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Research

Impact of Malnutrition on Prognosis in Patients with HER2-negative Metastatic Gastric Cancer

Metastatik HER2-negatif Mide Kanseri Hastalarında Malnütrisyonun Prognoz Üzerine Etkisi

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ABSTRACT

Objective: Malnutrition is common in patients with gastric cancer and may adversely affect their prognosis. This study investigated the impact of malnutrition on overall survival (OS) in patients with metastatic gastric cancer by computing the Malnutrition Universal Screening Tool (MUST), one of the most used nutritional screening tools.

Methods: Seventy-seven patients diagnosed with HER2-negative metastatic gastric cancer were included in this retrospective study. All patients had pathologically metastatic disease at diagnosis for gastric adenocarcinoma and received standard-based chemotherapy as first-line treatment. The MUST was used to evaluate the malnutrition risk. It was considered the participants with a MUST score ≥1 (moderate and high risk) as malnourished patients and those with a MUST score of 0 (low risk) as not malnourished patients. We analyzed the patient characteristics, the MUST score and the OS outcomes.

Results: The mean age was 58.7±13.6, and 68.8% were male. The most common metastatic sites were the peritoneum (64.9%) and liver (44.2%). The median MUST score was 2 (0-4). According to the MUST, 50 patients (64.9%) had moderate-high risk in our study. The median OS was 11.2 months in this study. Patients with moderate and high risk had a shorter median OS than patients with low risk (8.8 months vs. 14.0 months, p=0.034). In the univariate Cox regression analysis for death risk, >10% of weight loss [hazard ratio (HR): 1.60], MUST score ≥1 (HR: 1.69), and albumin <3.5 g/dL (HR: 1.64) were found to be an increased risk factor for death. But, statistically significant results were not obtained in the multivariate analysis.

Conclusion: The median OS was significantly lower in malnourished patients than in non-malnourished patients. However, the effects of moderate-high risk MUST, low serum albumin, and >10% of weight loss on the death risk may not be evaluated independently. The high prevalence of malnutrition and its relation to poor survival highlights the significance of routine screening for malnutrition with MUST in patients with gastric cancer.

Keywords: Albumin, gastric cancer, malnutrition, Malnutrition Universal Screening Tool, overall survival, weight loss

ÖZ

Amaç: Mide kanseri hastalarında malnütrisyon yaygındır ve hastaların prognozlarını olumsuz etkileyebilir. Bu çalışma, en çok kullanılan malnütrisyon tarama araçlarından biri olan Malnutrition Universal Screening Tool (MUST) skorunu hesaplayarak metastatik mide kanserli hastalarda malnütrisyonun genel sağkalım (GSK) üzerine olan etkisini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya HER2-negatif metastatik mide kanseri tanılı 77 hasta dahil edildi. Tüm hastalar mide adenokarsinom tanısı sırasında patolojik olarak metastatik hastalığa sahipti ve birinci basamak tedavi olarak standart bazlı kemoterapi almışlardı. MUST, malnütrisyon riskini değerlendirmek için kullanıldı. MUST puanı ≥1 (orta ve yüksek riskli) olan katılımcılar malnütrise, MUST puanı 0 (düşük riskli) olanlar malnütrisyonu olmayan hasta olarak kabul edildi. Hasta özelliklerini, MUST skorunu ve GSK sonuçlarını analiz ettik.

Bulgular: Yaş ortalaması 58,7±13,6 idi ve %68,8'i erkekti. En sık metastatik bölgeler periton (%64,9) ve karaciğer (%44,2) idi. Medyan MUST skoru 2 (0-4) idi. MUST'ye göre çalışmamızda 50 hastada (%64,9) orta-yüksek risk vardı. Medyan GSK çalışmamızda 11,2 aydı. Orta ve yüksek riskli hastalar düşük riskli hastalara göre daha kısa medyan GSK'ye sahiplerdi (8,8 ay ve 14,0 ay, p=0,034). Ölüm riski için tek değişkenli Cox regresyon analizinde >%10 kilo kaybı [risk oranı (HR): 1,60], MUST skor ≥1 (HR: 1,69) ve albümin <3,5 g/dL (HR: 1,64) ölüm için artmış birer risk faktörleri olarak bulunmuştur. Ancak çok değişkenli analizde istatistiksel olarak anlamlı sonuçlar elde edilememiştir.

