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Prognostic Value of Inflammatory Markers, CA 19-9, MELD Score, and ECOG in Stage 4 Gastric Cancer with Liver Metastases

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ABSTRACT

Aim: This study aimed to investigate the prognostic significance of the Model for End-Stage Liver Disease (MELD) score in patients with stage 4 liver metastatic gastric cancer and to investigate whether other clinical pathological data are prognostic indicators.

Methods: Stage 4 liver metastatic gastric cancer patients who were followed up retrospectively between January 2014 and November 2024 were included in the study. Demographic and clinical data of the patients were entered into the database. Survival analyses were performed using the Kaplan-Meier method and the log-rank test. Independent effects of prognostic factors were evaluated using the Cox proportional hazards regression model (Cox). Statistical significance was accepted as $p<0.05$.

Results: One hundred and fifty patients were included in the study. The median age of the patients was 64 years, and 26.3% were female. The estimated median overall survival (mOS) was 7.9 months. The mOS was 10.5 months in the Eastern Cooperative Oncology Group (ECOG) 0-1 group compared to 3.6 months in the ECOG 2-3 group ($p<0.001$). According to the ideal cut-off value of carbohydrate antigen (CA) 19-9, survival was 9.7 months in the ≤37.1 U/mL group and 6.7 months in the >37.1 U/mL group ($p=0.017$). There was no difference in survival according to the determined categories of age ($p=0.395$), gender ($p=0.670$), smoking status ($p=0.764$), body mass index (BMI) ($p=0.563$), carcinoembryonic antigen (CEA) ($p=0.057$), neutrophil-to-lymphocyte ratio (NLR) ($p=0.359$), platelet-to-lymphocyte ratio (PLR) ($p=0.158$), monocyte-to-lymphocyte ratio (MLR) ($p=0.811$), and MELD score ($p=0.561$). In univariate Cox regression analysis, an ECOG score of 2 and above [hazard ratio (HR) 4.03; $p<0.001$] and a CA 19-9>37.1 U/mL (HR 1.54; $p=0.018$) were determined as poor prognostic factors, and BMI, NLR, PLR, MLR, MELD score, and CEA did not show prognostic significance.

Conclusion: We found that CA 19-9 level and ECOG performance status are markers that can be used in determining prognosis in liver metastatic gastric cancer, and the analyzed blood values (NLR, PLR, MLR) and MELD score did not demonstrate any prognostic significance in this patient group.

Keywords: CA-19-9 antigen, clinical oncology, gastrointestinal cancer, MELD score, metastasis, oncology, stomach neoplasms

Introduction

Gastric cancer is the fifth most frequently diagnosed cancer worldwide, and it holds the fourth position among cancers causing mortality [1]. In recent years, its prevalence has been increasing, especially among young people, due to changing consumption habits [1]. With early-stage diagnosis and curative treatments, 5-year survival rates can reach 70% [2]. However, despite early diagnosis and screening programs, the emergence of cancer-related symptoms often leads to diagnosis in locally advanced or metastatic stages. Despite the development of the health system and innovative treatments,

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one-year survival rates are still below 25%, and the median overall survival (OS) in the metastatic stage is less than one year [3,4].

Cancer is a disease that affects not only the specific organ, but also all systems. Systemic inflammation occurs with the development of cancer, leading to decreased performance, cachexia, and later failure of systems and death. Some prognostic markers have been proposed for stomach cancer and many other types of cancer, with parameters beginning with inflammation and affecting other systems [5]. Although the tumor, node, metastasis staging system is also used as a prognostic factor in stomach cancer, it defines stage 4 stomach cancer in a single category [6]. Patients with similar stages can show a heterogeneous prognosis. Therefore, in recent years, prognostic indicators based on simple hematological indicators reflecting systemic inflammation and nutritional status have become increasingly important [7]. Inflammatory parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) obtained from complete blood count provide indirect information about the immune response, tumor microenvironment, and systemic inflammation level [8,9]. However, low body mass index (BMI) values, in particular, can also predict a negative prognosis as an indicator of malnutrition and poor immunity [2].

The Model for End-Stage Liver Disease (MELD) score, which is a similar blood parameter and reflects liver dysfunction, has also been associated with morbidity and mortality, especially after surgery, in gastric cancer patients in some studies [10,11]. Although the MELD score does not directly indicate tumor burden in patients with metastatic gastric cancer, it can provide prognostic information by indicating the severity of liver function impairment due to cancer [12]. However, there is insufficient information on whether these markers are prognostic in the group with liver metastatic gastric cancer that will progress to liver failure.

