Clinics in Oncology

Research Article
Published: 31 Oct, 2023

Neutrophil–Lymphocyte Ratio Predicts Overall Survival in Elderly Patients with Unresectable or Recurrent Gastric Cancer

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Abstract

Introduction: The correlations between various inflammatory biomarkers and outcomes in patients with solid cancers has been reported. However, the relevance of these markers is unclear in elderly patients with unresectable or recurrent gastric cancer. This retrospective study was conducted to identify specific factors associated with the survival of elderly patients with gastric cancer.

Material and Methods: Gastric cancer patients undergoing chemotherapy (n=112) were categorized into groups (young: <70 years; elderly: ≥ 70 years). The association between overall survival and pre-treatment values of systemic biomarkers, including the Neutrophil–Lymphocyte Ratio (NLR), Platelet–Lymphocyte Ratio (PLR), and Glasgow Prognostic Score (GPS), was evaluated in each group using the Kaplan–Meier method and log-rank test. Univariate and multivariate analyses using Cox proportional hazards regression were performed to investigate the prognostic factors associated with overall survival in each group.

Results: In both groups (n=56), a NLR and GPS were associated with poor overall survival, whereas the PLR was not. Univariate and multivariate Cox regression analyses revealed that poor performance status was correlated with poor overall survival in the young group. However, in the elderly group, the NLR was the only independent prognostic factor of overall survival. Poor performance status was an independent marker of poor prognosis in the young group, whereas a high NLR was an independent marker in the elderly group.

Conclusion: Thus, the NLR may be a specific biomarker for predicting the overall survival of elderly patients with unresectable gastric cancer.

Keywords: Elderly; Gastric cancer; Glasgow prognostic score; Neutrophil–lymphocyte ratio; Platelet–lymphocyte ratio

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Received Date: *10 Oct 2023*
Accepted Date: *25 Oct 2023*
Published Date: *31 Oct 2023*

Citation:
Yamauchi Y, Sofuni A, Suzuki Y, Iwasaki K, Fukuzawa M, Nagakawa Y. Neutrophil–Lymphocyte Ratio Predicts Overall Survival in Elderly Patients with Unresectable or Recurrent Gastric Cancer. Clin Oncol. 2023; 8: 2027.

ISSN: 2474-1663

Abbreviations

GC: Gastric Cancer; PS: Performance Status; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil–Lymphocyte Ratio; PLR: Platelet–Lymphocyte Ratio; GPS: Glasgow Prognostic Score; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval; Y group: Young group; E group: Elderly group

Introduction

Worldwide, Gastric Cancer (GC) is one of the most common malignant tumors of the digestive system, the fifth most common type of cancer, and the third leading cause of cancer-related deaths [1]. Most patients with GC are elderly, and it is estimated that patients aged 65 years or older account for approximately 70% of the total cases of GC [2]. Consequently, the number of elderly patients with advanced GC has increased because of increased life expectancy and general population aging [3]. There is widespread concern regarding the ability of elderly patients to tolerate chemotherapy, given their higher likelihood of frailty and multiple comorbidities. This may result in chemotherapy not being offered or the planned treatment being modified or stopped early with potentially negative prognostic implications. Generally, chemotherapy is selected based on the patient's overall health, including their Performance Status (PS), organ function, and the presence of comorbidities. As defined by the Eastern Cooperative Oncology Group (ECOG), the PS is an

important factor associated with patient clinical outcomes and is useful for determining the indication of chemotherapy in cancer patients [4,5]. However, these factors are considered less reliable in the elderly than in younger individuals because of the physical, psychological, and social complexities associated with elderly patients [6]. Thus, it is important to identify the markers that can predict clinical outcomes in elderly patients.

Recently, many studies have identified an association between systematic inflammation and cancer progression. Furthermore, several studies have suggested that some routine blood biomarkers, such as the Neutrophil–Lymphocyte Ratio (NLR), Platelet–Lymphocyte Ratio (PLR), and Glasgow Prognostic Score (GPS), can help to evaluate the clinical outcomes of cancer patients [7-12]. These parameters may be useful as practical biomarkers in routine practice. However, the prognostic value of these biomarkers for elderly patients remains uncertain as most studies on inflammatory biomarkers have been performed on young individuals, and only a few studies have included the elderly. Thus, in the present study, we investigated the specific factors affecting the Overall Survival (OS) of elderly patients with unresectable GC.

