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Prognostic and predictive value of systemic inflammatory markers in patients with metastatic gastric and GEJ adenocarcinoma with PD-L1 CPS score ≥ 5: Turkish Oncology Group (TOG) study

Maral Martin Mildanoglu[1]✉, Yasin Kutlu[2], Onur Bas[3], Bahadır Koylu[4], Shute Ailia Dae[5], Abdullah Sakin[6], Dilek Erdem[7], Mehmet Ali Nahit Sendur[8], Elif Senocak Tasci[9], Faysal Dane[10], Ali Osman Kaya[11], Musa Baris Aykan[12], Yakup Ergun[13], Sedat Biter[14], Omer Dizdar[3], Umut Disel[15], Fatih Selcukbiricik[4], Fatih Kose[5], Omer Fatih Olmez[1], Gokhan Demir[16], Suayib Yalcin[3] & Ahmet Bilici[1]

Our understanding of prognostic and predictive factors in the context of nivolumab combined with chemotherapy remains limited. In our multicenter study conducted across 16 centers, data from 153 patients with metastatic gastric adenocarcinoma and a PD-L1 CPS score ≥ 5, who received nivolumab in combination with chemotherapy as first-line treatment, were retrospectively analyzed for the period between 2021 and 2024. The study aimed to investigate the prognostic and predictive significance of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Immune-Inflammation Index (SII), as well as various clinical parameters. The estimated median progression-free survival (PFS) was 11.06 months while the estimated median overall survival (OS) was 16.03 months. Patients who were initially diagnosed with metastatic disease had a significantly worse prognosis, as was those with lung metastases. Lower NLR, PLR, and SII values were associated with longer PFS and OS in the univariate analysis; however, their statistical significance was not mantained in the multivariate analysis. SII and PD-L1 CPS score were determined as independent predictive factors for nivolumab plus chemotherapy treatment response. Our study is the only one to date that sheds light on prognostic and predictive factors in patients with metastatic gastric or GEJ adenocarcinoma and a PD-L1 CPS score ≥ 5, who received nivolumab in combination with chemotherapy.

Keywords Gastric adenocarcinoma, Nivolumab, NLR, PLR, SII

[1]Department of Medical Oncology, Faculty of Medicine, Medipol University, Istanbul 34083, Turkey. [2]Department of Medical Oncology, Tokat State Hospital, Tokat 60100, Turkey. [3]Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara 06800, Turkey. [4]Department of Medical Oncology, Faculty of Medicine, Koc University, Istanbul 34460, Turkey. [5]Department of Medical Oncology, Faculty of Medicine, Baskent University, Adana 01140, Turkey. [6]Department of Medical Oncology, Medipol University Bahcelievler Hospital, Istanbul 34196, Turkey. [7]Department of Medical Oncology, VM Medical Park Samsun Hospital, Samsun 55200, Turkey. [8]Department of Medical Oncology, Ankara Bilkent City Hospital, Ankara 06800, Turkey. [9]Department of Medical Oncology, Acibadem Atakent Hospital, Istanbul 34303, Turkey. [10]Department of Medical Oncology, Acibadem Altunizade Hospital, Istanbul 34662, Turkey. [11]Department of Medical Oncology, Medicana International Hospital, Istanbul 34520, Turkey. [12]Department of Medical Oncology, Gulhane Training and Research Hospital, Ankara 06010, Turkey. [13]Department of Medical Oncology, Bower Hospital, Diyarbakir 21100, Turkey. [14]Department of Medical Oncology, Faculty of Medicine, Cukurova University, Adana 01330, Turkey. [15]Department of Medical Oncology, Acibadem Adana Hospital, Adana 01130, Turkey. [16]Department of Medical Oncology, Acibadem Maslak Hospital, Istanbul 34398, Turkey. ✉email: mmildanoglu@gmail.com

Gastric and GEJ adenocarcinoma rank among the most frequently diagnosed and lethal cancers globally[1,2]. For many years, fluoropyrimidine- and platinum-based chemotherapy has been the standard treatment for patients with HER2 (human epidermal growth factor receptor 2) negative unresectable advanced or metastatic gastric cancer[3,4]. Following studies on immune checkpoint inhibitors (ICI) in PD-L1 (programmed death ligand 1) positive, HER-2-negative, unresectable advanced or metastatic gastric or GEJ adenocarcinoma, first-line treatment has shifted towards a combination of chemotherapy and ICI[5–7].

The CheckMate (CM) 649 trial, a phase 3, randomized, open-label study, demonstrated that nivolumab, a fully human IgG4 monoclonal antibody targeting PD-1, improved outcomes when combined with chemotherapy as a first-line treatment in patients with PD-L1 expression and a combined positive score (CPS) of 5 or higher[8]. The addition of nivolumab to chemotherapy increased median progression-free survival (PFS) from 6.1 months to 7.7 months and median overall survival (OS) from 11.1 months to 14.4 months[8]. Additionally, in patients with a CPS ≥ 5, the addition of nivolumab to chemotherapy increased the objective response rate (ORR) from 45 to 60% and extended the median duration of response (DoR) from 7 months to 9.7 months[8,9]. In light of these findings, the combination of nivolumab with chemotherapy was approved the combination of nivolumab with chemotherapy for the treatment of metastatic gastric and gastroesophageal junction (GEJ) cancer[9,10]. Afterthat, the three-year follow-up analysis of the CheckMate 649 trial showed that these combination continued to provide clinically significant long-term survival benefits over chemotherapy alone, while maintaining an acceptable safety profile[11].