In this study, we aimed to investigate prognostic markers, especially the MELD score, in patients with liver metastatic gastric cancer.

Methods

This retrospective study included stage 4 gastric cancer patients with liver metastases who had complete follow-ups between January 2014 and November 2024. This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ministry of Health of the Republic of Türkiye (decision no: 118/05, date: 23.08.2023).

Inclusion criteria were being have pathologically confirmed gastric cancer, 18 years of age and older, patients with radiological or pathological liver metastases, and complete follow-ups, no concurrent chronic kidney disease, no current or past history of malignancy, and patients with gastric adenocarcinoma who were not receiving active infectious disease, immunosuppressive drugs or nutritional support. Patients with multiple cancers, patients without liver metastases, patients with esophageal junction tumors, and patients with known human epidermal growth factor receptor 2 gastric cancers were excluded in the study.

Demographic information, patient clinicopathological parameters, and serum blood parameters measured before chemotherapy were obtained from the hospital automation system.

Calculating Indexes

- BMI=Weight (kg) / [height (m)]^2
- NLR=Absolute neutrophil count / absolute lymphocyte count
- PLR=Platelet count / lymphocyte count
- MLR=Monocyte count / lymphocyte count
- MELD=3.78×ln(bilirubin)+11.2×ln[international normalized ratio (INR)]+9.57×ln(creatinine)+6.43

Statistical Analysis

Statistical analyses in this study were carried out using Statistical Package for the Social Sciences (SPSS) statistics software version 24 (SPSS Inc., Chicago, IL). In the study, variables were categorized, and the ratio of each to the total patient group was written as a percentage. In the study, the receiver operating characteristic (ROC) curves and the area under the curve (AUC) analyses were performed to determine the ideal cut-off points to be used in the analyses. In the parameters for which a specific cut-off could not be determined by the ROC-AUC method, the median value was used as the cut-off. Survival analyses were performed using the Kaplan-Meier technique. Group comparisons were statistically analyzed using the log-rank test. Factors affecting survival were evaluated using univariate Cox proportional hazards (Cox) regression analysis. OS was calculated as the time from the date of diagnosis of metastasis to the date of death or last follow-up. A p of <0.05 was used as the criterion for statistical significance.

Results

The research encompassed 150 patients in its entirety. The median age of the patients was 64 (minimum: 32, maximum: 89). Forty-one of the patients were female (26.3%) and 84 of the patients (56.0%) had a smoking history of 10 packs/year or more. Other clinical data are shown in Table 1. The ideal cut-off values of carcinoembryonic antigen (CEA), CA199, NLR, PLR, MLR, and MELD score for gastric cancer were investigated using ROC-curve analysis. The ideal cut-off values were determined as 10.7 for CEA (cut-off sensitivity: 54.7%, specificity: 62.7%) and 37.1 for carbohydrate antigen (CA) 19-9 (cut-off sensitivity: 54.7%, specificity: 61.3%). The ideal cut-off value for NLR, PLR, MLR, and MELD score could not be determined, and median values were used in the analyses (3.6, 192.5, 0.40, 7.2, respectively) (Figure 1, Table 2).

Median OS was determined as 7.9 months [95% confidence interval (CI): 6.4-9.4 months]. In the group with Eastern Cooperative Oncology Group (ECOG) performance status 0-1,

Table 1. Clinical and laboratory data of the patients and estimated median overall survival analyses

