Research Article

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The effect of pre-treatment inflammatory response markers on survival in locally advanced unresectable and metastatic gastric cancer: a retrospective cross-sectional study

Lokal ileri rezeke edilemeyen ve metastatik mide kanserinde tedavi öncesi inflamasyon yanıtı belirteçlerinin sağkalım üzerine etkisi

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Abstract

Purpose: We evaluated the effect of pre-treatment inflammation response markers on overall survival (OS) and progression-free survival (PFS) in patients with locally advanced unresectable and metastatic gastric cancer.

Material and method: Patients with locally advanced unresectable and metastatic gastric cancer between January 2016 and December 2021 were included. Among these patients, 114 patients with ECOG (Eastern Cooperative Oncology Group) Performance status 0-2, who received at least one line of chemotherapy, had no comorbidities and brain metastases were included in the study. Pre-treatment platelet, lymphocyte, leukocyte, neutrophil, monocyte, albumin, C-reactive protein (CRP), lactatedehydrogenase (LDH) levels, histology types, age, surgical history, treatment history and ECOG Performance status were retrospectively analysed from their records. Threshold values were determined by ROC analysis. Kaplan-Meier survival analyses were used for survival analyses. Hazard ratio (HR) and confidence intervals (CI) of the factors affecting overall survival (OS) and progression-free survival (PFS) were calculated using Coxproportional-hazards model.

Results: The median age of the patients was 63.5±11.9 (28-80). Among the patients, 69 (60.5%) were in metastatic stage. 106 (93.0%) patients had poorly differentiated carcinoma histology. Progression developed in 88.6% (101) of patients and 98 patients (86%) were deceased. In the whole group, mPFS was 9.4±0.9 (95%CI 7.7-11.0) months and mOS was 14.1±1.6 (95%CI 10.8-17.2) months. When the Coxproportional-hazards model was used, the factors affecting OS were advanced age, metastatic stage, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), derived neutrophil lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH), while the factors affecting PFS were advanced age, metastatic stage, NLR, dNLR and LDH.

Conclusion: While NLR, PLR, dNLR, dNLR and LDH affect OS, LDH affects PFS. Systemic inflammatory markers of locally advanced unresectable and metastatic gastric cancers before chemotherapy can be used to predict prognosis.

Key words: Gastric cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis.

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Öz

Amaç: Lokal ileri rezeke edilemeyen ve metastatik mide kanserli hastalarda tedavi öncesi inflamasyon yanıtı belirteçlerinin tüm sağkalım (TSK) ve progresyonsuz sağkalım (PSK) üzerine etkisini değerlendirildi.

Gereç ve yöntem: Ocak 2016-Aralık 2021 tarihleri arasında lokal ileri rezeke edilemeyen ve metastatik mide kanserli hastalar alındı. Bu hastalardan en az bir sıra kemoterapi almış ECOG (Eastern Cooperative Oncology Group) Performans durumu 0-2 olan, komorbiditesi ve beyin metastazı olmayan 114 hasta çalışmaya dahil edildi. Tedavi öncesi platelet, lenfosit, lökosit, nötrofil, monosit, albümin, C-reaktif protein (CRP), laktatdehidrogenaz (LDH) düzeyleri, histoloji tipleri, yaşı, cerrahi öyküsü, tedavi öyküsü ve ECOG Performans durumu dosyalarından retrospektif olarak incelendi. Tüm değerlerin eşik değeri ROC analizi ile belirlendi. Sağkalım analizleri için Kaplan-Meier Sağkalım analizleri kullanıldı. Coxproportional-hazards modeli kullanılarak tüm sağkalım (TSK) ve progresyonsuz sağkalım (PSK)'ı etkileyen faktörlerin hazardratio (HR) ve güven aralıkları (CI) hesaplandı.

Bulgular: Hastaların ortanca yaşı 63,5±11,9 (28-80) yıl. Hastaların 69 (%60,5)'u metastatik evredeydi. Yüzaltı (%93,0) hastanın histolojisi az differasiye karsinomdu. Hastaların %88,6'sında (101) progresyon gelişti ve 98 hasta (%86) vefat etti. Tüm grupta mPSK 9,4+0,9 (%95CI 7,7-11,0) ay ve mOS 14,1+1,6 (%95CI 10,8-17,2) ay saptandı. Coxproportional-hazards modeli kullanıldığında TSK'i etkileyen faktörler ileri yaş, metastatik evre, nötrofil lenfosit oranı (NLO), platelet lenfosit oranı (PLO), derive nötrofil lenfosit oranı (dNLO) ve laktak dehidrogenaz (LDH) iken; PSK'yi etkileyen faktörler ileri yaş, metastatik evre, NLO, dNLO ve LDH olarak bulundu.