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Sonuç: Medyan GSK malnütrise hastalarda, malnütrisyonu olmayan hastalardan önemli ölçüde daha kısaydı. Ancak orta-yüksek risk MUST, düşük serum albümini ve >%10 kilo kaybının ölüm riski üzerindeki etkileri birbirlerinden bağımsız olarak değerlendirilemeyebilir. Malnütrisyonun yüksek prevalansı ve daha kötü sağkalım ile ilişkisi, mide kanserli hastalarda MUST ile rutin malnütrisyon taramasının önemini vurgulamaktadır.

Anahtar Kelimeler: Albümin, mide kanseri, malnütrisyon, Malnutrition Universal Screening Tool, genel sağkalım, kilo kaybı

INTRODUCTION

Gastric cancer is a highly lethal and frequently incurable malignancy. Most patients have pathological human epidermal growth factor receptor-2 (HER2)-negative disease at an advanced stage. While systemic chemotherapy is the most preferred treatment option, it often requires nutritional, pain, and other supportive management (1,2).

Malnutrition is a deficiency in energy and nutrients and skeletal muscle loss, associated with functional and physical impairment, increased adverse effects of chemotherapy, poor tumor response to chemotherapy, quality of life, and overall survival (OS). Malnutrition is present in 40%-80% of cancer patients and is significantly related to morbidity and mortality in patients with metastatic cancer (3-6). Malnutrition is also more common and severe in gastrointestinal tract cancer than in other malignancies (7,8). Thus, malnutrition might affect prognosis in gastric cancer patients; hence, screening for malnutrition might be crucial for providing appropriate nutritional management, clinical benefit, and the survival advantage in gastric cancer.

Several screening tools have been improved to evaluate the risk of malnutrition. Among them, the Malnutrition Universal Screening Tool (MUST) is a validated simple screening tool frequently used in patients with cancer (7,9-11). Additionally, the European Society for Clinical Nutrition and Metabolism (ESPEN) suggests routine screening in gastrointestinal cancer patients using validated scales to notice and treat malnutrition (12).

This study analyzed the impact of malnutrition on OS in patients with metastatic gastric cancer by computing the MUST score, one of the most used nutritional screening tools.

METHODS

Study Design and Patients

A total of 77 patients diagnosed with metastatic gastric cancer between January 2013 and March 2020 were included in this retrospective study. The inclusion criteria comprised [1] those who had pathological metastatic disease at diagnosis for gastric adenocarcinoma and [2] those who received standard-based chemotherapy as first-line treatment. The exclusion criteria were [1] those who did not receive chemotherapy; [2] those aged <18 years; [3] those who had Eastern Cooperative Oncology Group Performance Status (ECOG PS) >3; [4] those who could not be assessed by MUST because of lack of patient data; [5] and those who had HER2-positive disease.

Patient Evaluation

Patients' general clinical characteristics were noted. Disease evaluations were assessed with computed tomography as a standard. Treatment response was determined by Response Evaluation Criteria in Solid Tumors version 1.1 criteria. OS was defined as the time from the date of metastatic disease diagnosis until the last date the patient was alive or dead. Malnutrition risk status was screened for using MUST at the diagnosis of metastatic disease. The Bezmialem Vakif University Non-Interventional Research Ethics Committee approved the study with the reference number 2021/395 (date: 30.11.2021).

