ORIGINAL

Low prognostic nutrition index as a prognostic biomarker in elderly patients with early gastric cancer after gastrectomy

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Abstract : *Purpose* Non-invasive biomarkers including systemic inflammatory or nutrition-based index including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) lymphocyte to monocyte ratio (LMR), and prognostic nutritional index (PNI) can be useful in determining treatment strategies for elderly patients with early gastric cancer (EGC). The aim of this study was to investigate the significance of these index for predicting the long-term survival of EGC patients aged 80 years over. *Methods* This study included 80 elderly EGC patients with pStageIA after gastrectomy. Optimal cutoff value for PNI, NLR, PLR and LMR were set by using receiver operating curve analysis. The long-term outcomes after gastrectomy were analyzed by univariate and multivariate Cox regression analyses. *Results* Cut-off value for PNI, NLR, PLR and LMR was set at 46.5, 2.8, 210 and 4.6, respectively. By univariate analyses, low PNI, high NLR, high PLR and low LMR were significantly associated with worse prognosis. By multivariate analysis, low PNI was confirmed as an independent prognostic factor after gastrectomy (HR 0.17 ; 95% CI 0.03–0.91 ; P = 0.04). 5-year overall survival rate of patients with low PNI (≤ 46.5) were 52.4%. *Conclusion* Low PNI might be useful biomarker to predict worse prognosis of elderly EGC patients after gastrectomy. J. Med. Invest. 71 : 113-120, February, 2024

***Keywords* :** *early gastric cancer, prognostic nutrition index, elderly patients*

INTRODUCTION

The incidence of gastric cancer (GC) ranks sixth, and an estimated 1,089,103 new stomach cancer cases and 768,793 deaths occurred in 2020 worldwide (1). On the other hand, in Japan, life expectancy has now reached 80 years of age, and the population aged 80 and over accounts for approximately 9.9% in data from the Statistics Bureau of Japan (2). As a result, the number of elderly cancer patients aged 80 and over is also increasing. With regard to GC, 33% of GC patients in Japan were over 80 years old in 2011 (3).

In the 2011 annual report of the national clinical database of the gastric cancer registry, 43% of the 24,263 patients surgically treated in Japan were pStage IA (4). Accordingly, patients aged 80 and over with early GC (EGC) are considered to be increasing. However, it is unknown whether all elderly EGC patients should be treated because they can often be more likely to die from other illnesses or complications associated with old age than from GC itself. If elderly EGC patients who are not candidates for endoscopic resection undergo gastrectomy, the risk of postoperative physical deterioration might increase and even shorten their lifespan. Therefore, accurately identifying EGC patients who can benefit from surgery is crucial in selecting treatment strategies.

Increasing evidence has demonstrated that systemic inflammatory or nutrition-based biomarkers, including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and prognostic nutritional index (PNI), are associated with the prognosis of gastrointestinal cancers (5-9). We have also introduced PNI as a candidate for predicting overall survival in elderly GC patients who are 80 years old or older after curative gastrectomy in a previous report (10). In that study, a low PNI can be a comprehensive indicator of prognosis in elderly GC patients prior to surgery. However, many advanced GC patients were included in that study, and few studies focusing on biomarkers for EGC exist.

The aim of this study was to evaluate the prognostic significance of the NLR, PLR, LMR, and PNI in elderly EGC patients and identify a noninvasive biomarker for the prediction of long-term survival for those patients after gastric surgery.

METHODS

Patients

This study enrolled 82 patients who were aged 80 years old and older and underwent gastrectomy for primary GC diagnosed as pStage IA according to the 7th edition of the American Joint Committee on Cancer TNM classification system (11) in the Department of Surgery, Ogaki Municipal Hospital from January 2009 to April 2018. Among the 82 patients, one patient whose preoperative number of lymphocytes was unknown and one patient who died postoperatively were excluded. Then, a total of 80 elderly patients with pStage IA after gastric surgery were retrospectively evaluated in this study. Data on the patients' clinical characteristics as well as laboratory, treatment, and pathological data were collected from their medical records. The extents of gastrectomy and lymph node dissection were decided in accordance with the Japanese Gastric Cancer Treatment Guidelines (12). Informed consent was obtained from all patients, and this study was approved by the institutional review board of the Ogaki Municipal Hospital (No. 20181220-17).