Parameter	Category	N	%	Median OS (months) (95% CI)	p*
Age	<60	47	31.3	8.10 (3.86-12.34)	0.395
	≥60	103	68.7	7.70 (6.19-9.21)	
Gender	Female	41	27.3	7.00 (4.96-9.04)	0.670
	Male	109	72.7	8.50 (6.38-10.62)	
ECOG	0-1	113	75.3	10.50 (7.71-13.29)	**<0.001**
	≥2	37	24.7	3.60 (2.17-5.03)	
Smoking status	No	66	44.0	8.10 (5.96-10.24)	0.764
	Yes	84	56.0	7.20 (5.26-9.14)	
BMI	<20	15	10.0	12.40 (9.39-15.41)	0.563
	≥20	135	90.0	7.70 (6.40-8.99)	
CEA	<10.7	81	54.0	10.20 (7.15-13.25)	0.057
	>10.7	69	46.0	7.00 (6.02-7.98)	
CA 19-9	≤37.1	81	54.0	9.70 (7.30-12.10)	**0.017**
	>37.1	69	46.0	6.70 (5.33-8.07)	
NLR	≤3.6 (median)	77	51.3	9.50 (7.59-11.41)	0.359
	>3.6	73	48.7	6.50 (4.87-8.13)	
PLR	<192.5 (median)	75	50.0	9.70 (7.98-11.42)	0.158
	≥192.5	75	50.0	7.00 (5.26-8.75)	
MLR	≤0.40 (median)	77	51.3	8.40 (6.28-10.52)	0.811
	>0.40	73	48.7	7.70 (5.66-9.74)	
MELD	≤7.19 (median)	79	52.7	8.80 (6.42-11.02)	0.561
	>7.19	71	47.3	7.20 (6.03-8.37)	

*p values were obtained by Kaplan-Meier analysis.
OS: Overall survival, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for end-stage liver disease

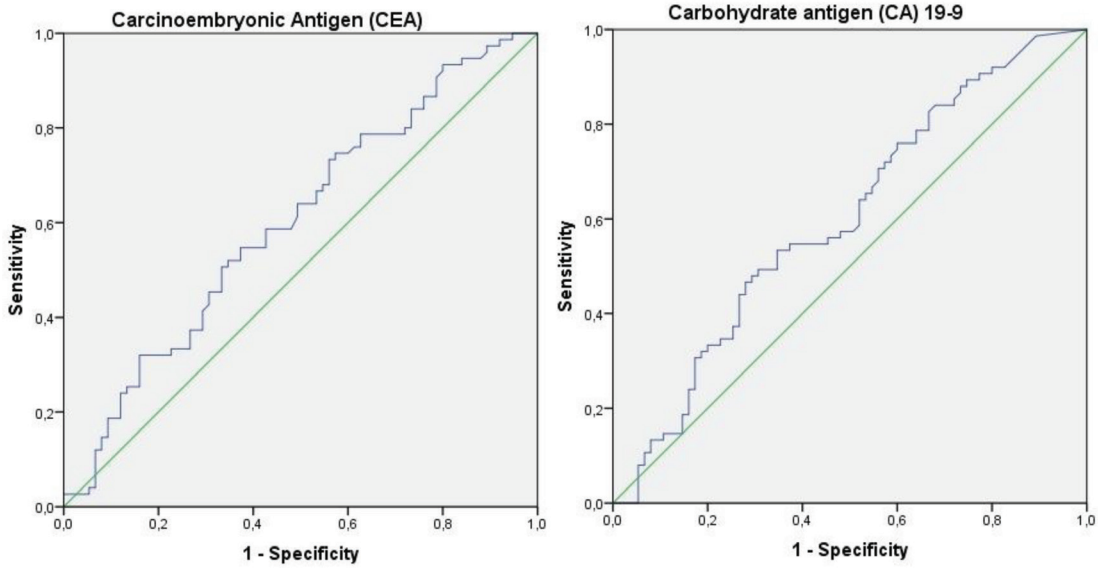

Figure 1. ROC-curve analysis to determine the ideal cut-off for variables
ROC: Receiver operating characteristic

median OS was 10.50 months (95% CI: 7.71-13.29) and in the group with ECOG 2-3, median OS was 3.60 months (95% CI: 2.17-5.03) (log-rank p<0.001). In the CA 19-9 ≤37.1 U/mL group, OS was 9.70 months (7.30-12.10), and in the >37.1 U/mL group, OS was 6.70 months (95% CI: 5.33-8.07) (log-rank p=0.017). For CEA <10.7 ng/mL, the median OS was 10.20 months (95% CI: 7.15-13.25), while for CEA >10.7 ng/mL, it was 7.00 months (log-rank p=0.001). Smoking status (log-rank p=0.764), BMI (<20 vs. ≥20 kg/m²; log-rank p=0.563), NLR (≤3.6 vs >3.6; log-rank p=0.359), PLR (<192.5 vs. ≥192.5; log-rank p=0.158), MLR (≤0.40 vs. >0.40; log-rank p=0.811), and MELD (≤7.19 vs. >7.19; log-rank p=0.563) were not found to be statistically significant for OS (Table 1).