Malnutrition Screening Tool

The MUST was used to evaluate the malnutrition risk. The MUST scale is the sum of scores of 3 factors: the body mass index (BMI) at presentation (>20.0=0, BMI 18.5-20.0=1, BMI<18.5=2), the percentage of total body weight loss over the last 3-6 months (weight loss <5%=0, weight loss 5%-10%=1, weight loss >10%=2), and acute disease effect score (adding a score of 2 if there is no nutritional intake for >5 days). The overall risk of malnutrition was defined as low risk if MUST score=0, moderate risk if the MUST score=1, and high risk if MUST score≥2. Finally, we considered the participants with a MUST score≥1 as malnourished patients and those with a MUST score of 0 as not malnourished patients. MUST scores were calculated at diagnosis of metastatic disease.

Statistical Analysis

Statistical data were provided using the Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were detailed by frequencies and percentages, and continuous and ordinal variables were detailed by mean, standard deviation, median and range. Kolmogorov-Smirnov test was performed to determine the normal distribution range. The Pearson $\chi 2$ test was used to compare qualitative variables. Patients' characteristics were assessed with descriptive analysis. The median cut-off value of the prognostic nutrition index (PNI) and neutrophil-to-lymphocyte ratio (NLR) was detected by performing the receiver operating characteristic curve analysis. OS analysis

was assessed using Kaplan-Meier survival curves and the log-rank test. Univariate and multivariate Cox proportional hazard models were used to identify predictors of death risk. Statistical significance was set at a p-value of <0.05.

RESULTS

Patients with HER2-negative *de novo* metastatic gastric cancer (n=77) were included in the study. The mean age was 58.7±13.6, and 68.8% were male. The mean BMI was 24.5±5.2. The ECOG PS of 76.6% of the patients was 0-1. All patients had metastatic disease at diagnosis. Standard chemotherapies were initiated for all patients as first-line treatment. The rate of patients who started second-line chemotherapy was 36.4%, the rate of patients who started third-line chemotherapy was 15.6%, and the rate of patients who began fourth-line chemotherapy was 2.6%. The most common metastatic sites were the peritoneum (64.9%) and liver (44.2%). Thirty-one (40.3%) patients had single-organ metastasis. The MUST was used to evaluate the malnutrition risk as a nutritional screening tool. The median MUST score was 2 (0-4). According to the MUST, 27 patients (35.1%) had a low risk, 8 patients (10.4%) had a moderate risk, and 42 patients (54.5%) had a high risk. Thus, 50 patients (64.9%) had moderate-high risk in our study. The participants with moderate and high risk were considered malnourished patients. While the number of patients with weight loss of >10% and loss of appetite was significantly higher in patients with moderate and high risk than in low-risk patients, the mean BMI and the number of patients with obesity was substantially lower. The baseline characteristics of the 77 patients are shown in Table 1. The comparison of the biochemical variables was also evaluated according to the MUST in our study, but no significant difference was found between the groups (Table 2).

The median follow-up time was 11.2 months (1.1-30.3) in our study. The median OS was 11.2 months [9.1-13.3, 95% confidence interval (CI)]. The rate of patients who reached median OS was 88% at 6 months, 46% at 1 year, and 9% at 2 years. Patients with moderate and high risk had a shorter median OS than patients with low risk [8.8 months (6.6-11.1, 95% CI) vs. 14.0 months (11.7-16.4, 95% CI), p=0.034; Figure 1].

In the univariate Cox regression analysis for death risk, >10% of weight loss [hazard ratio (HR): 1.60], MUST score≥1 (moderate-high risk) (HR: 1.69), and albumin <3.5 g/dL (HR: 1.64) were found to be an increased risk factor for death. Statistically significant results were not obtained in the multivariate analysis, but the MUST score reached an almost statistically significant result (p=0.051). The results of univariate and multivariate analyses for death risk are shown in Table 3.

