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Functional, nutritional, and inflammatory predictors of survival in early-onset gastric cancer

Erken başlangıçlı gastrik kanserde sağkalımın fonksiyonel, nutrisyonel ve inflamatuvar belirleyicileri

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ABSTRACT

Aim: Early-onset gastric cancer (EOGC) represents a distinct subgroup with aggressive clinicopathological features; however, prognostic data in younger patients remain limited. This study aimed to evaluate clinicopathological characteristics and identify prognostic factors associated with survival in patients aged ≤ 50 years with gastric cancer.

Materials and Methods: A total of 60 patients aged ≤ 50 years diagnosed with gastric cancer between 2014 and 2024 were included in this retrospective single-center study. Survival outcomes were analyzed using the Kaplan–Meier method, and prognostic factors were evaluated with Cox proportional hazards regression analysis.

Results: The median age was 40.9 years, and 51.7% of patients were female. Diffuse or signet-ring cell histology and advanced-stage disease were frequently observed. Median progression-free survival (PFS) and overall survival (OS) were 19.3 and 26.0 months, respectively. Signet-ring cell histology, low Prognostic Nutritional Index (PNI), and elevated platelet-to-lymphocyte ratio (PLR) were associated with shorter PFS. In univariate analysis, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS), low PNI, advanced stage, and total gastrectomy were associated with inferior survival. In multivariate analysis, ECOG PS 3 and elevated PLR independently predicted mortality.

Conclusions: EOGC commonly presents with advanced disease and unfavorable outcomes. Both tumor-related factors and host-related parameters—including functional status, nutritional condition, and systemic inflammatory markers—play an important role in determining prognosis and may improve risk stratification in younger patients.

Keywords: Early-onset cancer; stomach neoplasms; performance status; prognostic nutritional index; survival

ÖZ

Amaç: *Erken başlangıçlı gastrik kanser* (EOGC)*, agresif klinikopatolojik özelliklere sahip ayrı bir alt grup olarak kabul edilmektedir; ancak genç hastalarda prognostik veriler sınırlıdır. Bu çalışmanın amacı, 50 yaş ve altındaki gastrik kanser hastalarında klinikopatolojik özellikleri değerlendirmek ve sağkalımı etkileyen prognostik faktörleri belirlemektir.*

Gereç ve Yöntem: *Bu retrospektif, tek merkezli çalışmaya 2014 ile 2024 tarihleri arasında gastrik kanser tanısı alan 50 yaş ve altındaki toplam 60 hasta dahil edildi. Sağkalım sonuçları Kaplan–Meier yöntemi ile analiz edildi ve prognostik faktörler Cox regresyon analizi ile değerlendirildi.*

Bulgular: *Medyan yaş 40,9 yıl olup hastaların %51,7'si kadındı. Diffüz veya taşlı yüzük hücreli histoloji ve ileri evre hastalık sıklıkla gözlendi.*

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Medyan progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) sırasıyla 19,3 ve 26,0 ay olarak bulundu. Taşlı yüzük hücreli histoloji, düşük Prognostik Nütrisyonel İndeks (PNI) ve yüksek trombosit-lenfosit oranı (PLR) daha kısa progresyonsuz sağkalım ile ilişkiliydi. Genel sağkalım için yapılan tek değişkenli analizde kötü ECOG performans durumu, düşük PNI, ileri evre ve total gastrektomi daha kötü sağkalım ile ilişkiliydi. Çok değişkenli analizde ECOG performans durumu 3 ve yüksek PLR mortalitenin bağımsız belirleyicileri olarak saptandı.

Sonuç: *EBGK sıklıkla ileri evrede ve olumsuz klinik sonuçlarla ortaya çıkmaktadır. Fonksiyonel durum, nutrisyonel durum ve sistemik inflamatuvar belirteçler gibi tümöre ve konağa ait faktörler prognozun belirlenmesinde önemli rol oynamakta ve genç hastalarda risk sınıflamasının iyileştirilmesine katkı sağlayabilir.*

Anahtar Sözcükler: *Erken başlangıçlı kanser; mide neoplazileri; performans durumu; prognostik nütrisyonel indeks; sağkalım*

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide, with nearly one million new cases and over 700,000 deaths annually (1). Although incidence has declined in some regions due to improved screening and Helicobacter pylori eradication, it continues to be a major health burden, particularly in East Asia, Eastern Europe, and South America (1). Gastric cancer typically develops in older adults, with a median age at diagnosis around 68 years; however, a subset of patients present at younger ages, comprising approximately 5–10% of all cases (2).