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are biomarkers that reflect the systemic inflammatory burden in patients. Previous studies have demonstrated their prognostic significance across various types of cancer[12,13]. Additionally the predictive role of Systemic Immune-Inflammation Index (SII), NLR, PLR in ICI therapy for non-small cell lung cancer (NSCLC) has been identified[14]. However, in gastric cancer patients, the predictive role of NLR has been more extensively investigated, while studies evaluating the predictive role of PLR and SII have generally included a limited number of patients, and their role are still vague[15]. Therefore we aimed to conduct a nationwide, multicenter study investigating the prognostic and predictive role of these inflammatory parameters in the first-line treatment of patients with unresectable advanced or metastatic gastric and GEJ adenocarcinoma with PD-L1 CPS ≥ 5, receiving a combination of nivolumab and chemotherapy.

Results

Patient characteristics

Table 1 presents the general characteristics of the 153 patients (65 women and 88 men, median age: 58 years). At the time of diagnosis, 3 patients had stage 2, 26 had stage 3, and 127 had stage 4 disease. A total of 38 patients had undergone curative surgery for the primary malignancy, while 115 patients had not undergone curative surgical intervention. The most common sites of metastasis were the liver and peritoneum, observed in 68 patients, followed by distant lymph node metastases in 49 patients and lung metastases in 24 patients. Regarding PD-L1 CPS scores, 42 patients had a score of 5–9%, 47 patients had 10–19%, 38 patients had 20–49%, and 26 patients had ≥ 50%. Microsatellite instability (MSI) status was assessed in fewer than half of the patients included in the study ($n = 70$, 45.7%). Among these patients, only 6 (3.9%) were found to have deficient mismatch repair (dMMR).

Survival outcomes

In the study cohort, the median PFS was calculated as 11.06 months (95% CI = 9.64–12.48 months, Fig. 1). The univariate and multivariate analyses of prognostic factors for PFS are presented in Table 2. In the univariate analysis for PFS, the following were identified as potential prognostic factors: disease stage at diagnosis ($p < 0.001$), presence of lung metastases ($p = 0.036$), presence of brain metastases ($p = 0.002$), history of curative surgery ($p < 0.001$), NLR ($p = 0.011$), PLR ($p = 0.035$), and SII ($p = 0.002$). On the other hand, the multivariate analysis for PFS revealed that patients who were metastatic at diagnosis ($p < 0.001$, HR, 8. CI 95% 3.2–19.8) or patients who had lung metastases ($p = 0.011$, HR 0.47.CI 95% 0.27–0.84) exhibited poorer prognosis. Conversely, patients with a history of curative surgery demonstrated a better prognosis ($p = 0.017$, HR 2.66 CI 95% 1.19–5.96). The median OS was calculated as 16.03 months (95% CI = 13.81–18.25 months, Fig. 2). The univariate and multivariate analyses of prognostic factors for OS are shown in Table 3. The univariate analysis indicated that the following variables could be potential prognostic factors for OS: disease stage at initial diagnosis ($p = 0.002$), ECOG PS ($p = 0.018$), presence of lung metastases ($p = 0.022$), presence of brain metastases ($p < 0.001$), history of curative surgery ($p < 0.001$), NLR ($p = 0.005$), PLR ($p = 0.035$), and SII ($p = 0.04$). Multivariate analysis for OS identified metastatic disease at initial diagnosis ($p = 0.034$, HR, 2.69. CI 95% 1.07–6.73), the presence of lung metastasis ($p = 0.027$, HR, 0.46. CI 95% 0.24–0.91), and brain metastasis ($p = 0.002$, HR, 0.086. CI 95% 0.018–0.39) as independent adverse prognostic factors. Lower NLR, PLR, and SII values were identified as favorable prognostic factors for both PFS and OS in the univariate analysis; however, their statistical significance was not retained in the multivariate analysis. Figures 3 and 4 provides a summary of the association between inflammatory markers and survival outcomes in the univariate analyses.

Treatment Repsonse

Median count of nivolumab cycle was 10 (range:3–35). Among 153 patients, 14 (9.1%) achieved a CR, 84 (54.9%) had a PR, and 30 (19.6%) experienced SD. PD was observed in 22 patients (14.4%), while treatment response could not be assessed in 3 patients (2%). ORR was calculated as 64% and DCR as 83.6% (Table 4).

In the logistic regression analysis conducted to identify factors predicting treatment response to nivolumab plus chemotherapy, SII ($p = 0.009$, OR, 3.93. CI 95% 1.4-10.99) and PD-L1 CPS ($p = 0.026$, OR, 0.64. CI 95% 0.43–0.94) were determined as independent predictive factors. The logistic regression analysis of predictive factors shown in Table 5.

Characteristic	*n* (%)
Sex	
Female	65 (42,5)
Male	88 (57,5)
Age	
< 65 ≥ 65	101 (66) 51 (33,3)
ECOG PS	
0	82 (53,6)
1	60 (39,2)
2	10 (6,5)
Smoking history	
Never smoked	75 (49)
Ex-smoker	39 (25.5)
Current smoker	16 (10.5)
Pathologic subtype	
Intestinal	90 (58,8)
Diffuse	63 (41,2)
Primary tumor location	
Gastric	120 (78,4)
GEJ	33 (21,6)
Curative surgery for primary tumor	
Present	38 (24,8)
Absent	115 (75,2)
Initial stage	
Locally advanced	29 (19)
Metastatic	124 (81)
Site of metastasis	
Liver	68 (44,4)
Periton	68 (44,4)
Distant lymph nodes	49 (32)
Lung	24 (15,7)
Bone	20 (13,1)
Brain	2 (1,3)
Chemoterapy regimen	
FOLFOX	138 (90,2)
XELOX	9 (5,9)
FOLFIRI	4 (2,6)
DCF	2 (1,3)
PD-L1 CPS (%)	
5–9	42 (27,5)
10–19	47 (30,7)
20–49	38 (24,8)
Continued	

Characteristic	*n* (%)
≥ 50	26 (17)
MSI Status	
dMMR	6 (3.9)
pMMR	64 (41.8)
Unknown	83 (54.3)

Table 1. General characteristics of 153 study patient. ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; FOLFOX, folinic acid, fluorouracil, oxaliplatin; XELOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; DCF, Docetaxel, Cysplatin, Fluorouracil; PD-L1, programmed death-ligand 1; CPS, combined positive score; MSI, Microsatellite instability, dMMR, Deficient missmatch repair; pMMR, Proficient missmatch repair.