ECOG performance status was found to be predictive of survival in the 0-1 vs 2-3 comparison [hazard ratio (HR) 4.03; 2.625-6.194; p<0.001]. CA 19-9>37.1 was associated with decreased OS compared to CA 19-9 levels of 37.1, U/mL and below (HR 1.54; 1.077-2.201; p=0.018). Other factors such as age (<60 vs ≥60 years; HR 1.18; 0.806-1.720; p=0.398), gender (female vs male; HR 0.92; 0.617-1.364; p=0.671), smoking status, BMI (0.566), CEA (0.059), NLR (0.361), PLR (0.161), MLR (0.812), and MELD (0.563) scores were not significantly associated with OS (Figure 2, Table 3).

Discussion

In this study, data of 150 metastatic gastric cancer patients with liver metastases were analyzed. Patients with ECOG performance score 0-1 had an estimated median OS of 10.5 months, while patients with ECOG 2-3 had only an mOS of 3.6 months (p<0.0001). Patients with high CA 19-9 had worse survival rates than those with low CA 19-9 (p=0.017). When evaluated with Cox regression analysis, CA 19-9 and ECOG were prognostic markers, while NLR, PLR, MLR, and MELD score were found to be not prognostic markers in liver metastatic gastric cancer.

In stage 4 gastric cancer, many guidelines recommend chemotherapy to prolong survival and achieve a longer life span [13]. However, in some patients, survival is shorter than expected, and palliative care is offered as an option [14]. In metastatic gastric cancer, ECOG performance score plays a major role as a determinant in predicting prognosis and chemotherapy toxicity [15,16] In their study, ECOG was determined as a prognostic indicator. Similar results were presented in the study by Demirelli et al [17]. In our study, ECOG performance score served as a prognostic indicator, which is consistent with the literature.

Table 2. Determination of ideal cut-off values of variables using ROC-curve analysis

Variables	AUC (95% confidence interval)	Ideal cut-off	Sensitivity for cut-off	Specificity for cut-off	p
CEA	0.601 (0.510-0.691)	10.7	54.7%	62.7%	0.034
CA 19-9	0.600 (0.509-0.690)	37.1	54.7%	61.3%	0.035
NLR	0.529 (0.436-0.621)	3.6 (median)			0.545
PLR	0.554 (0.462-0.646)	192.5 (median)			0.256
MLR	0.516 (0.423-0.609)	0.40 (median)			0.735
MELD	0.549 (0.456-0.641)	7.2 (median)			0.303

CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for End-Stage Liver Disease, ROC: Receiver operating characteristic, AUC: Area under the curve

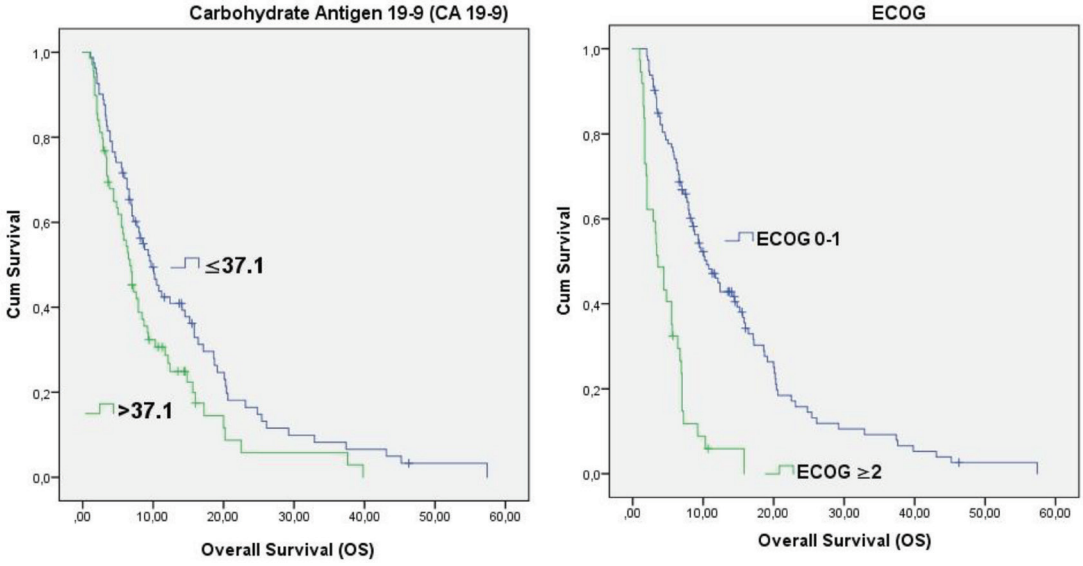

Figure 2. Survival graph of ECOG and CA 19-9
ECOG: Eastern Cooperative Oncology Group, CA: Carbohydrate antigen