Sonuç: Tedavi öncesi inflamasyon yanıtı belirteçlerinden NLO, PLO, dNLO ve LDH OS'yi etkilerken; LDH PSK'yi etkilemektedir. Lokal ileri rezeke edilemeyen ve metastatik evre mide kanserlerinin kemoterapi öncesi sistemik inflamatuvar belirteçleri prognozu öngörmede kullanılabilir.

Anahtar kelimeler: Mide kanseri, nötrofil-lenfosit oranı, platelet-lenfosit oranı, prognoz.

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Introduction

Gastric cancer is the 5th most common cancer. It is the 4th most common cause of death [1]. Generally, being asymptomatic in the early stages of the disease, the diagnosis can be made in advanced stages. Fifty percent of gastric cancers are metastatic at the time of diagnosis [2]. In locally advanced stage, surgery, neoadjuvant/adjuvant chemotherapy and radiotherapy are the treatment options, while in metastatic stage, targeted therapy, palliative chemotherapy and immunotherapy are used to prolong survival and improve quality of life [3-5]. Despite many innovations in the treatment of gastric cancer in recent years, the median survival is still below 1 year [6]. Stage is the most important factor determining the treatment strategy and survival. However, the fact that patients at the same stage have different survival results when they receive the same treatment suggests different mechanisms such as systemic inflammation in the progression of gastric cancer [7]. In many cancers, systemic inflammation is known to lead to tumour initiation and progression by inhibiting apoptosis, stimulating angiogenesis and causing DNA damage [8, 9]. Lymphocytes, monocytes and neutrophils make an important contribution to the systemic inflammatory response, while platelet activation increases the inflammatory response by stimulating proinflammatory cytokines [10, 11]. In addition, the effect of lymphocytes on tumour suppressor activity [12], the contribution of neutrophils to the tumour development process with cytokine production [13], the effect of platelets on transendothelial migration and early steps of metastasis [14], and the behaviour of monocytes as pro-tumour cells that increase metastasis emphasize the importance of the role of peripheral blood cells in cancer prognosis [15].

The fact that some tumour markers used in the treatment response and prognosis of gastric cancer are not cost-effective and have low sensitivity and specificity limits their use in daily practice. Therefore, evaluation of peripheral blood cells and NLR, PLR, CRP, albumin and LDH levels may be guiding in daily practice. In the literature, these markers and ratios have been shown to be prognostic in many solid tumours such as colon cancer, lung cancer, breast cancer and gastric cancer [16-20].

Due to the limited number of studies that may enable the use of these markers in clinical practice in locally advanced and metastatic gastric cancer, we aimed to evaluate the effect of pre-treatment inflammation response markers on overall survival (OS) and progression-free survival (PFS) in patients with locally advanced unresectable and metastatic gastric cancer.

Material and method

Patients with locally advanced unresectable and metastatic gastric cancer who applied to Pamukkale University Medical Oncology Department Outpatient Clinic between January 2016 and December 2021 were retrospectively analysed. Among these patients, 114 patients who received at least one line of chemotherapy, ECOG performance score status 0-2, without comorbidities and brain metastasis were included in the study. Pre-treatment platelet, lymphocyte, leukocyte, neutrophil, monocyte, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH) levels of all patients were obtained from the hospital laboratory information system. NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio), dNLR (derived neutrophil to lymphocyte ratio) and LMR (lymphocyte to monocyte ratio) were calculated. The formula dNLR: neutrophil count / white blood cell count - neutrophil count was used. Haemogram parameters were analysed by electrical impedance and optical density method in Mindray CAL 8000 (Shanghai, China) auto analyser; LDH, CRP and albumin levels were analysed by electro chemiluminescent method in Cobas 702 (Roche Diagnostics, Manheim, Germany) analysers. In addition, histology types, age at diagnosis, surgical history, treatment and ECOG Performance status were analysed from patient files.

Overall survival (OS) was defined as the time from the date of metastasis diagnosis until the time of death, and progression-free survival (PFS) was defined as the time from the date of metastasis diagnosis until disease progression.