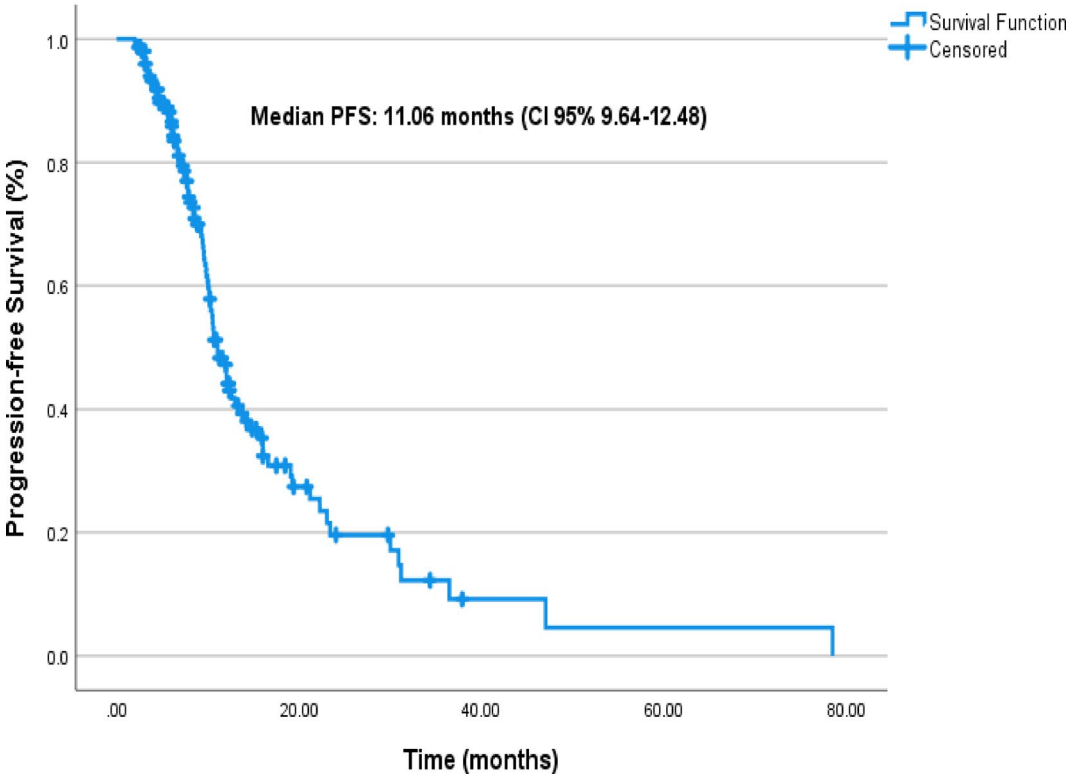

Fig. 1. Progression-free survival curve in all cohort.

Treatment related adverse events

Table 6 summarizes the TRAEs observed with chemotherapy and nivolumab treatment. The majority of reported TRAEs were grade 1 and grade 2. Among grade 1–2 TRAEs, the most frequently observed were fatigue (42.5%), anemia (45.7%), nausea (44.4%), neutropenia (33.3%), and peripheral neuropathy (29.4%). The most common grade 3–4 TRAEs were anemia (11.7%), neutropenia (9.1%), fatigue (5.8%), and thrombocytopenia (4.5%). The most frequently encountered immune-related adverse event was hypothyroidism (8.4%).

Discussion

Given the data from the CM-649 trial, the combination of nivolumab and chemotherapy was approved for the treatment of HER-2 negative, PD-L1 CPS ≥ 5, metastatic gastric and GEJ adenocarcinoma[9,10]. Moreover, the 3-year follow-up update of the CM-649 trial demonstrated a PFS of 8.3 months (95% CI, 7.0-9.3), OS of 14.4 months (95% CI, 13.1–16.2), and an ORR of 60% (95% CI, 54.7–64.8)[11]. A real-world data previous study conducted by the TOG group in our country reported a PFS of 11.7 months (95% CI = 10.2–13.2 months), an OS of 18.2 months (95% CI = 15.0–21.2 months), and an ORR of 70.3%[16]. In our study, the PFS of 11 months (95% CI = 9.6–12.5 months) was consistent with the previous real-world data results from our country. However, the OS of 16 months (95% CI = 13.8–18.2 months) was shorter compared to the previous TOG study, which may be attributed to a longer follow-up period and a larger patient cohort[16]. From an efficacy perspective, our study findings align with the existing literature, with no contradictory results observed[11,16].