Materials and Methods

Patients and study design

This retrospective study included patients with unresectable or recurrent GC treated with chemotherapy from January 2014 to April 2020 at our institution. All diagnoses were based on pathological confirmation, and patients' medical records were reviewed. The patients were divided into two groups based on their age: The Young (Y) group included patients under 70 years of age, and the Elderly (E) group comprised patients aged 70 years and above. The exclusion criteria were insufficient information and not having undergone chemotherapy at our institution.

Inflammatory biomarker evaluation

Prior to chemotherapy, data were collected, including patient demographics, tumor localization, complete blood count, serum albumin level (g/dL), C-reactive protein level (mg/dL), blood count, and other clinicopathological parameters.

NLR, PLR, and GPS were evaluated as biomarkers of inflammation. GPS was determined according to the following scoring system: Patients with both increased C-reactive protein (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) received a score of 2, whereas those satisfying only one of these criteria received a score of 1, and those with neither of these findings received a score of 0. Owing to the relatively small number of patients, the optimal cutoff value was not determined by a receiver operating characteristic curve. Rather, the cutoff value for each parameter was determined as previously reported: NLR=4, set by Shimada et al. [13], and PLR=150, set by Song et al. [14]. A GPS score of 1 or 2 was regarded as high.

Statistical analysis

OS was defined as the interval from the initiation of treatment until death. Patients who were still alive were censored at the final follow-up.

The Y and E groups were compared using Student's t-test or Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Univariate and multivariate analyses with the Cox proportional hazards regression model were used to identify independent risk factors for survival and estimate the respective Hazard Ratio (HR) and 95% Confidence Interval (CI) values for the various factors. Differences were considered significant at $p<0.05$. All calculations were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 112 patient records with sufficient information and follow-up data were included in the final analysis. Patient characteristics are summarized in Table 1. The median age was 69.5 years (range, 37–87 years), and 75% of the patients were male. Eighty-one patients (72%) had ECOG PS of 0 or 1. The median OS time of all patients was 9.77 months (range, 0.33–69.37 months). Intestinal type histology was observed in 32 patients (29%). Thirty patients (27%) had liver metastasis, and 42 (38%) had peritoneal seeding. Twenty-one patients (19%) had undergone gastrectomy. The median body mass index of the patients was 21.13 kg/m^2 (range, 13.42–29.83), and the median NLR and PLR were 3.22 (range, 1.15–20.32) and 208.9 (range, 15.1–990.64), respectively. GPS was 0 in 43 patients (38%), 1 in 38 patients (34%), and 2 in 31 patients (28%). With respect to group differences, PLR was significantly higher in the Y group than in the E group (Table 1).

After a median follow-up of 9.77 months (range, 0.33–69.37 months), 71 patients (64%) did not survive. Results of the Kaplan–Meier curve analysis and the log-rank test showed that, in the Y group, NLR and GPS were significantly associated with OS ($p<0.01$, $p<0.01$, respectively), whereas PLR was not ($p=0.296$) (Figure 1). Similarly, in the E group, NLR and GPS were significantly associated with OS ($p<0.001$, $p=0.03$, respectively) but PLR was not ($p=0.35$) (Figure 2).

Univariate analysis of OS indicated that poor PS (HR: 2.64, 95% CI: 1.11–6.3, $p=0.03$), histological diffuse/mixed type (HR: 2.18, 95% CI: 1.05–4.52, $p=0.04$), peritoneal seeding (HR: 2.33, 95% CI: 1.23–4.42, $p=0.01$), high NLR (HR: 2.64, 95% CI: 1.38–5.03, $p<0.01$), and high GPS (HR: 2.29, 95% CI: 1.21–4.35, $p=0.01$) were significant prognostic factors in the Y group. Further, multivariate analysis demonstrated that poor PS was an independent prognostic factor for OS in the Y group (HR: 2.56, 95% CI: 1.02–6.43, $p<0.05$) (Table 2). Univariate analysis of OS of the E group indicated that poor PS (HR: 3.45, 95% CI: 1.53–7.8, $p<0.01$), high NLR (HR: 4.73, 95% CI: 2.08–10.78, $p=0.001$), and high GPS (HR: 2.46, 95% CI: 1.04–5.79, $p<0.03$) were significant prognostic factors. Further, multivariate analysis demonstrated that a high NLR was an independent prognostic factor for OS in the E group (HR: 4.22, 95% CI: 1.69–10.56, $p<0.01$; Table 3). In summary, the independent prognostic factor for OS in the Y and E groups was PS and NLR, respectively.