DISCUSSION

Malnutrition is common in patients with gastric cancer and may adversely affect their prognosis (7,13,14). Therefore, the ESPEN recommends performing a nutritional assessment for patients with gastric cancer at diagnosis using validated scales to determine and treat malnutrition (12). Because metastatic gastric cancer is not curable, the aim is an OS advantage and best supportive care. These patients are thought to have a higher risk of malnutrition; hence, they should be evaluated from this perspective (1,7). Moreover, the malnutrition might reduce the OS in patients with gastric cancer.

Our study analyzed the risk of malnutrition by computing the MUST in 77 patients with HER2-negative metastatic gastric cancer and evaluated the effect of their malnutrition risk on OS. The HER2-positive patients were excluded from our study because of their different prognostic features and treatment. All patients were treated with standard chemotherapies. In our study, the prevalence of malnourished patients, according to the MUST, was 64.9%. They were considered moderate- and high-risk patients. We found that the malnourished patients with metastatic gastric cancer had a shorter median OS than non-malnourished patients (8.8 months vs. 14.0 months, p=0.034). Additionally, we found that albumin of <3.5 g/dL (HR: 1.64), weight loss of >10% (HR: 1.60), and the moderate-high risk by the MUST (HR: 1.69) were significant risk factors for death by the univariate analysis. However, the multivariate analysis found no statistically independent factors when we incorporated other variables on death risk. Nevertheless, the moderate-high risk MUST status showed a trend toward statistical significance (p=0.051). Therefore, the MUST score should be evaluated with albumin and weight loss status to predict the prognosis. We thought that these factors might be related to each other regarding the death risk.

The MUST is cited as one of the best scales to identify malnourished patients with gastrointestinal cancer (10,11,15). According to MUST, moderate and high risk are generally considered equal status for malnourished patients, as in our study (16-18). In a study, the prevalence of cancer patients receiving chemotherapy with moderate-high risk of malnutrition, according to the MUST, was 42% (19). In another study in Spain, the authors detected that 69.9% of the patients with cancer were at nutritional risk using the MUST, and malnutrition was associated with the length of hospital stay (20). In another study, the prevalence of elderly

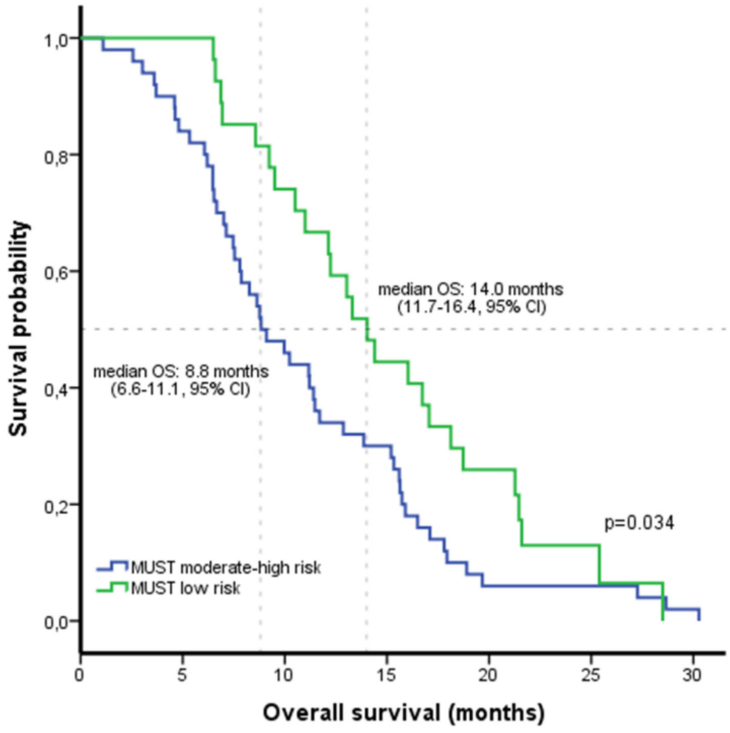

Figure 1. Kaplan-Meier curves of overall survival in patients with low risk and moderate-high risk according to the MUST
MUST: Malnutrition Universal Screening Tool, OS: Overall survival, CI: Confidence interval