Early-onset gastric cancer (EOGC), often defined as diagnosis before the age of 40 or 50 years, has been recognized as a distinct clinical entity. Previous studies have shown that EOGC is characterized by aggressive biological features, including diffuse-type histology, signet-ring cell carcinoma, poor differentiation, and advanced stage at presentation (3-7). Population-based analyses further suggest demographic differences, with younger patients more frequently female or non-White, and often presenting with metastatic disease compared to older adults (8). A rising incidence has been reported in specific subgroups, such as young Hispanic men in the United States (9).

Despite these adverse pathological and clinical features, younger patients may tolerate multimodality treatment better due to fewer comorbidities, leading to conflicting findings regarding prognosis. Some reports suggest that survival may be comparable or even superior to that of older patients when curative resection is feasible (10), whereas others describe worse outcomes owing to aggressive tumor biology (3-7).

In recent years, novel host-related prognostic markers have gained importance. Performance status has consistently been shown to predict survival in gastric cancer, with impaired Eastern Cooperative Oncology Group (ECOG) performance status (PS) correlating with reduced tolerance to systemic therapy and poorer outcomes (11, 12). Nutritional indices, such as the Prognostic Nutritional Index (PNI), integrate serum albumin and lymphocyte count and reflect both nutritional reserve and immune competence; several meta-analyses have validated PNI as an independent prognostic marker (13-16). In addition, systemic inflammatory markers, such as the platelet-to-lymphocyte ratio (PLR), have emerged as cost-effective, easily measurable predictors of tumor progression and survival across multiple malignancies, including gastric cancer (17-21).

Given the relative scarcity of data focusing on younger patients, particularly regarding nutritional and inflammatory biomarkers, this single-center retrospective study aimed to evaluate the clinicopathological features and identify prognostic factors affecting survival in patients aged ≤ 50 years with gastric cancer.

MATERIALS and METHODS

Study Design and Patient Population

This retrospective, observational, single-center study included 60 patients diagnosed with gastric cancer between 2014 and 2024. The inclusion criteria were age ≤ 50 years at diagnosis, histopathologically confirmed gastric adenocarcinoma including diffuse and signet-ring cell subtypes, and availability of clinical, pathological, treatment, and follow-up data. Patients who underwent curative-intent gastrectomy as well as those who received

systemic or palliative treatment for advanced disease were included in the analysis. Exclusion criteria included age >50 years, histological diagnoses other than adenocarcinoma (such as gastrointestinal stromal tumors, lymphomas, or neuroendocrine tumors) and incomplete medical records.

Data Collection

Demographic and clinical data were retrospectively obtained from hospital records. Variables including age at diagnosis, sex, comorbidities, ECOG PS, tumor histology, tumor location, tumor grade, and clinical and pathological stage were recorded.

Nutritional and hematological parameters including serum albumin, platelet, lymphocyte, PLR, and PNI were evaluated. Information regarding surgical procedures, neoadjuvant and adjuvant therapies, and palliative systemic treatments was also collected. Data on disease recurrence, progression, and mortality were obtained from follow-up records.

ECOG performance status was analyzed as a categorical variable (0, 1, 2, and 3) in statistical analyses; however, for clinical interpretation, patients were occasionally grouped (e.g., ECOG PS ≥ 2) to reflect poor functional status.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), whereas categorical variables were presented as frequency and percentage.

The Prognostic Nutritional Index was calculated as: PNI = (10 × serum albumin [g/dL]) + (0.005 × total lymphocyte count [/mm³]). The platelet-to-lymphocyte ratio was calculated by dividing the platelet count by the lymphocyte count.

Progression-free survival (PFS) was defined as the time from the date of diagnosis to the first documented disease progression, recurrence, or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from diagnosis to death from any cause.

Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression analysis was used to identify prognostic factors associated with PFS and OS. Variables with a p-value <0.10 in univariate analysis were included in the multivariate model. A p-value <0.05 was considered statistically significant.