Statistical analysis

Mann-Whitney U and chi-square or Fisher's exact test were used for the values and percentages of clinicopathological variables of the patients. Receiver operating characteristic (ROC) analysis was used for the threshold values of calculated NLR, PLR, LMR, dNLR values, Kaplan-Meier method and logrank analysis were used for survival analyses. Univariate and multivariate analyses were performed using the Coxproportional hazards model. Hazard ratios (HR) and corresponding 95% confidenceinterval (CI) were recorded for each factor. SPSS (version 23.0) software package (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A p value <0.05 was considered statistically significant.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study.

Results

114 patients were included in this study. The median age of the patients was 63.5±11.9 (28-80) years and 79 (69.3%) were male. ECOG PS was 0 in 67 (58.8%), 1 in 27 (23.7%), and 2 in 20 (17.5%) patients. 61 (53.5%) patients had smoking history. Primary tumour localization was cardia 34 (29.8%), antrum 51 (44.7%), pylorus 2 (1.8%), corpus 27 (23.7%), respectively. Among the patients, 69 (60.5%) were in metastatic stage. The histology of 93.0% (106) patients was low differentiated carcinoma. 69 (60.5%) patients had a history of surgery, 38 (33.3%) patients had a history of adjuvant chemotherapy, and 32 (28.1%) patients had a history of RT. 14 (12.3%) patients received FLOT, 60 (52.6%) patients received DCF/mDCF, 28 (24.6%) patients received CF/CX+trastuzumab, 12 (10.5%) patients received XELOX/FOLFOX. Progression developed in 88.6% (101) of patients and 98 patients (86%) died (Table 1).

The threshold values of all values were determined by ROC analysis (Table 2). OS and PFS values were found according to the threshold values of biochemical values determined by ROC analysis (Table 3). In the whole group, mPFS was 9.4+0.9 (95%CI 7.7-11.0) months and mOS was 14.1+1.6 (95%CI 10.8-17.2) months.

When Coxproportional-hazards model was used, the factors affecting OS were found to be advanced age (p=0.021), metastatic stage (p=0.009), NLR (p=0.002), PLR (p=0.009), dNLR (p=0.002) and LDH (p=0.000) (Table 4).

Using the Coxproportional-hazards model, the factors affecting PFS were found to be advanced age (p=0.051), metastatic stage (p=0.003) and LDH (p=0.007) (Table 5).

History of adjuvant chemotherapy or radiotherapy, histological type and chemotherapy regimens had no effect on PFS and OS. All survival charts are shown in Figure 1.

Table 1. Clinico-pathological characteristics of the patients

	Number of patients (%)
Age (year) (median)	63.5+11.9
Gender Male	79 (69.3)
Female	35 (31.7)
Performance status	
0	67 (58.8)
1	27 (23.7)
2	20 (17.5)
Tumour localization	
Cardia	34 (29.8)
Antrum	51 (44.7)
Pylorus	2 (1.8)
Corpus	27 (23.7)
Stage	
Locally advanced	45 (39.5)
Metastatic	69 (60.5)
Histology	
Less differentiated	106 (93.3)
Moderately to well differentiated	8 (6.7)
Smoking history	
yes	61 (54)
no	53 (46)
Surgical history	
yes	69 (60.5)
no	45 (39.5)
Adjuvant KT history	
yes	38 (33.3)
no	76 (66.7)
RT history	
yes	32 (28.1)
no	82 (71.9)
Chemotherapy regimens	
FLOT	14 (12.3)
XELOX/FOLFOX	12 (10.5)
CF/CX + trastuzumab	28 (24.6)
DCF/mDCF	60 (52.6)
Progression	
yes	101 (88.6)
no	13 (11.4)
Survival	
yes	98 (86)
deceased	16 (14)

Table 2. Values found by ROC analysis

	Cut-off	AUC (95CI%)	*P* value	Sensitivity (%)	Specificity (%)
Age (years)	55.5	0.65 (0.52-0.79)	0.046	74.5	62.5
Albumin (gr/dl)	4.07	0.66 (0.53-0.80)	0.032	66.8	68.8
CRP (mg(L)	2.04	0.52 (0.37-0.67)	0.75	56.8	51.7
NLR	2.76	0.72 (0.61-0.82)	0.006	69.4	68.8
PLR	149 843	0.66 (0.54-0.77)	0.041	58.9	56.3
LMR	3.43	0.64 (0.53-0.75)	0.062	63.2	68.8
dLNR	1.95	0.71 (0.58-0.63)	0.007	65.3	62.5