cancer patients at risk of malnutrition was 64.8%. However, the authors evaluated the patients for malnutrition risk with the Global Leadership Initiative on the Malnutrition scale. This study also found that the patients at risk of malnutrition showed worse OS than those without risk of malnutrition (21). Moreover, one study that evaluated the importance of malnutrition in patients with esophageal achalasia found that 70% of the patients were at moderate and high risk of malnutrition, according to the MUST. Additionally, the moderate and high risks for malnutrition were associated with the severity of symptoms (17). In a French study that evaluated the malnutrition risk on prognosis in metastatic colorectal cancer patients receiving chemotherapy, malnourished patients had shorter median OS than non-malnourished patients. Malnutrition was evaluated with the nutritional risk index, and it was diagnosed in 65% of patients (5). Moreover, a critical study on MUST identified increased mortality for colorectal cancer patients at moderate and high risk of malnutrition. This relationship was found to be independent (22). According to MUST, those with moderate-high risk had a lower median OS than those with low risk in our research. Although when looking at the risk of death, this risk was not independent. Compared to this study, the relatively small sample size or different primary cancer types might have caused this phenomenon. Nevertheless, one study demonstrated that nutritional screening tools, including MUST, did not strongly influence the prognosis of gastric cancer, where only sarcopenia had predictive value for the prognosis (23). In a Malaysian study, more than half of the cancer patients were at risk of malnutrition with the MUST, and weight loss was identified as an important risk factor for malnutrition. It was also observed that weight loss was associated with poor outcomes (24). In our study, the malnourished patients were significantly associated with poorer median OS, and weight loss was also significantly higher in malnourished patients. Additionally, both malnutrition and weight loss status were associated with an increased risk of death in the univariate analysis. However, no independent effects were found on the risk of death. It might be assumed that these factors cannot be considered independently. We think that these findings highlight the importance of routine malnutrition screening with the MUST in patients with cancer.

Systemic inflammation in cancer patients is an important factor for nutrition and prognosis (25-27). It also contributes to the development of cachexia. Therefore, it might be challenging to manage and reverse these patients' malnutrition and weight loss (25). Cancer patients receiving chemotherapy with weight loss before chemotherapy have a poorer prognosis than those who remain weight-

Table 1. Comparison of the baseline characteristics according to MUST (n=77)

		MUST		
Characteristics	**All n (%)**	**Low risk n (%)**	**Moderate-high risk n (%)**	**p-value**
Age, years (mean ± SD)	58.7± 3.6	59.6±10.7	58.2±15	0.675
BMI (kg/m^2)	24.5±5.2	27.4±5.5	22.9±4.3	<0.001
Age				
<65 years	50 (64.9%)	19 (38.0%)	31 (62.0%)	0.463
≥65 years	27 (35.1%)	8 (29.6%)	19 (70.4%)	
Gender				
Female	24 (31.2%)	8 (33.3%)	16 (66.7%)	0.830
Male	53 (68.8%)	19 (35.8%)	34 (64.2%)	
ECOG PS				
0-1	59 (76.6%)	20 (33.9%)	39 (66.1%)	0.698
2-3	18 (23.4%)	7 (38.9%)	11 (61.1%)	
Smoking				
Yes	26 (33.8%)	9 (34.6%)	17 (65.4%)	0.953
No	51 (66.2%)	18 (35.3%)	33 (64.7%)	
Obesity (BMI≥30 kg/m^2)				
Yes	14 (18.2%)	9 (64.3%)	5 (35.7%)	0.011
No	63 (81.8%)	18 (28.6%)	45 (71.4%)	
Weight loss (>10%)				
Yes	35 (45.5%)	1 (2.9%)	34 (97.1%)	<0.001
No	42 (54.5%)	26 (61.9%)	16 (38.1%)	
Loss of appetite				
Yes	55 (71.4%)	6 (10.9%)	49 (89.1%)	<0.001
No	22 (28.6%)	21 (95.5%)	1 (4.5%)	
At least ≥1 comorbidity				
Yes	43 (55.8%)	14 (32.6%)	29 (67.4%)	0.604
No	34 (44.2%)	13 (38.2%)	21 (61.8%)	
Localization				
Gastric	57 (74.0%)	18 (31.6%)	39 (68.4%)	0.279
GEJ	20 (26.0%)	9 (45.0%)	11 (55.0%)	
Histologic classification				
Adenocarcinoma	57 (74.0%)	21 (36.8%)	36 (63.2%)	0.581
Signet ring cell carcinoma	20 (26.0%)	6 (30.0%)	14 (70.0%)	
Grade				
Grade 1&2	18 (28.6%)	6 (33.3%)	12 (66.7%)	0.728
Grade 3	45 (71.4%)	13 (28.9%)	32 (71.1%)	