Ethical Approval

Ethical approval for this study was obtained from the Adıyaman University Ethics Committee (October 14, 2025; approval number: 2025/8-1). Due to the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Patient Characteristics

A total of 60 patients aged ≤ 50 years were analyzed. The mean age at diagnosis was 40.9 ± 6.3 years (range: 28–50), and 51.7% of the patients were female. Comorbidities were present in 10% of the cohort. Most patients had a good performance status, with ECOG PS 0–1 observed in 78.3% of the cohort (Table-1).

Adenocarcinoma was the most common subtype (51.2%), followed by signet-ring cell carcinoma (45%). The most frequent tumor location was the antrum (36%), and more than half of the tumors were grade 3 (53.3%). At presentation, 28.3% (n = 17) of patients had metastatic disease.

Among the 39 patients who underwent surgery, subtotal gastrectomy was performed in 71.8% and total gastrectomy in 28.2%. D2 lymphadenectomy was achieved in 59.0% of cases. Advanced tumor invasion was common, with pT3–T4 tumors comprising 79.5% of cases. Lymph node metastasis was also frequent, with pN3 disease observed in 38.5% of patients (Table-2).

Neoadjuvant chemotherapy was administered to 17.9% of patients, all of whom received the FLOT regimen. Adjuvant chemotherapy was delivered in 61.5% of cases, most commonly using XELOX or FOLFOX regimens. Additionally, 41% of the surgical cohort received adjuvant radiotherapy. The median number of neoadjuvant chemotherapy cycles was four, while the median number of adjuvant chemotherapy cycles was five.

Among the 17 patients with metastatic disease at diagnosis, the most frequent pattern of spread was peritoneal carcinomatosis with intra-

abdominal involvement. These patients received a mean of two lines of systemic chemotherapy.

The mean PNI for the overall cohort was 35.6, and 74% of patients had a PNI <40, suggesting severe malnutrition (Table-3).

Table-1. Descriptive statistics of demographic and clinical variables

	n / Mean ± SD	% / Median (min–max)
Age		42 (28 - 50)
Gender		
Female	31	51.7
Male	29	48.3
Comorbidities		
No	54	90.0
Yes	6	10.0
ECOG PS		
0	20	33.3
1	27	45.0
2	9	15.0
3	4	6.7
Histology		
Adenocarcinoma	31	51.7
Signet-ring cell carcinoma	27	45.0
Unknown	2	3.3
Tumor location		
Cardia	3	5.0
Corpus	17	28.3
Antrum	22	36.7
Pyloric	2	3.3
Unknown	16	26.7
Tumor grade		
1	3	5.0
2	2	3.3
3	32	53.3
Unknown	23	38.3
Her2		
Negative	17	28.3
Positive	8	13.3
Unknown	35	58.3
Pathological stage(n=40)		
0	1	2.5
1	5	12.5
2	9	22.5
3	23	57.5
4	2	5.0
Clinical stage		
Non-metastatic	43	71.7
Metastatic	17	28.3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; SD, standard deviation; Min, minimum; Max, maximum.
Note: Percentages for pathological stage were calculated based on the 40 patients with available pathological staging data.

Table-2. Pathological and surgical characteristics

	n / Mean ± SD	% / Median (min–max)
pT/ypT		
0	1	2.6
1	3	7.7
2	4	10.3
3	14	35.9
4	17	43.6

pN/ypN		
0	10	25.6
1	5	12.8
2	9	23.1
3	15	38.5
LVI		
Negative	7	17.9
Positive	9	23.2
Unknown	23	59
PNinv		
Negative	5	12.8
Positive	11	28.2
Unknown	23	59
Median number of lymph nodes examined	24.65 ± 13.39	20 (9 - 64)
Resection margin status		
Negative	35	89.7
Positive	1	2.6
Unknown	3	7.7
D2 lymphadenectomy		
No	13	33.3
Yes	23	59
Unknown	3	7.7
Type of gastrectomy		
Total	11	28.2
Subtotal	28	69.2
No surgery	1	2.6

Abbreviations: pT/ypT, pathological tumor stage; pN/ypN, pathological lymph node stage; LVI, lymphovascular invasion; PNinv, Perineural invasion; SD, standard deviation; Min, minimum; Max, maximum.