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Definition of the cutoff value of the PNI, NLR, PLR and LMR

The preoperative PNI was calculated according to the following formula : 10 ×serum albumin (g/dl) + 0.005 x peripheral lymphocyte count (per mm^3) (13). NLR was calculated as the ratio of the total count of neutrophils divided by the total count of lymphocytes, PLR as the ratio of the total count of platelets divided by the total count of lymphocytes and LMR as the ratio of the total count of lymphocytes divided by the total count of monocytes.

To determine the optimal cutoff value of the preoperative PNI, NLR, PLR and LMR, we used a receiver operating characteristic (ROC) curve analysis for survival outcomes (Fig. 1). The area under the curve (AUC) values with 95% confidence interval (CI) of PNI, NLR, PLR and LMR were 0.757 (95% CI 0.642–0.872, p = 0.001), 0.694 (95% CI 0.550–0.839, p = 0.012), 0.634 (95% CI 0.481–0.788, p = 0.078) and 0.633 (95% CI 0.473–0.792, p = 0.088), respectively. Cutoff values were established so that the Youden index (sensitivity + specificity − 1) would be maximized using the ROC curve. Then, the cutoff value for preoperative PNI was set at 46.5, NLR at 2.8, PLR at 210 and LMR at 4.6.

Statistical analysis

The data were analyzed using SPSS II version 11.01 J (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the mean ± standard deviation and were compared between the two groups using Student's t test or the Mann–Whitney U test. Categorical data were compared using the Pearson chi-squared (χ^2) test. Cancer-specific survival (CSS) and overall survival (OS) were calculated using Kaplan–Meier analysis. Comparison of survival between the two groups was analyzed by the log-rank test. A multivariate analysis was performed with the Cox proportional hazards model. Variables with a P value less than 0.1 according to the univariate analyses were included in the multivariate analysis using the Cox proportional hazards model. A P value < 0.05 was considered significant in all analyses.

RESULTS

Patient characteristics

The clinical characteristics of the 80 patients are shown in Table 1. At the time of gastrectomy, the mean age of all patients was 83.0 years, and the cohort included 54 men and 26 women. The ASA-PS of 25 patients (31.3%) was 3. The mean BMI of all the patients was 22.2. Seventeen patients (21.3%) underwent laparoscopic surgery. Nineteen patients (23.8%) underwent total gastrectomy, and D2 lymph node dissection was performed in 37 patients (46.3%). Forty-one patients (51.3%) were diagnosed with pathological T1b. The mean operation time was 133.8 min, and the mean blood loss was 183.8 ml. Postoperative complications of grade II or higher in the Clavien–Dindo classification were observed in 13 patients (16.3%).