Features	*n* (%)	Median PFS (months)	Univariate *p* value	Multivariate *p* value	HR (CI%)
Sex			0.34		
Female	65 (42.5)	10.2			
Male	88 (52.5)	12.3			
Median age, years	58 (31–86)		0.91		
< 65	101 (66)	10.6			
≥ 65	51 (33.3)	12.0			
ECOG performance status			0.07		
0	82 (53.6)	12			
1	60 (39.2)	10.6			
2	10 (6.5)	10.3			
Initial disease stage			***p < 0.001***	***p < 0.001***	**8 (3.2–19.8)**
Locally advanced	27 (17.6)	22.2			
Metastatic	126 (82.4)	10			
Curative surgery			***p < 0.001***	**0.017**	**2.66(1.19–5.96)**
Present	38 (24.8)	23.4			
Absent	115 (75.2)	9.6			
Site of metastasis					
Liver	68 (44.4)	10.4	0.48		
Peritoneum	68 (44.4)	12.9	0.15		
Distant lymph nodes	49 (32)	10.5	0.62		
Lung	24 (15.7)	11	**0.03**	**0.01**	**0.47 (0.27–0.84)**
Bone	20 (13.1)	10.4	0.056		
Brain	2 (1.3)	2	**0.002**	**0.09**	**0.26 (0.05–1.28)**
Chemotherapy regimen			0.59		
FOLFOX	138 (90.2)	11			
XELOX	9 (5.9)	10.2			
FOLFIRI	4 (2.6)	NA			
DCF	2 (1.3)	30			
PD-L1 CPS (%)			0.26		
5–9	42 (27.5)	11.7			
10–19	47 (30.7)	12			
20–49	38 (24.8)	11.2			
≥ %50	26 (17)	8.7			
NLR			**0.01**	0.55	1.17 (0.68-2)
< 3.41	75 (49)	14.1			
≥ 3.41	75 (49)	10			
PLR			**0.035**	0.71	0.88 (0.48–1.64)
< 169	75 (49)	12.1			
≥ 169	76 (49.6)	10.6			
SII			**0.002**	0.55	1.2 (0.63–2.36)
< 1001.2	77 (50.3)	15.6			
≥ 1001.2	76 (49.7)	9.9			

Table 2. Univariate and multivariate analysis for progression-free survival. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, oxaliplatin; XELOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; DCF, Docetaxel, Cysplatin, Fluorouracil; PD-L1: programmed death-ligand 1; CPS, combined positive score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index.

The presence of lung and peritoneal metastases has previously been found to be associated with shorter PFS but not as an indepedent prognostic factor[17]. Similarly, in our study, patients with lung metastases exhibited shorter PFS and OS. However, the presence of peritoneal metastases was not identified as an independent prognostic factor. De novo metastatic disease was also identified as independent negative prognostic factor for both PFS and OS in our cohort. On the other hand, undergoing curative surgery significantly prolonged PFS but did not have a meaningful impact on OS. The PFS benefit of curative surgery may be attributed to the fact that most patients ($n = 25$, 65.8%) who underwent surgery were at an earlier disease stage at the time of diagnosis.

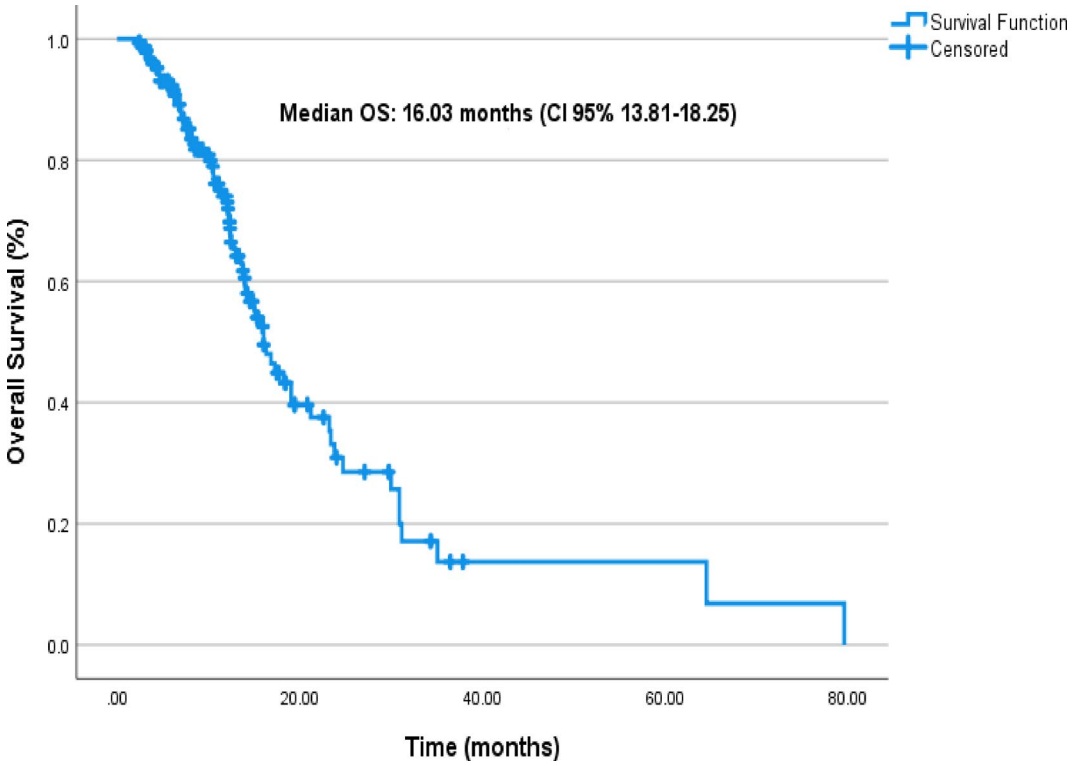

Fig. 2. Overall survival curve in the 153 study patients.

However, a subset of patients underwent surgery while in the metastatic stage. ($n = 13$, 34.2%). Although several studies have demonstrated a significant survival benefit of palliative gastrectomy, the REGATTA trial showed that gastrectomy does not provide an OS benefit in patients with metastatic disease[18,19]. Also a recent study showed no survival benefit of in oligometastatic patients[20]. Similarly, the lack of an OS benefit in our study may be associated with patients who underwent surgery while in the metastatic stage. Furthermore, the presence of brain metastases was identified as an independent negative prognostic factor for OS. The median OS of 2 months observed in two patients with brain metastases was consistent with the literature[21].