Table-3. Inflammatory Parameters

Parameter	n / Mean ± SD	% / Median (Min–Max)
PLR	182.57 ± 107.13	148.07 (41.28 – 624.55)
PNI (continuous)	35.65 ± 5.56	36.01 (21.01 – 45.01)
PNI (categorical)		
PNI <50 (Mild malnutrition)	2	3.4
PNI <45 (Moderate to severe malnutrition)	13	22.4
PNI <40 (Severe malnutrition)	43	74.1

Abbreviations: PNI, Prognostic Nutritional Index; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; Min, minimum; Max, maximum.

Survival Outcomes

For the entire cohort, the median PFS was 19.3 months, and the median OS was 26 months. At the time of analysis, 49% had experienced recurrence or progression, and 58.3% had died. Systemic recurrence was the most common relapse pattern (78.6%).

Prognostic Factors for Progression-Free Survival

As shown in Table-4, Kaplan–Meier analysis demonstrated significant differences in PFS according to ECOG PS, histological subtype, and PLR. Patients with poorer ECOG PS had markedly shorter PFS, with a median PFS of 46.7 months for ECOG PS 1 and 6.3 months for ECOG PS 2, whereas the median PFS was not reached (NR) in patients with ECOG PS 0 ($p = 0.007$) (Figure 1). Histological subtype was also associated with progression risk, as patients with signet-ring cell carcinoma had significantly worse outcomes than those with adenocarcinoma (median PFS: 14.7 months vs. NR, $p = 0.007$). In addition, systemic inflammatory status was significantly associated with PFS ($p = 0.041$). Patients with PLR >150 had shorter PFS compared with those with PLR ≤ 150 (median PFS: 14.7 months vs. NR) (Figure 2).

In univariate Cox regression analysis, lower PNI, ECOG PS 2, signet-ring cell histology, higher number of dissected lymph nodes, and PLR >150 were significantly associated with increased risk of progression. To minimize the risk of overfitting due

to the limited number of progression events relative to the sample size (n = 60, with 29 progression events), two separate multivariate Cox regression models were constructed. In the first multivariate model including PNI, ECOG PS, and histological subtype, both PNI (HR = 0.918, 95% CI 0.85–0.991, p = 0.028) and histological subtype (HR = 3.050, 95% CI 1.055–8.817, p = 0.040) remained independent predictors of progression. In the second model evaluating inflammatory markers, signet-ring cell histology (HR = 3.208, 95% CI 1.12–9.188, p = 0.030) and PLR >150 (HR = 3.400, 95% CI 1.269–9.108, p = 0.015) independently predicted poorer PFS.

Although ECOG PS 2 showed a trend toward increased progression risk, it did not remain statistically significant when evaluated together with other variables in the multivariate model (p>0.05) (Table-5).

Table-4. Kaplan–Meier analysis results for progression-free survival

	Median (95% CI)	**Test Statistic***	**p**
Gender			
Female	18.33 (0 - 68.63)	1.452	0.228
Male	---		
Comorbidity			
No	28.57 (0 - 65.27)	1.278	0.258
Yes	---		
ECOG PS			
0	---		
1	46.73 (0 - 93.49)	12.154	**0.007**
2	6.3 (5.97 - 6.63)		
3	---		
Histology			
Adenocarcinoma	---	7.359	**0.007**
Signet-ring cell carcinoma	14.67 (0 - 34.11)		
Tumor location			
Corpus	8.83 (0 - 24.45)	1.537	0.215
Antrum	---		
Her2			
Negative	24.23 (1.09 - 47.37)	0.012	0.912
Positive	9.1 (0.79 - 17.41)		
LVI			
Negative	---	3.299	0.069
Positive	28.57 (19.54 - 37.6)		
PNinv			
Negative	---	0.269	0.586
Positive	---		
PNI			
< 45 (Moderate to Severe Malnutrition)	---	2.830	0.093
< 40 (Severe Malnutrition)	18.33 (10.35 - 26.31)		
D2 lymphadenectomy			
No	---	0.383	0.530
Yes	---		
Type of gastrectomy			
Total	---	2.855	0.091
Subtotal	---		
PLR level			
≤150	---	4.172	**0.041**
>150	14.67 (5.32 - 24.02)		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion; PNinv, Perineural invasion; PNI, Prognostic Nutritional Index; PLR, platelet-to-lymphocyte ratio; CI, confidence interval.

