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

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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].

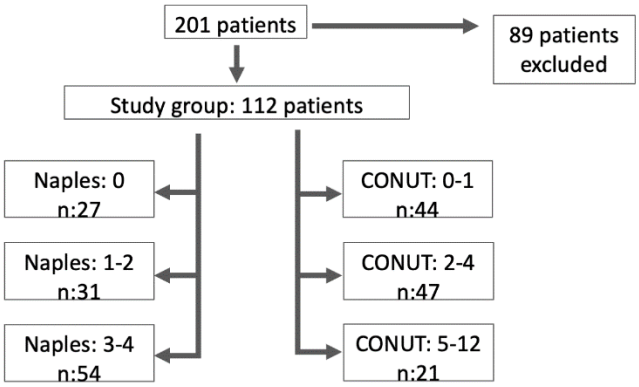
NPS was developed as a scoring system that assesses systemic inflammatory burden and malnutrition based on serum albumin, total cholesterol, lymphocyte-monocyte ratio (LMR), and NLR. NPS calculated before surgical treatment is associated with surgical outcomes in GC [12]. On the other hand, data on the 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

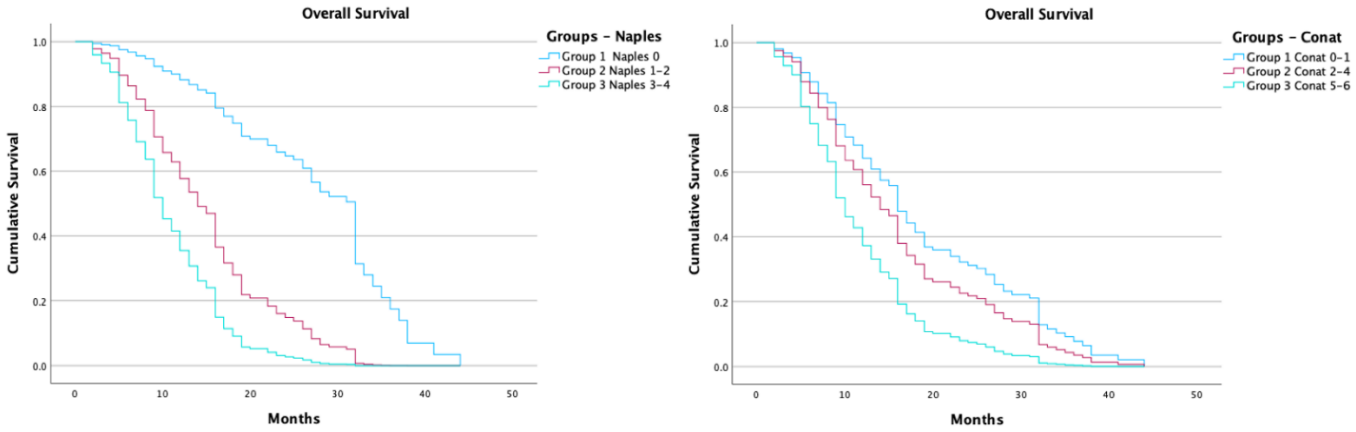


Figure 2. Overall survival of patients according to Naples (0; 1-2; 3-4) and CONUT (0-1; 2-4; 5-12) groups (Naples: Log Rank p<0.001; CONUT: Log Rank p:0.007)

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

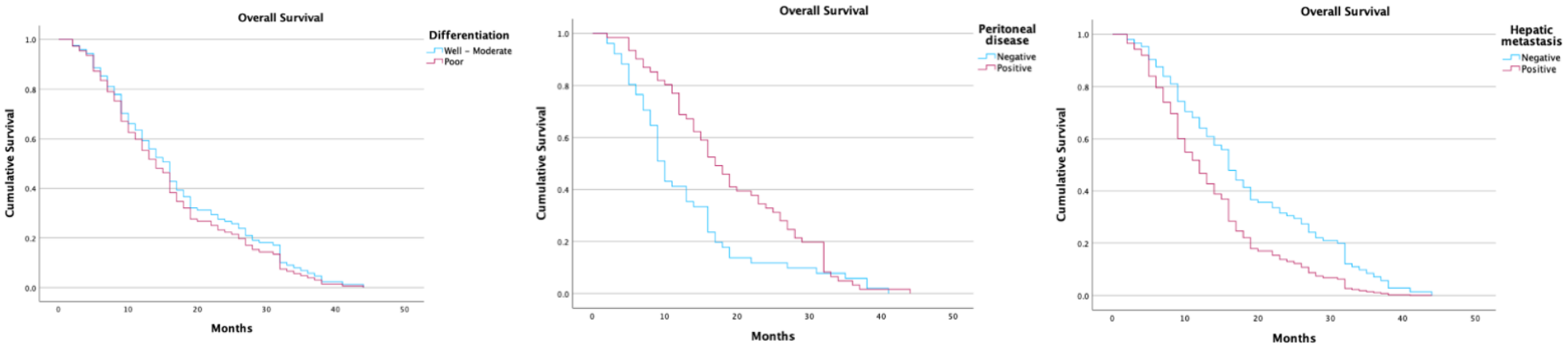


Figure 3. Overall survival of patients according to peritoneal and hepatic metastasis status (Log Rank p:0.008, p:0.004 respectively)

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.

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