Table 3. OS and PFS values according to the cut-off values determined by ROC analysis of biochemical values

Parameters	Overall survival (months) (95%CI)		Progression-free survival (months) (95%CI)	
Age ≤55.5 years	17.3±3.4 (10.5-24.1)	***p*=0.01**	12.2±3.8 (4.7-19.6)	***p*=0.003**
Age >55.5 years	11.8±1.6 (8.5-15.0)		8.4±0.7 (7.0-9.8)	
Male	14.6±1.7 (11.3-18.0)	***p*=0.134**	10.5±1.4 (7.8-13.1)	***p*=0.201**
Female	10.9±2.7 (5.4-16.3)		7.0±1.6 (3.8-10.2)	
Less differentiated	12.3±1.7 (8.7-15.8)	***p*=0.62**	8.7±0.6 (7.3-10.1)	***p*=0.79**
Moderately to well differentiated	15.7±4.9 (6.1-25.3)		11.5±1.1 (9.4-13.6)	
Locally advanced	22.3±2.8 (7.3-12.4)	***p*=0.000**	12.5±2.6 (7.4-17.6)	***p*=0.000**
Metastatic	9.3±1.3 (7.3-12.4)		7.3±0.6 (6.1-8.6)	
Albumin <4.07g/L	11.4±0.9 (9.5- 13.3)	***p*=0.01**	8.4±0.8 (6.9- 9.9)	***p*=0.043**
Albumin ≥4.07g/L	15.6±2.8 (10.1-21.3)		11.5±2.1 (7.3- 9.9)	
CRP <2.04 mg/L	15.5±1.5 (12.7-18.8)	***p*=0.038**	11.5±0.8 (9.9-13.2)	***p*=0.013**
CRP ≥2.04 mg/L	10.8±1.3 (8.2-13.4)		7.1±0.5 (6.1-8.1)	
NLR <2.76	19.0±4.2 (10.6-27.3)	***p*=0.003**	12.2±1.8 (8.5-15.8)	***p*=0.032**
NLR ≥2.76	11.8±1.6 (8.5-15.0)		8.4±1.1 (6.3-10.5)	
PLR ≥149 843	12.2±1.7 (8.7-15.5)	***p*=0.33**	8.7±0.8 (7.1-10.4)	***p*=0.42**
PLR <149 843	15.1±1.7 (11.5-18.5)		10.5±1.6 (7.3-13.7)	
LMR ≤3.43	10.8±1.1 (8.6-13.1)	***p*=0.022**	7.9±0.9 (6.3-9.7)	***p*=0.16**
LMR >3.43	16.3±2.4 (11.5-21.2)		12.0±0.9 (10.2-13.8)	
dNLR >1.95	12.2±1.8 (8.6-15.6)	***p*=0.037**	8.6±1.0 (6.6-10.6)	***p*=0.204**
dNLR ≤1.95	15.3±3.6 (8.1-22.5)		10.8±1.9 (7.1-14.6)	
LDH ≥180 (U/L)	11.1±1.1 (8.8-13.2)	***p*=0.043**	7.9±0.7 (6.6-9.3)	***p*=0.009**
LDH <180 (U/L)	16.3±3.7 (8.9-23.6)		12.1±1.1 (6.6-9.3)	

Table 4. Factors affecting overall survival

						95.0% CI forExp (B	
	B	**SE**	**Wald**	**Df**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	0.022	0.010	5.355	1	**0.021**	1.022	1.003	1.042
Type	-0.142	0.239	0.355	1	0.551	0.867	0.543	1.385
Histology	-0.201	0.408	0.243	1	0.622	0.818	0.368	1.820
Stage	0.643	0.244	6.917	1	**0.009**	1.902	1.178	3.071
Albumin	0.079	0.219	0.130	1	0.718	1.082	0.704	1.664
CRP	0.009	0.005	2.645	1	0.104	1.009	0.998	1.019
NLR	-0.166	0.053	9.814	1	**0.002**	0.847	0.764	0.940
PLR	0.000	0.000	6.916	1	**0.009**	1.000	1.000	1.000
LMR	-0.014	0.027	0.259	1	0.611	0.986	0.935	1.040
dNLR	0.428	0.136	9.877	1	**0.002**	1.534	1.175	2.004
LDH	0.003	0.001	14.109	1	**0.000**	1.003	1.001	1.004