*Log-rank test

Table-5. Univariate and multivariate Cox regression analyses of factors associated with progression-free survival.

	Univariate		Multivariate Model 1		Multivariate Model 2	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	0.985 (0.925 - 1.048)	0.624				
PNI	0.923 (0.865 - 0.985)	**0.015**	0.918 (0.85 - 0.991)	**0.028**		
ECOG PS (Ref : 0)						
1	1.3 (0.502 - 3.369)	0.589	1.195 (0.405 - 3.529)	0.747	1.308 (0.472 - 3.627)	0.606
2	5.435 (1.728 - 17.088)	**0.004**	2.247 (0.631 - 8.005)	0.212	3.147 (0.963 - 10.284)	0.058
3	3.936 (0.463 - 33.451)	0.210	0.66 (0.06 - 7.294)	0.735	1.046 (0.111 - 9.846)	0.968
Histology (Ref : Adenocarcinoma)	3.138 (1.317 - 7.48)	**0.010**	3.05 (1.055 - 8.817)	**0.040**	3.208 (1.12 - 9.188)	**0.030**
Number of lymph nodes	1.063 (1.011 - 1.118)	**0.018**				
PLR (Ref : <150)	2.371 (1.016 - 5.533)	**0.046**			3.4 (1.269 - 9.108)	**0.015**

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PNI, Prognostic Nutritional Index; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval. Model 1: $\chi^2 = 18.004$, p = 0.003; Model 2: $\chi^2 = 19.548$, p = 0.002.

Prognostic Factors for Overall Survival

As shown in Table-6, Kaplan–Meier analysis identified ECOG PS as the strongest prognostic factor for OS. Median OS was 40.4 months for ECOG PS 1, 7.1 months for ECOG PS 2, and 0.8 months for ECOG PS 3 (p <0.001) (Figure-1). Nutritional status was also significantly associated with survival; patients with PNI ≥ 45 had a median OS of 71.3 months compared with 21.6 months in those with PNI <40 (p = 0.043). Patients who underwent partial gastrectomy showed better survival than those who underwent total gastrectomy (NR vs. 30.4 months, p = 0.037). Advanced disease stage was associated with poorer outcomes, with shorter OS observed in patients with clinical stage IV disease (NR vs. 15 months, p = 0.004) and pT4 tumors (NR vs. 30.4 months, p = 0.036). Additionally, PLR was significantly associated with OS (p = 0.027), with shorter survival observed in patients with PLR >150 compared with those with PLR ≤150 (median OS: 21 vs. 65.8 months) (Figure-2).

In univariate Cox regression analysis, ECOG performance status was strongly associated with OS. Compared with ECOG PS 0, patients with ECOG PS 2 and 3 had significantly worse survival (HR = 9.46, 95% CI 3.212–27.887, p <0.001; HR = 12.39, 95% CI 3.331–46.104, p <0.001, respectively). Nutritional status also showed prognostic significance; increasing PNI was associated with a lower risk of death (HR = 0.925, 95% CI 0.873–0.979, p = 0.007), while patients with PNI <40 had a higher mortality risk compared with those with PNI >45 (HR = 2.34, 95% CI 1.002–5.438, p = 0.049). Similarly, higher PLR values were associated with increased mortality risk (HR = 1.004, 95% CI 1.001–1.007, p = 0.004). Patients who underwent partial gastrectomy had a lower risk of death than those who underwent total gastrectomy (HR = 0.317, 95% CI 0.102–0.986, p = 0.047). Advanced disease characteristics were also associated with poorer outcomes, including clinical stage IV disease (HR = 6.95, 95% CI 1.55–31.179, p = 0.011) and pT4 tumors (HR = 2.92, 95% CI 1.025–8.31, p = 0.045). In multivariate analysis, only ECOG PS 3 (HR = 377.05, 95% CI 8.28–17173.9, p = 0.002) and elevated PLR (HR = 1.006, 95% CI 1.001–1.010, p = 0.024) remained independent predictors of poor OS (Table-7).