Table 1. Continued

Characteristics	All n (%)	MUST Low risk n (%)	MUST Moderate-high risk n (%)	p-value
Metastatic organs				
1	31 (40.3%)	11 (35.5%)	20 (64.5%)	0.950
>1	46 (59.7%)	16 (34.8%)	30 (65.2%)	
Liver metastasis				
Yes	34 (44.2%)	11 (32.4%)	23 (67.6%)	0.657
No	43 (55.8%)	16 (37.2%)	27 (62.8%)	
Peritoneum metastasis				
Yes	50 (64.9%)	15 (30.0%)	35 (70.0%)	0.205
No	27 (35.1%)	12 (44.4%)	15 (55.6%)	
Lung metastasis				
Yes	19 (24.7%)	6 (31.6%)	13 (68.4%)	0.714
No	58 (75.3%)	21 (36.2%)	37 (63.8%)	

BMI: Body mass index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, GEJ: Gastroesophageal junction, MUST: Malnutrition Universal Screening Tool, SD: Standard deviation

Table 2. Comparison of the biochemical variables according to MUST

Variables	All n (%)	MUST Low risk n (%)	MUST Moderate-high risk n (%)	p-value
PNI				
≤45.5	44 (57.9%)	14 (31.8%)	30 (68.2%)	0.606
>45.5	32 (42.1%)	12 (37.5%)	20 (62.5%)	
NLR				
≤3.08	30 (39.5%)	12 (40.0%)	18 (60.0%)	0.390
>3.08	46 (60.5%)	14 (30.4%)	32 (69.6%)	
Albumin				
<3.5 g/dL	35 (46.1%)	13 (37.1%)	22 (62.9%)	0.619
≥3.5 g/dL	41 (53.9%)	13 (31.7%)	28 (68.3%)	
Hemoglobin				
≤10 g/dL	24 (31.6%)	9 (37.5%)	15 (62.5%)	0.681
>10 g/dL	52 (68.4%)	17 (32.7%)	35 (67.3%)	

PNI: Prognostic nutrition index, NLR: Neutrophil to lymphocyte ratio, MUST: Malnutrition Universal Screening Tool

*It was considered the participants with moderate-high risk for MUST score ≥1 as malnourished patients

stable (25). The relationship between weight loss, systemic inflammation, and poor prognosis in patients with advanced gastrointestinal cancer had been previously demonstrated (25,28,29). However, the effect of weight loss on prognosis is still unclear in cancer patients. A comprehensive study showed that weight loss alone does not determine the full impact of cachexia and is not a prognostic factor. Weight loss, systemic inflammation, and loss of appetite affect patients' prognosis (30). Low serum albumin might reflect malnutrition, and recent studies showed that low serum albumin might be associated with poorer survival in patients with gastric cancer (31,32). One study showed that low serum albumin reflected both malnutrition risk and systemic inflammatory response and it was independently associated with poorer survival in patients with colorectal cancer (33). In our study, we found that low serum albumin increased the risk of death in the univariate analysis. However, it was not significant in the multivariate analysis. NLR and PNI, which were systemic inflammation markers in this study, did not significantly affect death risk.