In the study conducted by Ogata et al., higher NLR values were associated with shorter PFS and OS in patients with advanced gastric cancer receiving nivolumab in second-line and later treatment settings. However, in this study only univariate analysis has been performed[22]. Two separate meta-analyses demonstrated that higher NLR values were associated with worse PFS and OS outcomes in patients with advanced gastric cancer receiving immunotherapy[15,23]. Similarly, in our study, patients with higher NLR levels at the start of treatment had shorter PFS and OS in the univariate analysis. However, this difference did not reach statistical significance in the multivariate analysis. Chen et al. demonstrated that no significant association was found between PLR levels and PFS in patients with advanced gastric cancer receiving ICIs. While higher PLR levels were associated with shorter OS in univariate analysis, this significance was lost in the multivariate analysis[24]. Notably, 41% of the patients in this study received a combination of chemotherapy and ICI therapy, a feature that distinguishes it from other studies and aligns it more closely with our study[24]. Conversely, a meta-analysis reported opposite findings, showing that higher PLR levels were associated with both shorter PFS and OS[23]. In our study, higher PLR values were associated with shorter PFS and OS in univariate analysis; however, this difference did not reach statistical significance in multivariate analysis. Although the number of patients receiving nivolumab was quite small, a study that included patients with advanced gastric cancer receiving first-line anti–PD-1 therapy found no association between SII and PFS or OS[17]. Similarly, Chen et al. reported no significant association between SII levels and PFS, whereas higher SII levels were correlated with shorter OS[24]. In our study, higher SII values were observed to be associated with shorter PFS and OS; however, this association did not reach statistical significance in the multivariate analysis.

Although PD-L1 CPS was not identified as an independent prognostic factor for PFS and OS, it was determined to be an independent predictive factor for treatment response. While SII has previously been evaluated for its prognostic significance, there was no available data regarding its predictive value. In our study, SII was identified as an independent predictive factor for treatment response for nivolumab in combination with chemotherapy.

In our study, fatigue was the most commonly observed adverse event, followed by nausea and peripheral neuropathy. The vast majority of adverse events were of Grade 1–2 severity. It is noteworthy that the incidence of fatigue in our patient cohort was higher compared to previously reported studies, which may represent a clinically relevant observation. In contrast, the frequencies of other adverse events were largely consistent with those documented in the existing literature[11,16].

Features	*n* (%)	Median OS (months)	Univariate *p* value	Multivariate *p* value	HR (CI%)
Sex			0.74		
Female	65 (42.5)	16			
Male	88 (52.5)	16			
Median age, years	58 (31–86)		0.83		
< 65	101 (66)	16			
≥ 65	51 (33.3)	16.3			
ECOG performance status			**0.018**	0.35	1.22 (0.79–1.88)
0	82 (53.6)	18			
1	60 (39.2)	14			
2	10 (6.5)	11.3			
Initial disease stage			**0.002**	**0.034**	**2.69 (1.07–6.73)**
Locally advanced	27 (17.6)	23.8			
Metastatic	126 (82.4)	14.3			
Curative surgery			< **0.001**	0.26	1.65 (0.67-4)
Present	38 (24.8)	23.8			
Absent	115 (75.2)	14			
Site of metastasis					
Liver	68 (44.4)	16.3	0.26		
Peritoneum	68 (44.4)	17.2	0.93		
Distant lymph nodes	49 (32)	13.6	0.1		
Lung	24 (15.7)	13	**0.02**	**0.027**	**0.46 (0.24–0.91)**
Bone	20 (13.1)	14	0.25		
Brain	2 (1.3)	2	< **0.001**	**0.002**	**0.086 (0.018–0.39)**
Chemotherapy regimen			0.9		
FOLFOX	138 (90.2)	16.03			
XELOX	9 (5.9)	12.4			
FOLFIRI	4 (2.6)	12.4			
DCF	2 (1.3)	30			
PD-L1 CPS (%)			0.36		
5–9	42 (27.5)	16.3			
10–19	47 (30.7)	12.8			
20–49	38 (24.8)	14			
≥ %50	26 (17)	21.2			
NLR			**0.005**	**0.055**	**1.81 (0.98–3.34)**
< 3.41	75 (49)	23.4			
≥ 3.41	75 (49)	13.6			
PLR			**0.035**	0.65	1.17 (0.57–2.4)
< 169	75 (49)	21.2			
≥ 169	76 (49.6)	15			
SII			**0.04**	0.22	0.63 (0.3–1.3)
< 1001.2	77 (50.3)	19			
≥ 1001.2	76 (49.7)	14			

Table 3. Univariate and multivariate analysis for overall survival. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, oxaliplatin; XELOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; DCF, Docetaxel, Cysplatin, Fluorouracil; PD-L1: programmed death-ligand 1; CPS, combined positive score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index.

To the best of our knowledge, there is no real-word study in the literature that has comprehensively investigated the prognostic and predictive roles of inflammatory biomarkers in patients with unresectable or metastatic gastric or GEJ adenocarcinoma receiving first-line chemotherapy plus nivolumab, as in our study. Since this treatment regimen represents the majority of our daily clinical practice and prognostic and predictive factors remain uncertain, addressing this issue has become a necessity.

Our findings should be interpreted considering several limitations. First, the retrospective design of the study may introduce potential biases and confounding variables, which could influence the interpretation of results.