Table-6. Kaplan–Meier analysis results for overall survival

	Median (95% CI)	Test Statistic*	p
Gender			
Female	29.37 (10.16 - 48.59)	0.004	0.948
Male	30.47 (15.02 - 45.92)		
Comorbidity			
No	29.73 (18.9 - 40.56)	0.788	0.375
Yes	-		
ECOG PS			
0	-		
1	40.37 (18.88 - 61.86)	33.224	**<0.001**
2	7.07 (5.78 - 8.36)		
3	0.77 (0 - 7.73)		
Histology			
Adenocarcinoma			
Signet-ring cell carcinoma			
Tumor location			
Corpus	21 (7.57 - 34.43)	3.358	0.067
Antrum	46.4 (7.62 - 85.18)		
Her2			
Negative	30.47 (22.99 - 37.96)	0.440	0.507
Positive	15.03 (0 - 32.06)		
LVI			
Negative	35.67 (25.2 - 46.14)	2.266	0.132
Positive	-		
PNinv			
Negative	-	0.059	0.809
Positive	-		
PNI			
< 45 (Moderate to Severe Malnutrition)	71.27 (34.14 - 108.4)	4.081	**0.043**
< 40 (Severe Malnutrition)	21.63 (10.61 - 32.65)		
D2 lymphadenectomy			
No	-	0.429	0.512
Yes	-		
Type of gastrectomy			
Total	30.47 (12.68 - 48.26)	4.356	**0.037**
Subtotal	-		
Clinical stage			
1+2+3	-	8.302	**0.004**
4	15.23 (1.85 - 28.61)		
pT/ypT			
1+2+3	-	4.391	**0.036**
4	30.47 (24.71 - 36.23)		
PLR			
< 150	65.77 (26 - 105.54)	4.919	**0.027**
>150	21 (16.05 - 25.96)		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion; PNinv, Perineural invasion; PNI, Prognostic Nutritional Index; PLR, platelet-to-lymphocyte ratio; pT/ypT, pathological tumor stage; CI, confidence interval.

*Log-rank test

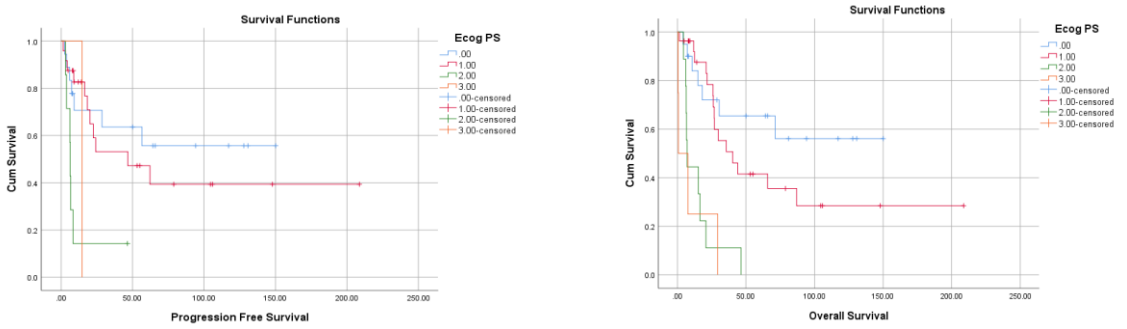

Figure-1. Kaplan–Meier survival curves demonstrating the impact of ECOG performance status on progression-free survival (PFS) and overall survival (OS) in patients with early-onset gastric cancer. Patients with poorer ECOG performance status showed significantly worse survival outcomes.