The nature of gastric cancer and using chemotherapy can also be considered additional risk factors for malnutrition. Chemotherapy has also been demonstrated to be a risk factor for malnutrition (14). All patients received chemotherapy in our study. Thus, it might be essential to evaluate the patients for malnutrition risk from the beginning.

Our study had some limitations. Firstly, this was a retrospective study. Thus, prospective studies with a

Table 3. Results of univariate and multivariate analyses of overall survival

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65 years	1.02 (0.63-1.64)	0.953	-	-
Male gender	1.12 (0.68-1.85)	0.665	-	-
ECOG PS 2-3	1.15 (0.66-1.97)	0.623	-	-
Smoking	0.96 (0.59-1.56)	0.864	-	-
Obesity (BMI≥30 kg/m^2)	1.07 (0.59-1.92)	0.825	-	-
Weight loss (>10%)	1.60 (1.01-2.55)	**0.046**	1.21 (0.68-2.17)	0.516
Localization (non-gastric)	0.70 (0.41-1.19)	0.189	-	-
Signet ring cell carcinoma	1.03 (0.60-1.77)	0.902	-	-
Grade 3	1.42 (0.82-2.48)	0.215	-	-
≥1 Comorbidity	0.96 (0.61-1.53)	0.867	-	-
>1 Metastatic organs	1.03 (0.65-1.63)	0.909	-	-
Liver metastasis	0.99 (0.63-1.57)	0.972	-	-
Peritoneum metastasis	1.46 (0.90-2.36)	0.130	-	-
Lung metastasis	1.11 (0.65-1.90)	0.696	-	-
MUST score≥1 (moderate-high risk)	1.69 (1.03-2.75)	**0.036**	1.64 (0.99-2.70)	0.051
PNI≤45.5	1.50 (0.93-2.40)	0.095	-	-
NLR>3.08	1.34 (0.83-2.18)	0.229	-	-
Albumin<3.5 g/dL	1.64 (1.03-2.63)	**0.038**	1.57 (0.98-2.51)	0.060
Hemoglobin≤10 g/dL	1.10 (0.66-1.87)	0.729	-	-

BMI: Body mass index, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: hazard ratio, CI: Confidence interval, NLR: Neutrophil to lymphocyte ratio, PNI: Prognostic nutrition index, MUST: Malnutrition Universal Screening Tool

larger number of patients can enable us to offer stronger recommendations. Second, the relationship of MUST with other clinical findings, such as quality of life, physical function, muscle strength measurement, and sarcopenia, should also be investigated. Additionally, the MUST was not compared with other malnutrition screening tools in this study.

CONCLUSION

In this study, the median OS was significantly lower in malnourished patients than in non-malnourished patients. It was found that moderate-high risk MUST, low serum albumin, and >10% of weight loss increased the death risk. However, these factors had no independent effects on the risk of death in the multivariate analysis. The high prevalence of malnutrition and its relation to poorer survival, as noted in many studies, highlights the significance of routine screening for malnutrition with MUST in patients with gastric cancer, as early intervention results in improved outcomes.

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ETHICS

Ethics Committee Approval: The Bezmialem Vakif University Non-Interventional Research Ethics Committee approved the study with the reference number 2021/395 (date: 30.11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.T., A.İ.Y., Concept: A.T., A.İ.Y., Design: A.T., A.İ.Y., Data Collection or Processing: A.T., A.İ.Y., Analysis or Interpretation: A.T., A.İ.Y., Literature Search: A.T., A.İ.Y., Writing: A.T., A.İ.Y.

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