Discussion

This study investigated the prognostic factors for young and elderly patients with recurrent and unresectable GC. In the Y group, poor PS was an independent factor for a short OS, whereas NLR was the independent prognostic factor in the E group. We hypothesized that two factors may have contributed to our finding that NLR, but not PS, was the prognostic factor in the E cohort.

Firstly, PS might have been less reliable as a prognostic factor of elderly patients. Generally, among oncologists, the PS is considered an important tool to determine the general condition of patients. Almost all physicians refer to the PS when evaluating whether a patient is eligible for treatment or participation in clinical trials.

Table 1: Patient characteristics.

		All patients	Young group (n=56)	Elderly group (n=56)	*p-value*
Age		69.5 (37-87)	62 (37-69)	75 (70-87)	<0.01
Gender	male	84	40	44	0.383
	female	28	16	12	
PS	0	44	20	24	0.611
	1	43	24	19	
	2	25	12	13	
OS (months)		9.77 (0.33-69.37)	11.9 (0.33-40.43)	9.3 (0.9-69.37)	0.459
Histological type					0.446
Intestinal type		32	14	18	
Mixed/diffuse type		79	41	38	
Liver metastasis		30	14	16	0.67
Peritoneal seeding		42	25	17	0.118
Gastrectomy		21	9	21	0.468
BMI		21.13 (13.4- 29.82)	20.41 (13.42-29.83)	21.45 (14.95-27.78)	0.74
CEA		4 (0.3-8143)	3.35 (0.3-1714)	5.15 (0.6-8143)	0.273
CA19-9		15.1 (0-8515)	9.75 (0-5104)	15.2 (1.5-8515)	0.488
NLR		3.22 (1.15-20.32)	3.66 (1.15-20.32)	2.77 (1.23-10.17)	0.62
PLR		208.89 (16.942-990.63)	243.67 (47.91-990.63)	172.63 (16.94-542.85)	<0.01
GPS	0	43	23	20	0.485
	1	38	26	22	
	2	31	27	14	

Abbreviation: PS: Performance Status; OS: Overall Survival; BMI: Body Mass Index; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; GPS: Glasgow Prognostic Score