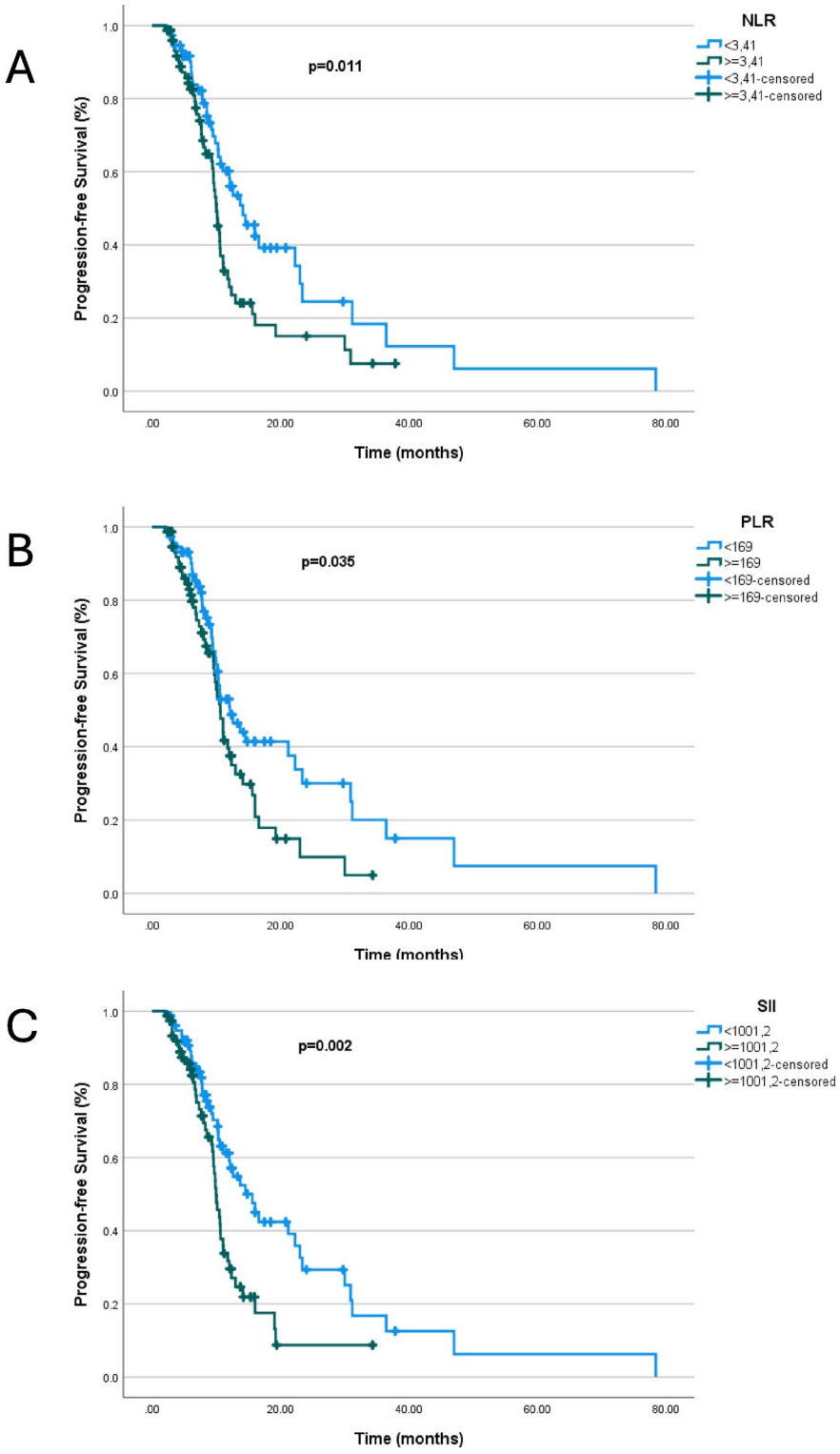

Fig. 3. Univariate analysis of inflammatory markers for PFS; **A**: NLR, **B**: PLR **C**: SII.

Prospective studies with predefined data collection and analysis protocols would provide stronger evidence to validate the conclusions derived from this study. Second, the small number of patients with specific metastatic sites, such as brain metastases, may have limited the statistical power of the analysis. Third, this study did not assess patient-reported outcomes or quality-adjusted survival[25], which are crucial factors in the comprehensive evaluation of cancer treatments. However, we believe that our study will contribute to the literature because it contains real-life data with a sufficient number of patients that analyze both prognostic and predictive factors in