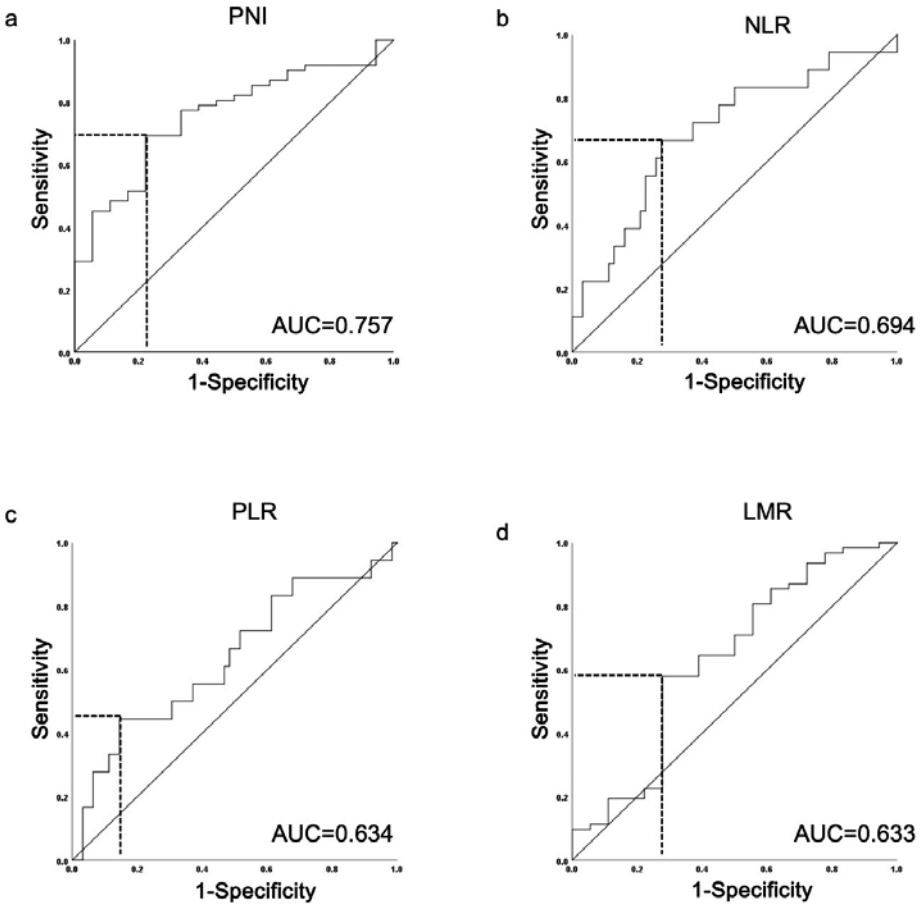

Fig 1. Receiver operating characteristic (ROC) curve for preoperative PNI, NLR, PLR and LMR and survival.

Table 1. Clinicopathological characteristics in 80 elderly gastric cancer patients with pStage IA after gastric surgery

	n = 80
Mean age, (SD), years old	83.0 ± 2.5
Gender, n (%)	
Male	54 (67.5)
Female	26 (32.5)
ASA-PS, n (%)	
1	15 (18.8)
2	40 (50.0)
3	25 (31.3)
Mean BMI $(kg/m)^2$	22.2 ± 3.2
Location of tumor, n (%)	
EGJ/U	21 (26.3)
M	35 (43.8)
L	24 (30.0)
Approach, n (%)	
Open	63 (78.8)
Laparoscopic	17 (21.3)
Operative procedure, n (%)	
Total	19 (23.8)
Proximal	7 (8.8)
Distral	54 (67.5)
Lymph node dissection, n (%)	
D1	29 (36.3)
D1+	14 (17.5)
D2	37 (46.3)
Pathological dofferentiation, n (%)	
Well	32 (40.0)
Moderate	32 (40.0)
Poor	13 (16.3)
Others	3 (3.8)
Depth of Tumor, n (%)	
T1a	39 (48.8)
T1b	41 (51.3)
Operation time (min)	133.8 ± 41.8
Blood loss (ml)	183.8 ± 248.4
Postoperative complication*, n (%)	
No	67 (83.8)
Yes	13 (16.3)

ASA-PS ASA physical status classification, *BMI* Body mass index, *Clavien-Dido classification ≥ grade II

Comparison of the clinicopathological characteristics between the patients with PNI≤46.5 and >46.5

Table 2 shows the comparison of the clinicopathological characteristics of the PNI≤46.5 (n=26) and PNI>46.5 (n=54) groups. The age, sex, ASA-PS and tumor location distributions were similar between the two groups. The mean BMI was significantly lower (P=0.04) in the low PNI group than in the high PNI group. In the low PNI group, the mean neutrophil count was significantly higher (P=0.04) than that in the high PNI group. On the other hand, the mean lymphocyte count and albumin level were significantly lower (P<0.01) in the low PNI group than in the high PNI group. As a result, the LMR was significantly lower (P<0.01) and the NLR and PLR were significantly higher (P<0.01) in the low PNI group than in the high PNI group.

Distributions of operative approach, operative procedure, lymph node dissection, depth of tumor and postoperative complications were not significantly different between the two groups. The mean operative time and blood loss were not significantly different between the two groups.