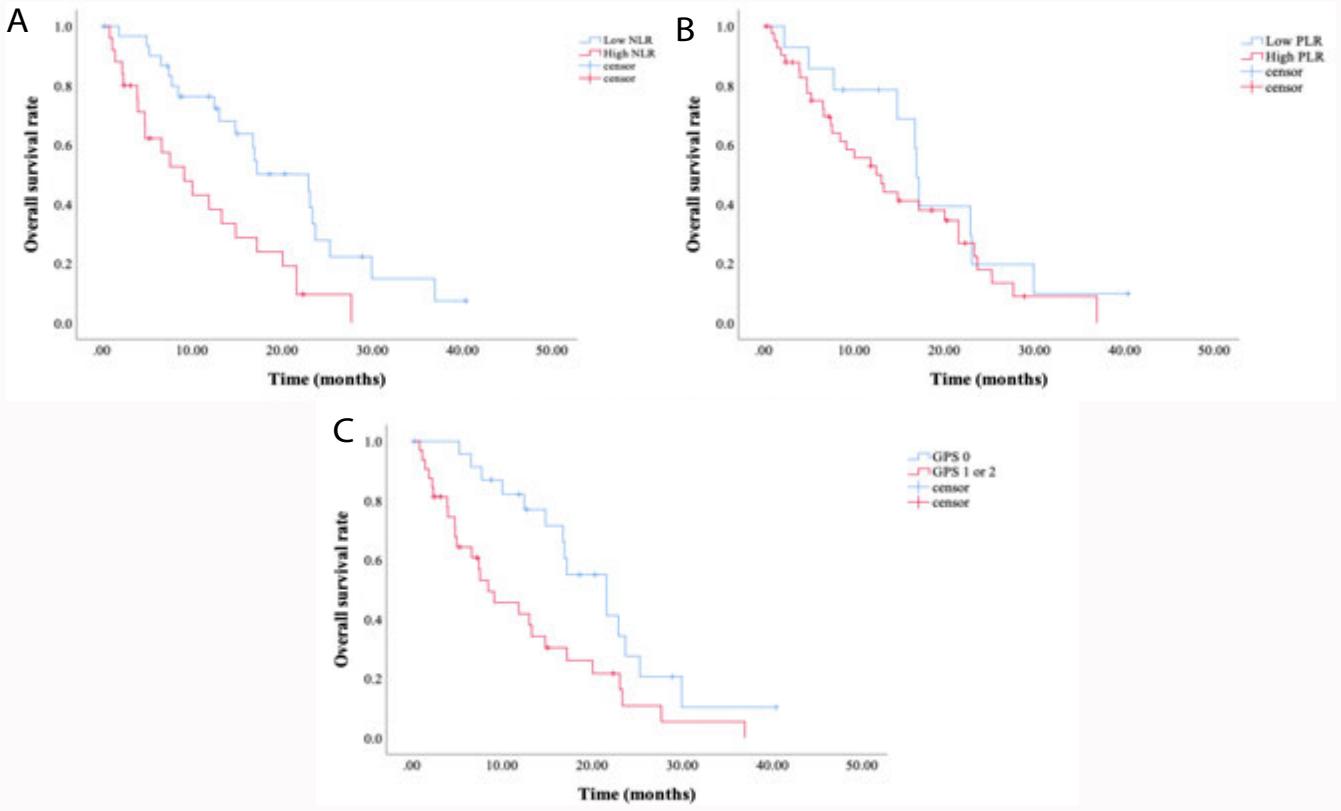

Figure 1: Kaplan Meier survival curves for overall survival according to inflammation-based scores in young group. A) Neutrophil-lymphocyte ratio; B) Platelet-lymphocyte ratio; C) Glasgow prognostic score. High-NLR and GPS 1/2 were significantly associated with poor OS (p=0.002, p=0.009) in young group.

Table 2: Univariate and multivariate analyses of overall in young group.

Univariate				Multivariate	
Variable		HR 95% CI	p-value	HR 95% CI	p-value
Gender	male	1	0.769		
	female	1.11 (0.57-2.15)			
PS	0 or 1	1	0.029	2.56 (1.02-6.43)	0.045
	2	2.64 (1.11-6.3)			
Histological type	Intestinal type	1	0.038	1	0.164
	Mixed/diffuse type	2.18 (1.05-4.52)		1.81 (0.79-4.16)	
Liver metastasis	no	1	0.249		
	yes	1.53 (0.74-3.16)			
Peritoneal seeding	no	1	0.01	1	0.365
	yes	2.33 (1.23-4.42)		1.42 (0.66-3.05)	
Gastrectomy	no	1	0.848		
	yes	1.08 (0.48-2.47)			
PPI	no	1	0.618		
	yes	1.17 (0.63-2.2)			
BMI	18.5 ≦, <25	1	0.451		
	18.5>, ≧25	0.79 (0.42-1.48)			
NLR	<4	1	0.003	1	0.153
	>4	2.64 (1.38-5.03)		1.91 (0.79-4.65)	
PLR	<150	1	0.3		
	>150	1.46 (0.71-3.01)			
GPS	0, 1	1	0.011	1	0.583
	2	2.29 (1.21-4.35)		1.26 (0.79-4.16)	
CEA	≦ 5	1	0.299		
	>5	0.71 (0.37-1.36)			
CA19-9	≦ 37	1	0.092	1	0.469
	>37	1.73 (0.92-3.27)		1.31 (0.63-2.74)	

Abbreviation: PS: Performance Status: OS: Overall Survival; PPI: Proton Pomp Inhibitor; BMI: Body Mass Index; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; GPS: Glasgow Prognostic Score

Poor PS has been reported as a predictor of poor clinical outcome, including increased adverse events and decreased treatment efficacy, in patients receiving chemotherapy [15-17]. However, the PS may not be sufficient when assessing elderly patients for chemotherapy [18], because of the high heterogeneity in this population and factors such as medical history, organ function, and nutritional status [19].