Table 3. Univariate COX-regression analysis of variables for overall survival

Variable	Category	HR (95% CI)	p
Age	<60 years vs. ≥60 years	1.18 (0.806-1.720)	0.398
Gender	Male vs. female	0.92 (0.617-1.364)	0.671
ECOG performance status	0-1 vs. 2-3	4.03 (2.625-6.194)	**<0.001**
Smoking status	<10 pack-years vs. ≥10 pack-years	1.06 (0.739-1.508)	0.765
BMI	<20 kg/m² vs. ≥20 kg/m²	1.19 (0.655-2.167)	0.566
CEA	≤10.7 ng/mL vs. >10.7 ng/mL	1.42 (0.987-2.032)	0.059
CA 19-9	≤37.1 U/mL vs. >37.1 U/mL	1.54 (1.077-2.201)	**0.018**
NLR	≤3.6 vs. >3.6	1.18 (0.827-1.683)	0.361
PLR	<192.5 vs. ≥192.5	1.29 (0.905-1.827)	0.161
MLR	≤0.40 vs. >0.40	0.96 (0.675-1.360)	0.812
MELD	≤7.19 vs. >7.19	1.11 (0.781-1.574)	0.563

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MELD: Model for End-Stage Liver Disease, Cox: Cox proportional hazards regression model, CI: Confidence interval, HR: Hazard ratio

CA 19-9, also known as sialyl-Lewis^a, is a glycoprotein complex with a tetrasaccharide structure located on the cell surface [18]. This antigen is naturally found in pancreatic ductal cells, bile duct epithelium, stomach, colon, endometrium, and salivary gland epithelium. Blood serum concentrations above 30-40 U/mL are usually pathological. CA 19-9 can be elevated in many types of cancer, especially in pancreatic and biliary tract cancers. In the study by Yu et al. [19], high levels of CA 19-9 were shown to be a prognostic marker in gastric cancers. In their study, Roşu et al. [20] showed that CA 19-9 was also a prognostic marker for gastric cancers. In our study, similar results were obtained as reported in the literature, and CA 19-9 was shown to be a prognostic marker.

The MELD score is a prognostic index based on laboratory data developed to estimate the 90-day mortality risk in patients with advanced liver disease who underwent a transjugular intrahepatic portosystemic shunt procedure [21]. The MELD score can evaluate the severity of liver failure, especially cirrhosis, using serum bilirubin, creatinine, and international normalized ratio values [22]. In their study on patients with liver metastatic colon cancer, Karadağ and Karakaya [23] showed that high MELD scores were an indicator of poor prognosis. It has been shown that it can be a marker of mortality in patients with gastric cancer who underwent surgery [11,24]. Although the MELD score is not a marker that directly reflects tumor biology in terms of metastatic gastric cancer, it can provide information about liver reserve, especially in patients with liver metastases, and this can predict prognosis. However, in our study, it was shown that the MELD score would not be a prognostic marker in patients with gastric cancer with liver metastasis. Although the MELD score indicates liver functions, mortality occurs following liver function deterioration in metastatic gastric cancer, which may explain why this score is not found to be prognostic.

Study Limitations

The most important limitation of our study is its retrospective design. Due to its retrospective nature, data were obtained from past records and may contain potential biases. In addition, since some data, such as ECOG performance scores, are based on subjective assessments, individual evaluation differences may have occurred in the results.

Conclusion

As a result, we demonstrated that CA 19-9 and ECOG performance score can be markers for prognosis in liver metastatic gastric cancer, and that NLR, PLR, MLR scores together with MELD score do not possess predictive properties. These results should be validated in future studies.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ministry of Health of the Republic of Türkiye (decision no: 118/05, date: 23.08.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.Z., T.E., G.İ.İ., S.G., Y.D., A.K., Design: E.Z., T.E., G.İ.İ., Y.D., A.K., Data Collection or Processing: S.G., Analysis or Interpretation: E.Z., S.G., Literature Search: E.Z., T.E., G.İ.İ., Y.D., Writing: E.Z., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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