Table 5. Factors affecting progression free survival

						95.0% CI forExp (B	
	B	**SE**	**Wald**	**Df**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	0.020	0.010	3.816	1	0.051	1.020	1.000	1.041
Type	-0.087	0.236	0.137	1	0.711	0.916	0.577	1.455
Histology	-0.256	0.397	0.415	1	0.519	0.774	0.356	1.686
Stage	0.721	0.242	8.833	1	0.003	2.056	1.278	3.306
Albumin	-0.104	0.215	0.234	1	0.629	0.901	0.591	1.373
CRP	0.004	0.005	0.533	1	0.466	1.004	0.994	1.014
NLR	-0.099	0.053	3.432	1	0.064	0.906	0.816	1.006
PLR	0.000	0.000	1.729	1	0.189	1.000	1.000	1.000
LMR	-0.023	0.026	0.787	1	0.375	0.977	0.928	1.028
dNLR	0.256	0.140	3.330	1	0.068	1.292	0.981	1.700
LDH	0.002	0.001	7.160	1	0.007	1.002	1.001	1.003

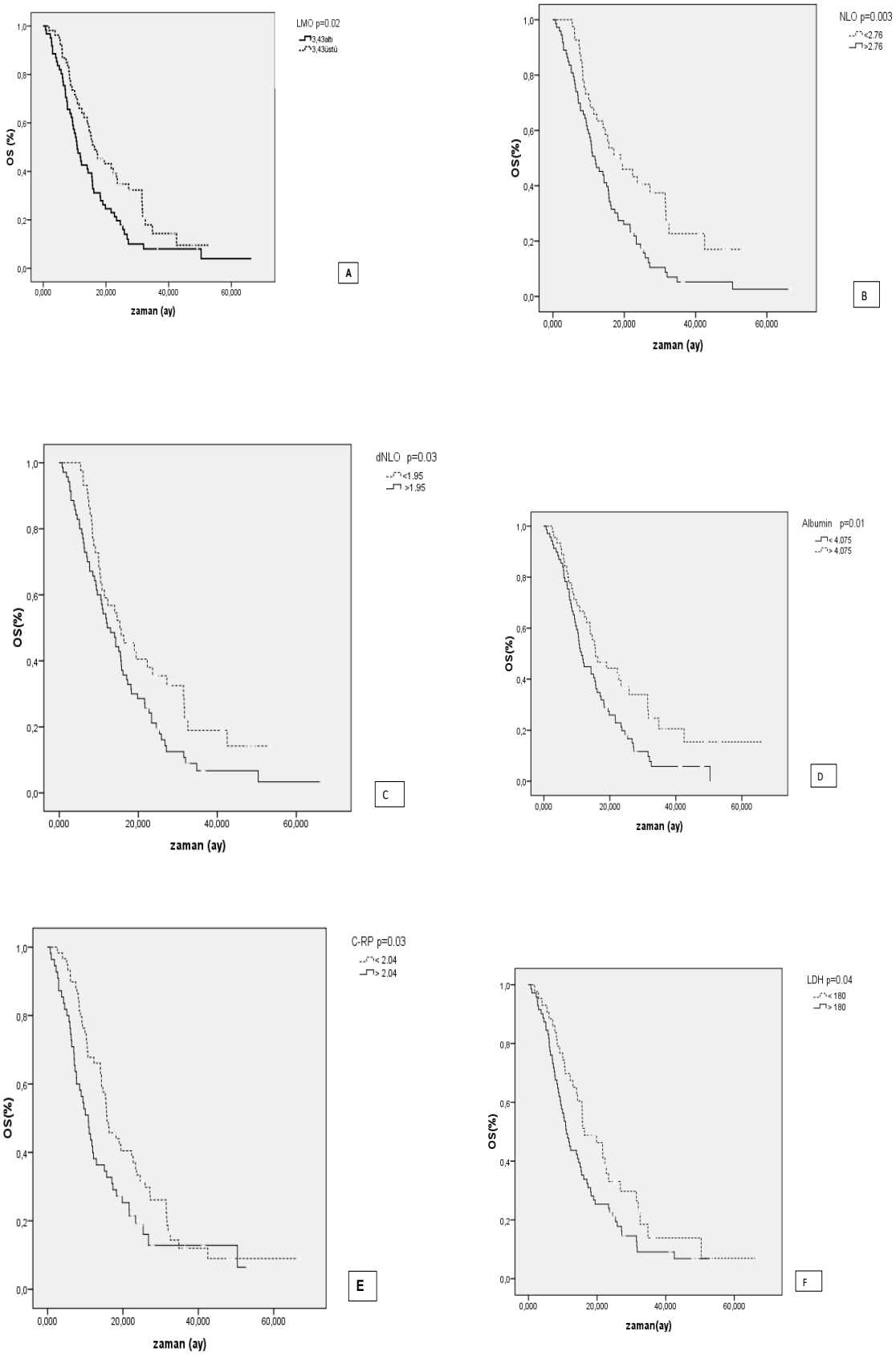

Figure 1. Kaplan-Meiers survival charts for factors affecting OS (A) LMR (B) NLR (C) dNLR (D) Albumin (E) CRP (F) LDH

Discussion

This study showed that NLR, LMR, dNLR, LDH, CRP and albumin, which are systemic inflammatory markers, have an effect on overall survival, and also NLR, LDH, CRP and albumin have an effect on progression-free survival in patients with metastatic and locally advanced unresectable gastric cancer. When prognostic factors were evaluated in multivariate analysis, NLR, dNLR and LDH were found to be the factors affecting both OS and PFS.

There is a synergy between systemic inflammation and tumour cells. While tumour cells contribute to the secretion of proinflammatory cytokines, systemic inflammation plays an important role in tumour invasion and progression. The most important peripheral blood cell involved in systemic inflammation is neutrophil. Neutrophils secrete inflammatory cytokines and provide adhesion and distant metastasis of circulating tumour cells. Lymphocytes contribute to the inhibition of proliferation and migration of tumour cells. Platelets, together with endothelial barriers, are involved in tumour cell escape from the immune system and epithelial mesenchymal transformation [9, 21]. Therefore, in recent years, it has been shown in many studies that the levels of these cells in peripheral blood and inflammation indices such as NLR, PLR, LMR) play a role as prognostic factors in many tumour types including gastric cancer [22-24].

Preoperative haematological parameters and ratios were evaluated in patients with early stage gastric cancer and they showed that low lymphocyte count, high PLR and NLR, low LMR were predictive for poor survival [25]. Furthermore, in a systemic review and meta-analysis, high NLR in early-stage patients who underwent curative resection was shown to correlate with older patients, male gender and short OS [26]. In another study, preoperative NLR in patients with stage II and III