Secondary, in E group NLR was associated with frailty which increases its reliability as a prognostic factor. NLR has been shown to be useful for predicting clinical outcomes in several studies that included both young and elderly patients with cancer [13,20,21]. A high NLR indicates an increased neutrophil count and/or a decreased lymphocyte count, as well as relative lymphopenia. The relationship between the NLR and prognosis of cancer patients remains poorly understood. However, both neutrophils and lymphocytes are considered to be related to cancer prognosis. Neutrophils play significant roles in cancer progression, including tumor initiation, growth, proliferation, and metastatic stage [22,23]. Furthermore, neutrophilia inhibits the cytotoxic activity of lymphocytes, such as T cells and natural killer cells, and facilitates the extravasation of tumor cells [24]. By contrast, lymphocytes play an important role in the immune response against cancers. Low peripheral lymphocyte counts have been associated with a poor outcome in various cancers [25-27] and are related to lymphatic invasion and lung cancer recurrence [7]. Lymphocytes thus play a crucial role in the antitumor immune response. Accordingly, a decreased lymphocyte count reduces the antitumor effect of the immune system, resulting in accelerated tumor occurrence and development [28]. Previous research has clearly demonstrated an association between the NLR and cancer immune environment. Consequently, NLR is considered to be related to clinical outcomes.

Previously, frailty has been identified as a poor prognostic factor in geriatric oncology [29,30]. Nishijima et al. reported an association between NLR and frailty in the elderly [31]. The mechanisms of association between NLR and frailty are uncertain. However, Gilmore et al. reported that chronic low-grade inflammation might be involved in the relationship between NLR and frailty [32]. Whereas, Collerton et al. reported negative association with between lymphocyte counts and frailty [33]. Accordingly, the high NLRs were considered to reflect frail by reflecting both chronic inflammation and immune aging.

Based on the above, because NLR might had been representing the tumor environment as well as the patient's own frailty included immune aging in the elderly, could have been a more sensitive prognostic predictor.