Comparison of follow-up data of the patients in the PNI≤46.5 and >46.5 groups

The median follow-up times of the low and high PNI groups were 49.5 (2.0-151.0) and 79.5 (27.0-155.0) months, respectively, and were significantly shorter in the low PNI group (P<0.01) than in the high PNI group (Table 3).

During the follow-ups, 9 patients (34.6%) in the low PNI group died due to noncancer-related diseases. 4 patients died due to pneumonia, 4 patients died due to cardiac disease, and one patient died due to liver cirrhosis. In contrast, 5 patients (9.3%) in the high PNI group died due to noncancer-related diseases. 2 patients died due to pneumonia, one patient died due to hematological disorder, one patient died due to trauma, and one patient died due to accidental death. In the low PNI group, more patients died due to noncancer-related disease (p=0.01).

Association of preoperative PNI, NLR, PLR, and LMR with OS

The overall survival rates according to PNI, NLR, PLR and LMR are shown in Fig. 2. The 5-year OS rates of the patients in the low PNI (≤ 46.5) and high PNI (> 46.5) groups were 52.4% and 87.2%, respectively (Fig. 2a). The 5-year OS rates in the high NLR group (> 2.8) and low NLR group (≤ 2.8) were 85.0% and 58.8%, respectively (Fig. 2b). The 5-year OS rates in the high PLR group (> 210) and low PLR group (≤ 210) were 82.1% and 55.0%, respectively (Fig. 2c). The 5-year OS rates of the patients in the low LMR (≤ 4.6) and high LMR (> 4.6) groups were 86.5% and 65.0%, respectively (Fig. 2d). Low PNI, high NLR, high PLR and low LMR were significantly associated with worse OS (p<0.01, p<0.01, p<0.01 and p=0.02, respectively).

Prognostic factors for postoperative survival after gastrectomy

The prognostic factors for postoperative survival after gastrectomy were assessed by univariate and multivariate analyses (Table 4). According to the univariate analysis, low PNI (P<0.01), high NLR (P<0.01), high PLR (P<0.01), and low LMR (P=0.02) were significant prognostic factors for worse OS. According to the multivariate analysis, only low PNI (HR 0.17 ; 95% CI 0.03–0.91 ; P=0.04) was confirmed as an independent prognostic factor for OS after gastrectomy.

DISCUSSION

In the present study, high NLR and PLR or low LMR and PNI were significantly associated with worse OS in elderly EGC patients who were 80 years old or older with pStage IA after gastrectomy. Furthermore, a low preoperative PNI (PNI ≤ 46.5) was an independent prognostic factor according to the multivariate analysis for those patients. The 5-year OS rate of the low PNI patients was only 52.4%, even though those patients were pStage IA. These results indicated that the preoperative PNI could be a biomarker to predict the long-term survival of elderly EGC patients after gastric surgery.

Table 2. Clinicopathological characteristics of 80 elderly gastric cancer patients with pStage IA after gastric surgery according to the PNI