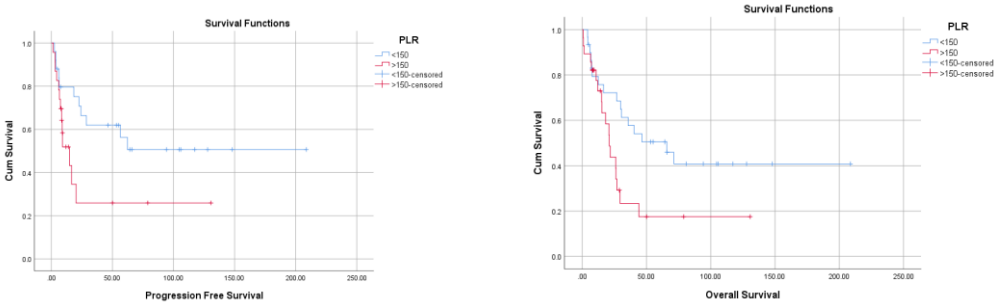

Figure-2. Kaplan–Meier survival curves demonstrating the association between systemic inflammatory status and survival outcomes in patients with early-onset gastric cancer. Patients with PLR >150 had significantly shorter progression-free survival (PFS) and overall survival (OS) compared with those with PLR ≤150.

Table-7. Univariate and multivariate Cox regression analyses of prognostic factors for overall survival

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age	0.992 (0.941 - 1.047)	0.782		
ECOG PS (Ref: 0)				
1	2.024 (0.783 - 5.234)	0.146	8.595 (0.966 - 76.492)	0.054
2	9.464 (3.212 - 27.887)	**<0.001**	17.452 (0.943 - 323.077)	0.055
3	12.393 (3.331 - 46.104)	**<0.001**	377.05 (8.278 - 17173.96)	**0.002**
PNI (continuous)	0.925 (0.873 - 0.979)	**0.007**	0.949 (0.844 - 1.068)	0.386
PNI (Ref : <45 (moderate-to-severe malnutrition))	2.335 (1.002 - 5.438)	**0.049**		
Number of lymph nodes	1.039 (0.989 - 1.09)	0.125		
Type of gastrectomy (Ref :Total)	0.317 (0.102 - 0.986)	**0.047**	0.348 (0.071 - 1.701)	0.192
PLR	1.004 (1.001 - 1.007)	**0.004**	1.006 (1.001 - 1.01)	**0.024**
Clinical stage (Ref : 1+2+3)	6.952 (1.55 - 31.179)	**0.011**		
pT/ypT (Ref : 1+2+3)	2.918 (1.025 - 8.31)	**0.045**		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PNI, Prognostic Nutritional Index; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

DISCUSSION

This study demonstrates that early-onset gastric cancer is frequently associated with aggressive biological features, including diffuse-type and signet-ring histology, advanced stage at diagnosis, and poor differentiation. These findings

are consistent with previous reports describing EOGC as a biologically unfavorable entity (3–7).

Large population-based studies have reported similar findings. De et al. demonstrated that patients younger than 40 years are more likely to present with metastatic disease, with clinical stage representing the strongest predictor of survival (8). Merchant et al. reported an increasing incidence of advanced gastric cancer among young Hispanic men in the United States, highlighting demographic variation (9). Similarly, Japanese and Korean studies have shown that younger patients are more frequently female and more likely to present with diffuse histology and advanced disease (3–4). In our cohort, the proportion of female patients was also relatively high, further supporting the concept that EOGC represents a distinct clinicopathological subgroup.

Among all evaluated factors, ECOG PS emerged as the strongest determinant of survival. Patients with ECOG PS ≥ 2 had significantly shorter survival compared with those with ECOG PS 0–1. Previous studies have similarly demonstrated that impaired functional status is associated with reduced treatment tolerance, increased chemotherapy toxicity, and poorer survival outcomes (11,12). Gómez-Ulloa et al. identified ECOG PS at the initiation of systemic therapy as a key prognostic factor in advanced gastric cancer, while Zeynelgil et al. confirmed its significance in stage IV disease with liver metastases (11,12). These findings highlight that functional status assessment remains crucial even in younger patients who are often assumed to have adequate physiological reserve.

Nutritional and immune status, evaluated using the PNI, also showed strong prognostic value. In our analysis, patients with PNI <40 had significantly inferior survival compared with those with higher scores. Several meta-analyses support this observation. Wang et al. demonstrated that low PNI is consistently associated with worse OS in gastric cancer (13), while Yang et al. reported its association with postoperative complications and long-term outcomes (14). Deng et al. further confirmed its prognostic value in a systematic review including more than 23,000 gastrectomy patients (15). Low PNI likely reflects both malnutrition and immunosuppression, conditions that adversely affect treatment tolerance and clinical outcomes. Our findings emphasize the importance of early nutritional assessment and supportive interventions even in younger patients.