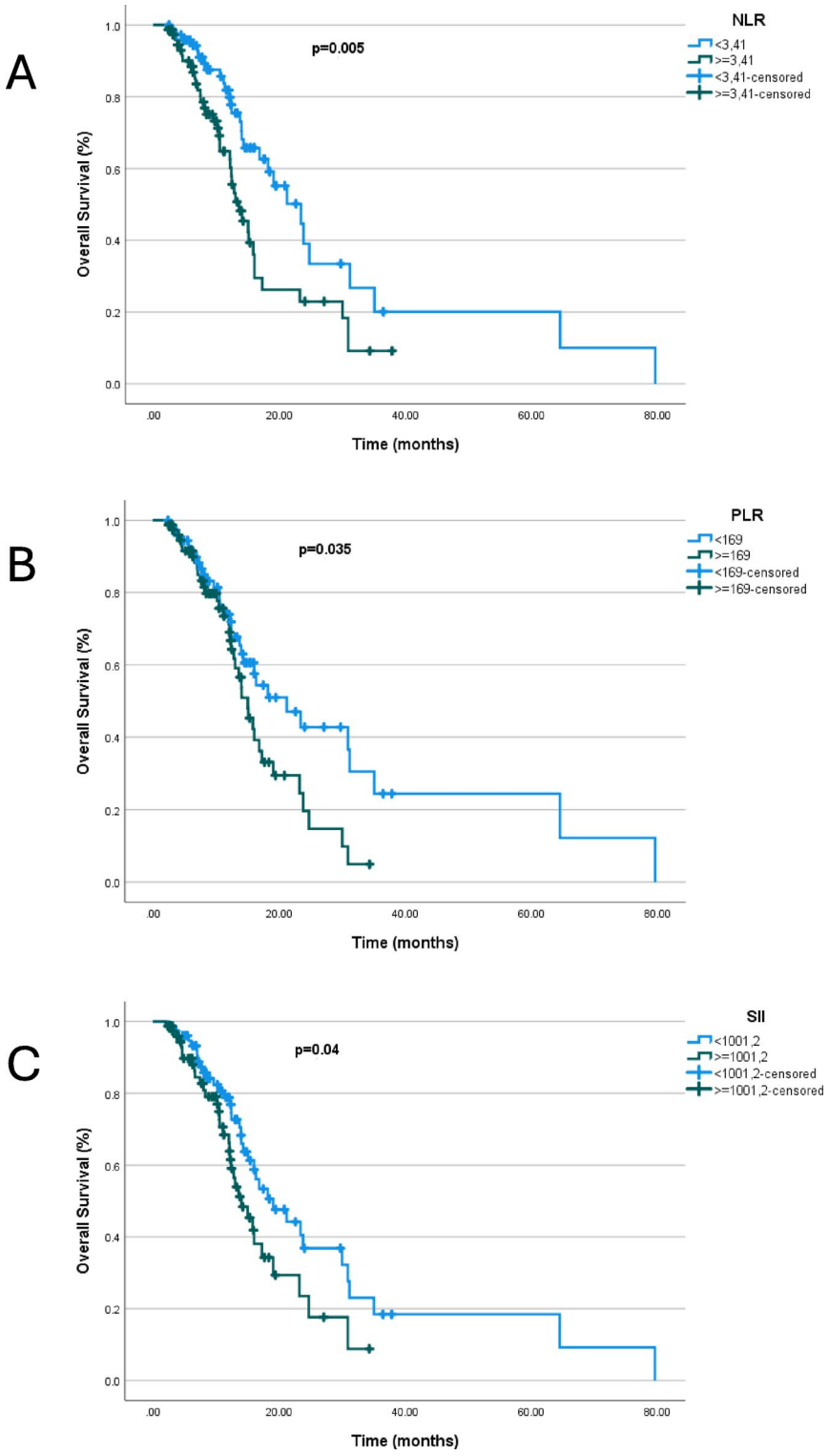

Fig. 4. Univariate analysis of inflammatory markers for OS; **A**: NLR, **B**: PLR, **C**: SII.

metastatic gastric and GEJ adenocarcinoma patients treated with nivolumab plus chemotherapy in the first-line setting.

Conclusion

In conclusion, our findings showed to be again proven treatment option of nivolumab in combination with chemotherapy regimen with the efficacy and safety in this population. Disease stage at diagnosis and the presence of lung metastases were identified as independent prognostic factors for both PFS and OS. None of the evaluated

Characteristics	*n*	%
CR	14	9.1
PR	84	54.9
SD	30	19.6
PD	22	14.4
ORR	98	64
DCR	128	83.6

Table 4. Overall response rates. CR, complete response; PR, partial response; SD, stable disease; PD, Proggressive disease; ORR, objective response rate; DCR, disease control rate.

Factors	Wald X^2	*p* value	OR	95% CI
NLR	0.007	0.935	1.036	0.439–2.445
PLR	0.690	0.406	0.652	0.237–1.789
SII	6.803	**0.009**	3.931	1.405–10.997
ECOG PS	0.924	0.336	1.324	0.747–2.349
PD-L1 CPS	4.933	**0.026**	0.641	0.433–0.949

Table 5. Multivariable logistic regression analysis for predictive factors of response to chemotherapy plus nivolumab treatment. OR: Odds ratio, CI: Confidence interval; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio. SII, Systemic Immune-Inflammation Index; ECOG, Eastern Cooperative Oncology Group; PD-L1: programmed death-ligand 1; CPS, combined positive score.

Advers event	Grade 1 or 2 *n* (%)	Grade 3 or 4 *n* (%)
Fatigue	71 (46.4)	9 (5.8)
Nausea	68 (44.4)	4 (2.6)
Vomiting	30 (19.6)	4 (2.6)
Peripheral neuropathy	45 (29.4)	5 (3.2)
Diarrhea	30 (19.6)	2 (1.3)
Stomatitis	30 (19.6)	3 (1.9)
Decreased appetite	28 (18.3)	2 (1.3)
Weight Loss	16 (10.4)	2 (1.3)
Rash	10 (6.5)	1 (0.6)
Anemia	70 (45.7)	18 (11.7)
Neutropenia	51 (33.3)	14 (9.1)
Trombocytopenia	29 (18.9)	7 (4.5)
Increased AST	27 (17.6)	3 (1.9)
Increased ALT	25 (%16.3)	3 (1.9)
Hypothyroidism	13 (8.4)	–
Immune related colitis	–	4 (2.6)
Immune related hepatitis	–	3 (1.9)

Table 6. Treatment-related adverse events. AST, Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

inflammatory biomarkers were found to be independent prognostic factors. However, PD-L1 CPS score and SII were identified as independent predictive factors for treatment response.

Considering the existing data in the literature, the prognostic and predictive roles of inflammatory markers have not yet been clearly established. Further clinical studies with larger patient populations and longer follow-up periods are needed to identify an inflammatory marker that could be standardized for use in clinical practice for patients with metastatic gastric and GEJ adenocarcinoma receving ICI.

Methods

Study design and participants

In this multicenter study involving 16 oncology centers, data from 153 patients over the age of 18 who were diagnosed with metastatic gastric or GEJ adenocarcinoma and had a PD-L1 CPS score ≥ 5 were reviewed retrospectively for the period between 2021 and 2024. The study population consisted of patients who received

nivolumab in combination with chemotherapy as first-line treatment for metastatic disease. Patients who received nivolumab in the second-line or later line treatment settings were not included in the study. Patient staging was performed based on both clinical and radiological findings, in accordance with the 8th of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Staging Manual. To be eligible for inclusion in the study, patients aged 18 years and older were required to have unresectable advanced or metastatic gastric or GEJ adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2[26].

The study protocol was reviewed and approved (reference number: E-10840098-202.3.02-1273) by the Ethics Committee at Medipol University (Istanbul, Turkey). Written informed consent was obtained from all patients or their designated legal representatives.