	PNI ≤ 46.5 (n = 26)	PNI > 46.5 (n = 54)	P value
Mean age, (SD), years old	82.9 ± 2.1	83.1 ± 2.7	0.70
Gender, n (%)			0.34
Male	18 (69.2)	36 (66.7)	0.82
Female	8 (30.8)	18 (33.3)	
ASA-PS, n (%)			0.33
1, 2	16 (61.5)	39 (72.2)	
3	10 (38.5)	15 (27.8)	
Mean BMI $(kg/m)^2$	21.2 ± 2.8	22.8 ± 3.3	**0.04**
Location of tumor, n (%)			0.66
EGJ/U	6 (23.1)	15 (27.8)	
M	12 (46.2)	23 (42.6)	
L	8 (30.8)	16 (29.6)	
Neutrophil count (/μL)	4544.9 ± 2193.5	3561.5 ± 1264.3	**0.04**
Platelet count (×104/μL)	24.1 ± 10.4	20.7 ± 5.4	0.05
Lymphocyte count (/μL)	1176.8 ± 514.8	1631.9 ± 458.3	**<0.01**
Monocyte count (/μL)	343.1 ± 119.2	345.4 ± 152.5	0.94
Albumin (mg/dL)	3.6 ± 0.4	4.1 ± 0.3	**<0.01**
PNI	42.1 ± 3.3	50.2 ± 2.6	**<0.01**
NLR	4.6 ± 3.1	2.3 ± 1.0	**<0.01**
PLR	240.4 ± 132.2	134.0 ± 42.9	**<0.01**
LMR	3.8 ± 2.0	5.3 ± 1.9	**<0.01**
Approach, n (%)			0.33
Open	19 (73.1)	44 (81.5)	
Laparoscopic	7 (26.9)	10 (18.5)	
Operative procedure, n (%)			0.39
Total	7 (26.9)	12 (22.2)	
Proximal/Distal	19 (73.1)	42 (77.8)	
Lymph node dissection, n (%)			0.20
D1	12 (46.2)	17 (31.5)	
D1+/D2	14 (53.8)	37 (68.5)	
Depth of Tumor, n (%)			0.75
T1a	12 (46.2)	27 (50.0)	
T1b	14 (53.8)	27 (50.0)	
Operation time (min)	128.0 ± 41.7	136.6 ± 42.0	0.39
Blood loss (ml)	203.0 ± 302.7	174.5 ± 220.2	0.63
Postoperative complication, n (%)			0.19
No	19 (73.1)	46 (85.2)	
Yes	7 (26.9)	8 (14.8)	

ASA-PS ASA physical status classification, *BMI* Body mass index

Table 3. The follow-up data of 80 elderly gastric cancer patients with pStage IA after gastric surgery

	All patients (n = 80)	PNI ≤ 46.5 (n = 26)	PNI > 46.5 (n = 54)	*P* value
Follow-up time (month, median(range))	65.5 (2.0-155.0)	49.5 (2.0-151.0)	79.5 (27.0-155.0)	**<0.01**
Tumor recurrence	2 (2.5)	1 (3.8)	1 (1.9)	0.59
5-year mortarity				
All	18 (22.5)	12 (46.2)	6 (11.1)	**<0.01**
Gastric cancer	1 (1.3)	1 (3.8)	0 (0.0)	0.15
Other cancers	2 (2.5)	1 (3.8)	1 (1.9)	0.59
Non-cancer-related diseases	14 (17.5)	9 (34.6)	5 (9.3)	**0.01**
Pneumonia		4 (15.4)	2 (3.7)	
Cardiac disease		4 (15.4)	0 (0.0)	
Liver cirrhosis		1 (3.8)	0 (0.0)	
Hematological disorder		0 (0.0)	1 (1.9)	
Trauma		0 (0.0)	1 (1.9)	
Accidental death		0 (0.0)	1 (1.9)	
Unknown	1 (1.3)	1 (3.8)	0 (0.0)	0.15