gastric cancer was shown to affect long-term and short-term outcomes, including postoperative complications [27]. Not only preoperatively but also postoperatively, low NLR in patients with early stage gastric cancer has been reported to favourably affect the prognosis in patients receiving adjuvant chemotherapy [28]. In patients with locally advanced unresectable gastric cancer, it has been shown that OS is shorter in the high NLR group [29]. In patients with locally advanced gastric cancer, neoadjuvant chemotherapy decreases all inflammatory markers such as NLR, PLR and LMR, and it has been emphasised that pre-treatment NLR and LMO are poor prognostic indicators. It has been reported that PLR and NLR before neoadjuvant chemotherapy decrease with chemotherapy and especially high PLR level is a poor survival indicator [30, 31]. In patients with locally advanced gastric cancer, high NLR and PLR negatively affected the degree of tumour regression after neoadjuvant chemotherapy [30], NLR was found to be predictive for PFS and OS, especially in female patients, and PLR was found to be predictive for PFS and OS in patients with stage III and dissected LN count <28 [32].

In metastatic gastric cancer, a scoring system using NLR and PLR before chemotherapy showed that patients with progression had a high score and a poor prognosis. In multivariate analysis, high NLR-PLR score was found to be an independent prognostic factor for OS [33]. In addition, in another study, it was found in patients with stage IV gastric cancer receiving cisplatin and S-1 treatment that the response rate was higher, progression was less common and OS was longer in patients with low NLR. In this study, it was also shown that CRP levels and NLR were correlated. It has been suggested that NLR is a useful marker for chemotherapy resistance, malnutrition, systemic inflammation and immunosuppression [34]. In PD-1 inhibitor recipients, low NLR was found to have a favourable effect on OS, but had no effect on response rate and disease control [35]. It has been suggested that the most important reasons for the effect of NLR on immunotherapy results may be due to the inhibition of the immune activity of lymphocytes by neutrophils by secreting various cytokines and chemokines and the reactions caused by the tumour inflammatory microenvironment. In addition, the predominance of lymphocytes at low NLR leads to a favourable inflammatory microenvironment. Therefore, patients with low NLR before immunotherapy have better treatment response and survival results [36]. In our study, NLR and dNLR were found to have an effect on OS in patients with locally advanced and metastatic gastric cancer in accordance with the literature.