In addition to performance and nutritional status, systemic inflammation also played a key role. A higher PLR independently predicted mortality in our multivariate analysis. Elevated PLR reflects increased platelet activity, which can promote tumor angiogenesis and metastasis, combined with lymphopenia, a marker of impaired host immunity. Both Zeng et al. and Cao et al. demonstrated that patients with elevated PLR not only had poorer OS but also appeared to derive greater benefit from chemotherapy, highlighting its dual role as a prognostic and predictive biomarker (17-18). Huang et al. further validated that systemic inflammatory indices, including PLR, predict outcomes after curative surgery (19). Beyond gastric cancer, Ethier et al. and Templeton et al. demonstrated that PLR is a robust, cost-effective biomarker across breast, colorectal, and lung cancers (20, 21). Our data therefore reinforce the role of PLR as an easily accessible marker to identify high-risk patients who may benefit from closer monitoring, more intensive supportive strategies, and potentially greater benefit from chemotherapy.

Surgical extent was also associated with prognosis in univariate analysis, with patients undergoing partial gastrectomy demonstrating better survival than those undergoing total gastrectomy. Although this result may partly reflect selection bias—since patients with proximal or more extensive disease are more likely to require total gastrectomy—differences in surgical complexity, perioperative morbidity, and tumor biology may also contribute (3, 4).

Previous reports indicate that curative resection may eliminate survival differences between younger and older patients, particularly in early-stage disease. Park et al. reported comparable outcomes between age groups after curative resection for stage I gastric cancer (10). However, most patients in our cohort presented with advanced-stage disease, underscoring the importance of early detection.

The mean age at diagnosis in our cohort was approximately 41 years, closely corresponding to the screening threshold of 40 years used in high-incidence countries such as Japan and South Korea. Population-based screening programs beginning at this age have been associated with substantial reductions in gastric cancer mortality.

Considering the increasing incidence of gastric cancer in our region, particularly in southeastern Turkey, these findings suggest that earlier or targeted endoscopic screening strategies may warrant consideration (1,22–24).

Taken together, our results indicate that EOGC represents a challenging subgroup of gastric cancer characterized by aggressive tumor biology and unfavorable long-term outcomes. Prognostic assessment should therefore incorporate not only tumor-related factors such as stage and histology but also host-related parameters including ECOG PS, PNI, and PLR. As inexpensive and readily available markers, PNI and PLR may help refine risk stratification, guide supportive care strategies, and facilitate more individualized treatment approaches for patients with early-onset gastric cancer. These markers may be incorporated into routine baseline assessment to support risk-adapted clinical decision-making.

Limitations

This study has several limitations that should be acknowledged. First, its retrospective and single-center design inherently introduces the risk of selection bias and limits the generalizability of our findings. Second, the relatively small sample size reduced the statistical power of subgroup analyses and restricted the ability to fully adjust for confounding factors. Due to the retrospective nature of the study, some pathological variables were unavailable for all patients. Third, there was heterogeneity in stage distribution, with nearly one-third of patients presenting with stage IV disease, which may have negatively influenced PFS and OS outcomes. Fourth, molecular profiling was not systematically performed during the study period, preventing the evaluation of potential genomic drivers and their prognostic implications in EOGC, including key biomarkers such as HER2, microsatellite instability (MSI), and PD-L1 expression. Finally, in the multivariate Cox regression models, some established prognostic factors such as clinical stage and pT stage could not be included due to the limited number of events, which may have underestimated their independent effects.

Despite these constraints, this study provides valuable real-world data in a rare subgroup of gastric cancer and serves as hypothesis-generating evidence for future research.

CONCLUSION

In conclusion, EOGC in our cohort was characterized by advanced disease at presentation and poor long-term survival. Among prognostic variables, ECOG PS, PNI, and PLR consistently emerged as strong determinants of outcome. These findings highlight the need to incorporate host-related parameters into clinical decision-making for younger patients, alongside traditional staging factors. Further multi-institutional prospective studies are required to validate these observations and to better define the biological and clinical behavior of this unique patient group.

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