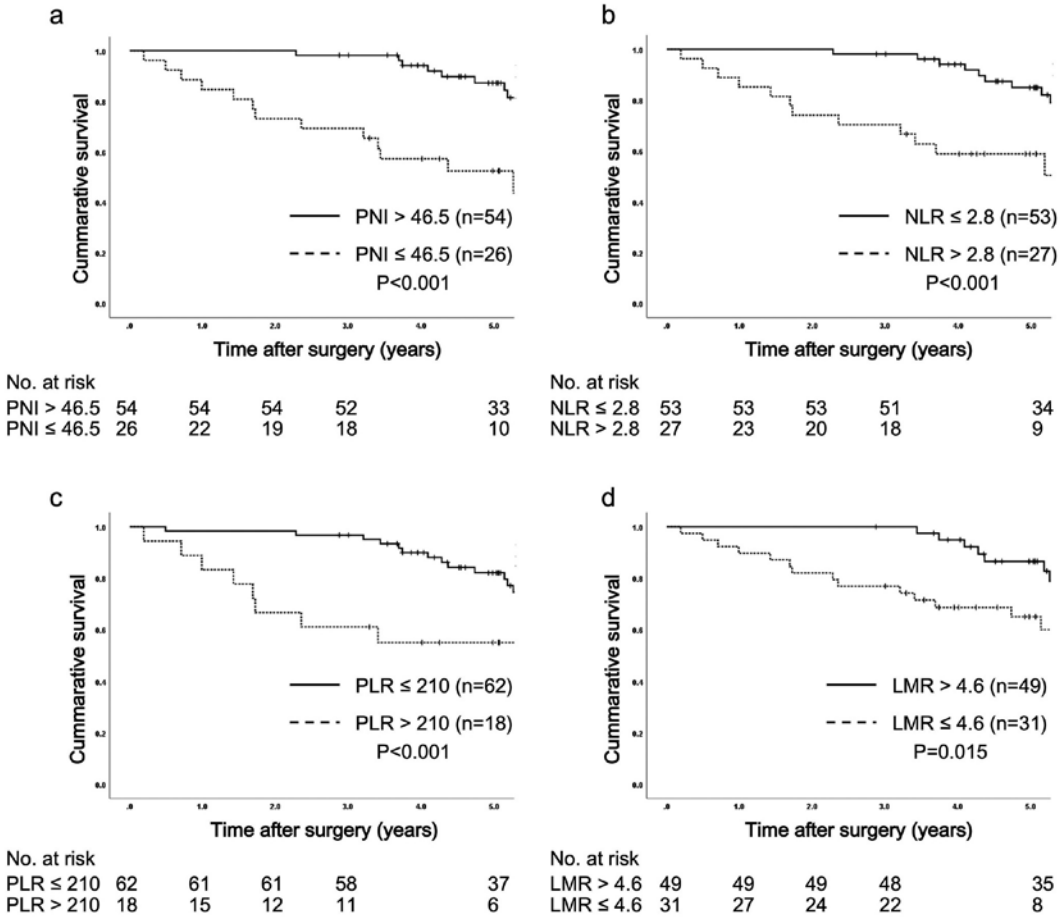

Fig 2. Kaplan-Meier overall survival curves stratified PNI, NLR, PLR and LMR

Table 4. Univariate and multivariate analyses in 80 elderly gastric cancer patients with pStage IA after gastric surgery

Variables	No. of patients	5-yr OS (%)	Univariate	Multivariate	
			P value	HR (95% CI)	*P* value
Gender			0.06	0.42 (0.12-1.51)	0.18
Male	54	69.8			
Female	26	88.5			
BMI (kg/m^2)			0.33		
<22	42	71.1			
≥22	38	81.0			
ASA-PS			0.05	3.01 (0.65-14.04)	0.16
0, 1	55	82.3			
3	25	62.4			
PNI			**<0.01**	0.17 (0.03-0.91)	**0.04**
≤46.5	26	52.4			
>46.5	54	87.2			
NLR			**<0.01**	2.01 (0.39-11.21)	0.39
≤2.8	53	85.0			
>2.8	27	58.8			
PLR			**<0.01**	1.87 (0.25-14.33)	0.55
≤210	62	82.1			
>210	18	55.0			
LMR			**0.02**	0.47 (0.09-2.41)	0.36
≤4.6	39	65.0			
>4.6	41	86.5			
Location of tumor			0.54		
EGJ, U	21	75.1			
M, L	59	76.3			
Operative procedure			0.44		
Proxmal, Distal	61	77.4			
Total	19	71.1			
Lymph node dissection			0.18		
D1	29	68.5			
D1+, D2	51	79.9			
Depth of Tumor			0.78		
T1a	39	71.3			
T1b	41	80.5			
Pathological differentiation			0.22		
Poor	13	92.3			
Others	67	72.7			
Operation time (min)					
<120	34	71.2			
≥120	46	79.6			
Blood loss (ml)			0.99		
<200	57	78.9			
≥200	23	69.6			
Postoperative complication*			0.63		
No	67	77.3			
Yes	13	69.2			