Treatment protocols

In the first-line treatment of metastatic disease, most patients received FOLFOX in combination with nivolumab at a dose of 240 mg every two weeks or 360 mg every three weeks, while a smaller proportion received XELOX, FOLFIRI, or DCF. The FOLFOX regimen was administered intravenously every two weeks over a 48-hour period, consisting of 85 mg/m² oxaliplatin on day 1, 400 mg/m² leucovorin on day 1, 400 mg/m² 5-fluorouracil as a bolus on day 1, and 2400 mg/m² 5-fluorouracil as a continuous infusion over 48 h. In the XELOX regimen, capecitabine (1000 mg/m², twice daily, orally) was administered for 14 consecutive days, followed by a one-week rest period. Oxaliplatin (130 mg/m², intravenously) was given on day 1 of each three-week cycle. The FOLFIRI regimen was administered every 14 days, with irinotecan (180 mg/m² IV), 5-fluorouracil (400 mg/m² IV bolus), and leucovorin (400 mg/m² IV) on day 1, followed by a continuous intravenous infusion of 5-fluorouracil (2400 mg/m²) over 48 h. The DCF regimen consisted of leucovorin (400 mg/m² IV on day 1), 5-fluorouracil (5-FU) (400 mg/m² IV on day 1), and a continuous 46-hour infusion of 5-FU (2400 mg/m² on days 1 and 2), along with docetaxel (60 mg/m² IV on day 1) and cisplatin (50 mg/m² IV on day 1). This regimen was administered every two weeks.

Data collection

The following patient data were collected from clinical records: age, sex, ECOG PS, smoking history, history of prior curative surgery, initial disease stage, presence of signet ring cell carcinoma, sites of metastases, administered chemotherapy regimen (FOLFOX, XELOX, FOLFIRI, or DCF) and SII, NLR, PLR. Additionally, PD-L1 CPS was determined by dividing the total number of PD-L1-stained tumor and immune cells by the total number of viable tumor cells, then multiplying by 100[27]. Tumor cell PD-L1 expression and PD-L1 CPS were assessed using the Dako PD-L1 IHC 28 – 8 pharmDx assay (Dako, an Agilent Technologies Inc. company, Santa Clara, CA, USA). Tumor cell PD-L1 expression was defined as the percentage of viable tumor cells exhibiting partial or complete membrane staining in a minimum of 100 viable tumor cells. CPS was established by rescoring PD-L1-stained slides, where PD-L1-positive tumor cells with partial or complete membrane staining, along with PD-L1-positive lymphocytes and macrophages (showing membrane staining, intracellular staining, or both), were counted, divided by the total number of viable tumor cells, and multiplied by 100. The PD-L1 CPS score was stratified into four groups: 5–9%, 10–19%, 20–49%, and ≥ 50%. In addition to the PD-L1 CPS score, the MSI (microsatellite instability) status of the patients (if assessed) was also recorded.

Efficacy

The primary efficacy endpoints included progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). PFS was defined as the time from treatment initiation to tumor progression, death from any cause, or the date of the last follow-up assessment, whichever occurred first. OS was calculated as the time from treatment initiation to death from any cause or, if the patient was still alive, the date of the last follow-up assessment. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[28]. Treatment responses were categorized into four groups: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The objective response rate (ORR) was defined as the proportion of patients who achieved either a CR or PR. Meanwhile, the disease control rate (DCR) encompassed patients who experienced a complete or partial response or maintained stable disease[28].

Safety

Treatment-related adverse events (TRAEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, established by the National Cancer Institute. The occurrence of TRAEs was documented separately for Grade 1–2 (mild to moderate) and Grade 3–4 (severe to potentially life-threatening) events. For analytical purposes, TRAEs of special interest included fatigue, nausea, vomiting, peripheral neuropathy, diarrhea, stomatitis, loss of appetite, weight loss, rash, anemia, neutropenia, thrombocytopenia, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Additionally, immune-related adverse events of interest included hypothyroidism, colitis, and hepatitis. The percentage of patients who experienced each TRAE was recorded for the entire study cohort.

Inflammatory biomarkers

NLR, PLR, and SII analyses were performed using blood samples collected from patients prior to their first nivolumab treatment. SII is calculated by multiplying the platelet count by the absolute neutrophil count, dividing the result by the absolute lymphocyte count, and then dividing by 1000 to normalize the value.

Statistycal analysis

Data from all participating centers were aggregated for analysis. Variables were summarized using descriptive statistics, including frequencies, percentages, means, standard deviations, medians, and ranges. Kaplan-Meier curves were constructed to illustrate survival estimates, and log-rank tests were applied for statistical comparisons. To evaluate the association between the studied variables and survival outcomes, both univariate and multivariate Cox proportional hazards regression analyses were conducted. A stepwise selection method was utilized, incorporating significant variables from the univariate analysis into the multivariate model. Predictive factors for response were evaluated using a logistic regression analysis. Findings were presented as hazard ratios (HRs) along with 95% confidence intervals (CIs). Statistical analyses were performed using SPSS software, version 27.0 (IBM, Armonk, NY, USA). A two-tailed p-value of < 0.05 was considered statistically significant.

Data availability

Due to the sensitive nature of the data, it is not publicly accessible; however, it may be provided by the corresponding author upon reasonable request.

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Author contributions
Conception/design: M.M.M., Y.K., A.B., O.F.O., S.Y. and G.D.; provision of study material or patients: O.B., B.K., E.S.T., S.A.D., A.S., D.E. and S.B.; collection and assembly of data: A.S., A.O.K., O.D. and M.A.N.S.; data analysis and interpretation: F.S., M.B.A., Y.E., F.D., F.K., U.D.; manuscript writing: M.M.M., A.B. and O.F.O.; final approval of manuscript: all authors.

Declarations

Competing interests
The authors declare no competing interests.

Ethical Approval
All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved (reference number: E-10840098-202.3.02-1273, 13 February 2025) by the Ethics Committee at Medipol University (Istanbul, Turkey).

Informed consent
Written informed consent was obtained from all patients or their designated legal representatives.

Additional information
Correspondence and requests for materials should be addressed to M.M.M.