Monocytes have an important role in cancer progression, angiogenesis, metastasis and suppression of immunity by releasing chemokines. High monocyte ratio leads to increased tissue-associated macrophage density, which is an indicator of poor survival outcomes in patients receiving immunotherapy [37]. LMR reflects the number of peripheral lymphocytes and monocytes infiltrating the tumour. Tumour-infiltrating lymphocytes are strong positive predictors in many tumour types, including gastric cancer [38]. Many studies have found an association between high preoperative LMR and PFS and OS in patients with gastric cancer [39, 40]. In gastric cancer, it has been suggested that low preoperative LMR affects survival and therefore more aggressive chemotherapy should be given in these patients [41]. However, there are no randomised clinical trials on this subject. Similarly, in a meta-analysis including patients with gastric cancer of different stages, low LMR was found to be prognostic for OS [42]. In our study, we found that LMR had no effect on OS and PFS. This may be due to the small number of patients and heterogeneity of the patient groups.

CRP, an important indicator of inflammation, is a classical acute phase reactant from the pentraxin family known to contribute to the progression of angiogenesis and metastases by increasing proinflammatory cytokines such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) [43]. Albumin is also frequently used in clinical practice as an important indicator of both inflammation and malnutrition. When CRP and albumin are evaluated together, they have been shown to be prognostic in many tumour types including gastric cancer [44-46]. In gastric cancers, reduced caloric intake due to stenosis in the gastric cardia or pylorus may lead to hypoalbuminemia. The demonstration of preoperative nutritional status by serum albumin is closely related to cancer prognosis. However, its clinical significance for gastric cancers is not fully understood. Ouyang et al. [47] found that preoperative low serum albumin levels, advanced stage and lymph node involvement were associated with an increased risk of death in 309 gastric cancer patients scheduled for surgery.

It has been reported that high CRP and low albumin levels affect OS duration in patients with locally advanced gastric cancer [48]. In a study conducted by Lu et al. [49] in 401 patients with gastric cancer, elevated CRP levels both preoperatively and postoperatively were found to be associated with poor prognosis. In our study, no correlation was found between CRP levels and OS and PFS. The reason for this may be that there are many factors affecting CRP levels. For example, the use of drugs, especially anti-inflammatory drugs, statins and metformin, may change CRP levels. The patient group included in Lu et al. [49] study was in stage 1-3 and the patient group in our study was in a more advanced stage. Advanced stage may also have affected crp levels.

Serum LDH levels are associated with tumour hypoxia, neo-angiogenesis and poor prognosis for many tumour types. In the metabolism of cancer cells, the oxidoreductase LDH acts by converting LDH to pyruvatyllactate in hypoxia and this has an important role in cancer metabolism. LDH is overexpressed in metastatic cancer cells and LDH levels have been correlated with tumour viability. Increased tumour LDH levels and increased mitotic index correlate with more aggressive cancer. Zhao et al. [50] evaluated serum LDH levels in 365 gastric cancer patients. High LDH levels were found to be an independent prognostic biomarker for poor prognosis. This study also showed the same result.

The main limitations of our study are its retrospective nature and the small number of patients. In the literature, most of the studies on systemic inflammation markers in patients with cancer are retrospective. Due to the retrospective nature of the studies, many different factors affecting inflammation could not be excluded. In these studies, inflammation markers have been shown to affect OS and PFS.

In conclusion, it has been shown that inflammation response markers can also be used in clinical practice to evaluate the prognosis of patients. Further studies are needed to determine the effects of inflammation markers on prognosis and to clarify the cut-off values.

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Authors' contributions to the article

T.D. and A.Y. constructed the main idea and hypothesis of the study. T.D. and A.Y. developed the theory and arranged/edited the material and method section. T.D., B.C.D., T.G.K., M.O. have done the evaluation of the data in the Results section. Discussion section of the article written by T.D., A.Y., A.G.D., and B.Y.T. S.D. and G.G.D reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.