was also administered, considering intracranial involvement, since it could not be differentiated in terms of etiology. Additionally, in our patient, the fact that a score that could objectively doc-ument the patient's neurological status before and after treatment was not recorded was an important limitation point.

As a result, our patient makes a significant contribution to the literature in terms of refer-ring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of AIHA etiology and treatment preference. Detailed screening of differ-ent organs and systems is of great importance in DLBCL cases where bone marrow biopsy is nor-mal and difficult to diagnose in the early period.

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REFERENCES

1. Iqbal J, Joshi S, Patel KN, Javed SI, Kucuk C, Aabida A, d'Amore F, Fu K. Clinical implication of genome-wide profiling in diffuse large B-cell lymphoma and other subtypes of B-cell lym-phoma. Indian J Cancer. 2007; 44(2): 72-86.

2. Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, Lipscomb J, Flowers CR. Ra-cial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the Unit-ed States. Cancer. 2011; 117(11): 2530-2540.

3. Morgan G, Vornanen M, Puitinen J, et al. Changing trends in the incidence of non-Hodgkin's lymphoma in Europe. Biomed Study Group. Ann Oncol. 1997; 8 Suppl 2: 49-54

4. Armitage JO. How I treat patients with diffuse large B-cell lymphoma. Blood. 2007; 110(1):29-36.

5. Candelaria M, Oñate-Ocaña LF, Corona-Herrera J, et al. Clinical characteristics of primary extranodal versus nodal diffuse large b-cell lymphoma: a retrospective cohort study in a cancer center. Rev Invest Clin. 2019; 71(5): 349-358.

6. Shim E, Song SE, Seo BK, Kim YS, Son GS. Lymphoma affecting the breast: a pictorial review of multimodal imaging findings. J Breast Cancer. 2013; 16(3): 254-265.

7. Mauermann ML. Neurologic Complications of Lymphoma, Leukemia, and Paraproteinemias. Continuum (Minneap Minn). 2017; 23(3): 669-690.
8. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. AJNR Am J Neuroradiol. 2011; 32(6): 984-92.
9. Zhou JC, Wu MQ, Peng ZM, Zhao WH, Bai ZJ. Clinical analysis of 20 patients with non-Hodgkin lymphoma and autoimmune hemolytic anemia: A retrospective study. Medicine (Balti-more). 2020; 99(7): 19015.
10. Fodor A, Molnar MZ, Krenacs L, Bagdi E, Csomor J, Matolcsy A, Demeter J. Autoimmune hemolytic anemia as a risk factor of poor outcome in patients with splenic marginal zone lymphoma. Pathol Oncol Res. 2009; 15(4): 597-603
11. Sallah S, Sigounas G, Vos P, Wan JY, Nguyen NP. Autoimmune hemolytic anemia in patients with non-Hodgkin's lymphoma: characteristics and significance. Ann Oncol. 2000; 11(12):1571-1577.
12. Jachiet V, Mekinian A, Carrat F, et al. French Network of systemic and immune disorders associated with hemopathies and cancer (MINHEMON). Autoimmune manifestations associated with lymphoma: characteristics and out-come in a multicenter retro-spective cohort study. Leuk Lymphoma. 2018; 59(6): 1399-1405.
13. Franco Pérez F, Lavernia J, Aguiar-Bujanda D, et al. Primary Breast Lymphoma: Analysis of 55 Cases of the Spanish Lymphoma Oncology Group. Clin Lymphoma Myeloma Leuk. 2017; 17(3): 186-191.
14. Abe Y, Narita K, Kobayashi H, et al. Clinical value of abnormal findings on brain magnetic resonance imaging in patients with intravascular large B-cell lymphoma. Ann Hematol. 2018; 97(12): 2345-2352.
15. Kawata E, Isa R, Yamaguchi J, et al. Diffuse large B-cell lymphoma presenting with central pontine myelinolysis: a case report. J Med Case Rep. 2015 Jun 5; 9: 131.

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Doi: 10.5505/aot.2023.14890