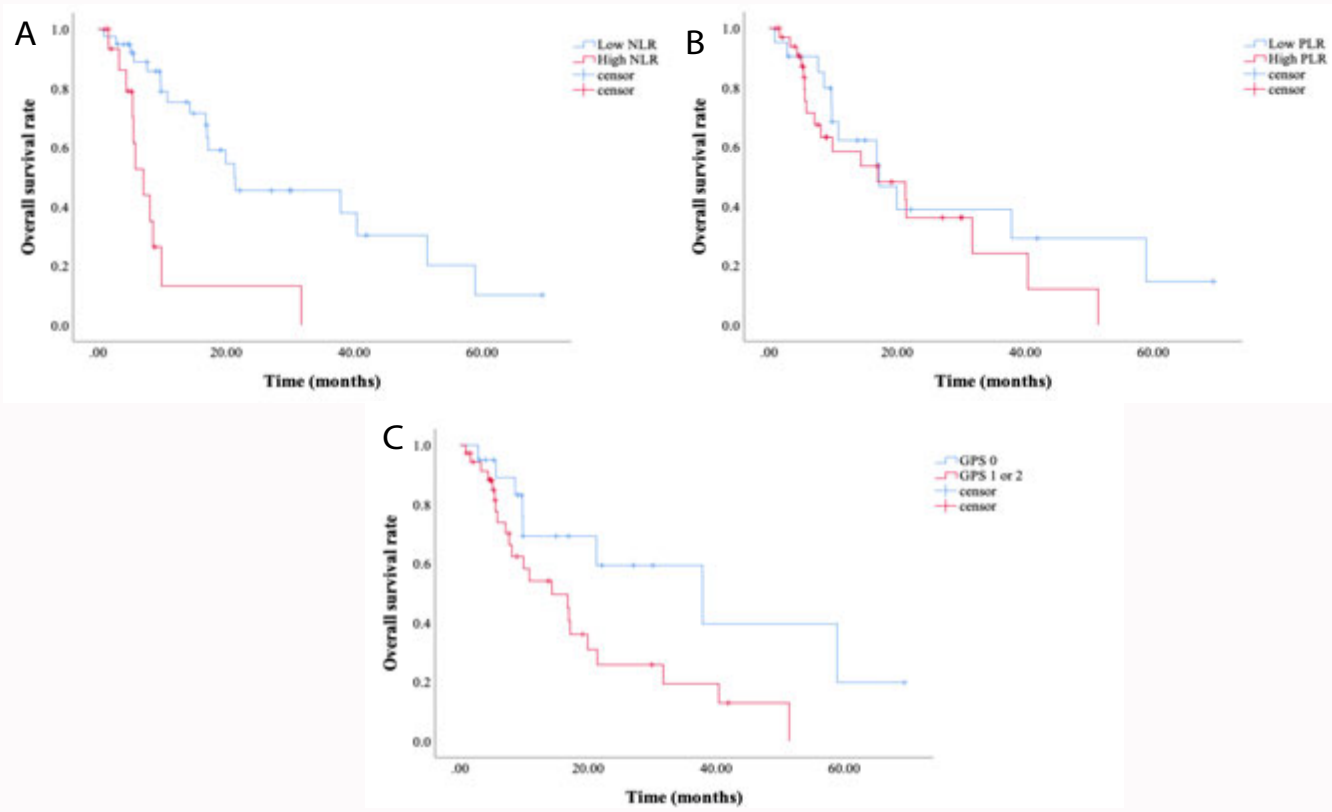

Figure 2: Kaplan Meier survival curves for overall survival according to inflammation-based scores in elderly group. A) Neutrophil-lymphocyte ratio; B) Platelet-lymphocyte ratio; C) Glasgow prognostic score. High-NLR and GPS 1/2 were significantly associated with poor OS (p<0001, p=0.034) in elderly group.

Table 3: Univariate and multivariate analyses of overall in elderly group.

Univariate				Multivariate	
Variable		**HR 95% CI**	**p-value**	**HR 95% CI**	**p-value**
Gender	male	1	0.854		
	female	1.08 (0.47-2.47)			
PS	0 or 1	1	0.003	2.22 (0.74-6.65)	0.153
	2	3.45 (1.53-7.80)			
Histological type	Intestinal type	1			
	Mixed/diffuse type	1.18 (0.65-2.16)	0.593		
Liver metastasis	no	1	0.912		
	yes	1.05 (0.48-2.26)			
Peritoneal seeding	no	1	0.286		
	yes	1.53 (0.7-3.36)			
Gastrectomy	no	1	0.433		
	yes	0.71 (0.3-1.68)			
PPI	no	1	0.053	2.02 (0.81-5.04)	0.131
	yes	2.25 (0.99-5.11)			
BMI	18.5 ≦, <25	1	0.277		
	18.5>, ≧ 25	0.65 (0.3-1.41)			
NLR	<4	1	<0.001	1	0.002
	>4	4.73 (2.08-10.78)		4.22 (1.69-10.56)	
PLR	<150	1	0.348		
	>150	1.44 (0.67-3.08)			
GPS	0, 1	1	0.028	1	0.327
	2	2.46 (1.04-5.79)		1.59 (0.63-4.01)	

CEA	≦ 5	1	0.16		
	>5	0.59 (0.28-1.24)			
CA19-9	≦ 37	1	0.949		
	>37	1.03 (0.47-2.25)			

Abbreviation: PS: Performance Status: OS: Overall Survival; BMI: Body Mass Index; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; GPS: Glasgow Prognostic Score

In brief, the results of the present study were obtained because the reliability of PS as a factor affecting prognosis in the elderly group decreased and that of NLR increased.

The present study had various limitations. First, as the data were collected from a single center, we could not entirely avoid selection bias associated with patients and chemotherapy regimens. Second, we could not completely exclude the possibility of complications such as subclinical infection that might have affected the prognostic values of biomarkers. This limitation might have strongly affected the results of the E group compared to the Y group because these patients had more complex comorbidities. The third and most significant limitation was the small number of patients investigated. Thus, validation will be required *via* prospective studies with a larger cohort. Additionally, the relatively small number of patients and events in our cohort did not allow for comprehensive multivariable analyses and precluded making definitive conclusions. However, the correlation of high NLR and poor prognosis in the E group was highly significant and seemed to be clinically meaningful.

Conclusion

In summary, our results suggest that the NLR is a useful prognostic factor that reflects not only the tumor immune environment but also the frailty of elderly patients with cancer. Contrastingly, the PS emerged as a useful marker for predicting survival in younger patients and may not be a significant prognostic factor in elderly patients because of its reduced reliability for this population, as suggested in previous reports. A poor PS was an independent marker of poor prognosis in the Y group, whereas high NLR was an independent marker of OS in the E group. Thus, NLR could specifically predict the OS of elderly patients with unresectable GC, offering a cost-effective prognostic biomarker. Further prospective studies with sufficient sample sizes are needed to validate our results.

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