According to the surgical case report of the Japan Gastric Cancer Association National Registration in 2013, the 5-year survival rate after surgery for GC was 89.7% in pStage IA (14). However, postoperative complications have been reported to be more frequent in elderly patients, with the frequency of the most serious surgical-related deaths and early postoperative deaths being even higher (15). In contrast, it has been reported that the progression time from EGC to advanced GC was approximately 34 months, and the 5-year survival rates of untreated EGC patients with cStage I were 46.2% (16). This was almost the same as the 52.4% 5-year OS rate of elderly EGC patients with a low PNI after gastrectomy in this study. Preoperative low PNI was associated with a significant risk of death due to other diseases. These results indicated that EGC patients with a low PNI may not have an improved prognosis after gastric surgery. On the other hand, patients with high PNI may have had their lifespan extended by undergoing surgery.

For elderly EGC patients who are not candidates for curative endoscopic resection (ER), gastrectomy is usually recommended. In the Japanese gastric cancer treatment guidelines 2021, indications for ER are classified into three categories, absolute, expanded, and relative indications, depending on the risk of lymph node metastasis (12). Kishida *et al*. revealed that ER may have acceptable long-term efficacy comparable to surgery in elderly patients (≥75 years) with a relative ER of EGC. Factors associated with OS were age and PNI in males (age ≥79) and age in females (age ≥82). Treatment was not a prognostic factor in that study (17). In this study, 41 patients (51.3%) had pT1b, and these patients could be candidates for relative ER. If elderly EGC patients with a low PNI and submucosal invasion hope to undergo any therapy, the relative ER might be considered as an optional treatment. Although it may take courage for surgeons or gastroenterologists to recommend not performing any therapies, observation could also be another suggestion for elderly EGC patients with a low PNI.

In this study, only 17 patients (21.2%) underwent laparoscopic surgery. In meta-analyses, laparoscopic gastrectomy has been reported to be a feasible and safe approach for EGC patients compared with open gastrectomy (18, 19). Laparoscopic gastrectomy enables less blood loss, faster postoperative recovery, and reduced postoperative morbidity. Also, regarding to survival benefit, Ito *et al*. reported that laparoscopic gastrectomy had greater survival benefits compared with open gastrectomy in frail patients with high NLR (20). Therefore, if more EGC patients underwent laparoscopic surgery, there is a possibility that OS of EGC patients with low PNI is improved.

OS was significantly different using all four markers : PNI, NLR, PLR, and LMR. However, by multivariate analysis, only low PNI was as an independent prognostic factor for OS in this study. AUC value of PNI was 0.757 (95% CI 0.642–0.872, $p = 0.001$). On the other hand, AUC values of NLR, PLR and LMR were less than 0.7. These results indicated that PNI was considered to be a better marker compared with the other three markers. Therefore, also by multivariate analysis, only low PNI might be confirmed as an independent biomarker for OS.

The limitation of this study is that it is a retrospective study from a single institute without any verifications. The indication for surgery was not definite. However, this is the first study to describe the prognostic impact for EGC patients who were 80 years old or older after gastrectomy. Further retrospective and prospective studies are needed.

In conclusion, a low PNI (PNI ≤ 46.5) is a worse prognostic factor after gastrectomy for EGC patients who are 80 years old or older. Low PNI might be a useful biomarker to predict the worse prognosis of elderly EGC patients after gastrectomy.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest Statement

TT, YK, AM, YT, HA, TH and KS declare no conflict of interest.

Ethical Review Board

This study has been approved by the Institutional ethic committee of the Ogaki Municipal Hospital (No. 20181220-17), and was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants and/or animals

This study does not contain any studies with animals performed by any of the authors.

Informed consent

An informed consent was obtained from each patient involved in this study.

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AUTHORSHIP CONTRIBUTION STATEMENT

All authors contributed to the study conception and design.
Takamasa Takahashi : Conceptualization ; Data curation ; Formal analysis ; Investigation ; Supervision ; Writing - original draft.
Yuji Kaneoka : Writing - review & editing.
Atsuyuki Maeda : Writing - review & editing.
Yuichi Takayama : Writing - review & editing.
Hiroki Aoyama : Writing - review & editing.
Takahiro Hosoi : Writing - review & editing.
Kazuaki Seita : Writing – review & editing.

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