


ORIGINAL ARTICLE

New index combining multiple inflammation-based prognostic scores for predicting the prognosis of gastric cancer patients

Kensuke Kudou,  Tetsuya Kusumoto, Sho Nambara, Yasuo Tsuda, Eiji Kusumoto, Rintaro Yoshida, Yoshihisa Sakaguchi and Koji Ikejiri

Department of Gastroenterological Surgery, Clinical Research Institute Cancer Research Division, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

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Correspondence

Kensuke Kudou, Department of Gastroenterological Surgery, Clinical Research Institute Cancer Research Division, National Hospital Organization Kyushu Medical Center, 1-8-1, Jigyohama, Chuo-ku, Fukuoka 810-8563, Japan.

Email: k.k.vermillion0920@gmail.com

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Abstract

Background and Aim: Several inflammation-based scores have prognostic value for patients diagnosed with various cancers. However, using only a single inflammation-based prognostic score may be unreliable, as the cut-off values and relative usefulness among various inflammation-based prognostic scores vary. We established a new combined index of four inflammation-based prognostic scores, namely the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, prognostic index, and prognostic nutritional index, and assessed its usefulness to predict the prognosis of gastric cancer.

Methods and Results: We reviewed the data of 635 patients who underwent surgical resection for gastric cancer. We calculated the combined index as the total value of each of the four included inflammation-based prognostic scores and analyzed the relationship between the combined index and postoperative prognosis of gastric cancer. The new combined index was represented as a value between 0 and 6 in each patient. The Kaplan–Meier survival curves showed that patients whose combined index was 0 had good long-term outcomes, while the prognosis of patients whose combined index ranged from 4 to 6 was poor.

Conclusion: This new combined index was strongly associated with poor prognosis in patients who underwent surgery for gastric cancer. It is inferred that it can predict patient prognosis after surgical resection for gastric cancer with a stronger correlation and clearer stratification than a single inflammation-based prognostic score.

Introduction

Gastric cancer is the fifth most common malignant disease and the third leading cause of cancer-related deaths worldwide.¹ An estimated 12.7 million new cancer cases and 7.6 million deaths due to gastric cancer occur yearly.² The treatment choice for gastric cancer depends on the degree of tumor progression and the patient's general condition. The tumor–node–metastasis (TNM) classification evaluates the clinical prognosis in gastric cancers by assessing the tumor depth, extent of lymph node metastasis, and distant metastasis.³ However, the actual prognosis of patients with the same TNM stage differs, suggesting the influence of other factors. Factors such as malnutrition, skeletal muscle loss, and systemic inflammatory response have been associated with poor outcomes in patients with various cancers.^{4–9}

Inflammatory cytokines and tumor-associated inflammatory cells contribute to tumor angiogenesis, invasion, and metastasis, which worsen patient prognosis.^{10,11} The blockade of inflammatory cytokines and chemokines inhibits the progression of various tumors, further proving the importance of these mediators in cancer.¹² Based on this relationship between cancer progression and inflammation, inflammation-based prognostic scores (IBPSs), including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), prognostic index (PI), and prognostic nutritional index (PNI), have been reported to have a prognostic value in malignant solid tumors.^{8,9,13–18} These scores use biomarkers that can be easily evaluated from peripheral venous blood. However, their cut-off values vary among reports. Several studies have compared the validity of multiple IBPSs to predict the prognosis of gastrointestinal malignancies.^{19–22} Toyokawa *et al.*¹⁹ evaluated the prognostic value of six IBPSs in patients with Stage II gastric cancer, suggesting that the C-reactive protein (CRP)/albumin ratio and the PNI score were independent prognostic factors that are superior to other biomarkers. Another study compared five IBPSs in patients with esophageal and gastric carcinomas and concluded that PLR and PNI scores were significant predictors of patient survival.²⁰ An additional study showed that the Glasgow Prognostic Score (GPS) is a robust predictor of gastric cancer survival in patients who underwent tumor resection.²¹ We previously compared seven IBPSs and found GPS, PI score, and PNI score were independent prognostic factors in patients with upper gastric cancer.²² Many reports support PNI as a more useful marker than other IBPSs. However, this remains controversial.

Therefore, using only one IBPS may be unreliable because its cut-off value and relative importance of usefulness among various IBPSs are not fixed. We hypothesized that patients with a majority of poor IBPSs tended to have worse prognoses than those with only one or two poor IBPSs. In this study, we created a new index that combines the values of multiple IBPSs, and verified its effectiveness by analyzing data from patients who underwent surgical resection for gastric cancer.

Methods

Patients. In this retrospective cohort study, we reviewed data from 801 patients diagnosed with gastric cancer who underwent surgical resection at the Department of Gastroenterological Surgery, National Kyushu Medical Center, from January 2010 to

March 2019. All patients were diagnosed with adenocarcinoma. We excluded patients who underwent palliative or non-curative surgery ($n = 48$) and whose clinical data comprised incomplete factors required for the calculation of IBPSs and information related to prognosis ($n = 118$). Ultimately, 635 patients who underwent curative surgery for gastric cancer and whose IBPSs such as NLR, PLR, PI, and PNI could be calculated accurately were eligible for analysis.

This study was approved by the Institutional Review Board of the National Kyushu Medical Center (19C066). All patients provided informed written consent prior to inclusion.

Inflammation-based prognostic scores. The NLR, PLR, PI, and PNI values were calculated. Patient baseline laboratory data were obtained by sampling peripheral venous blood within 1 week before surgery. NLR and PLR were defined as absolute neutrophil and platelet counts, respectively, divided by the absolute lymphocyte count.^{15,17} PI score calculation was based on the CRP level and white blood cell count. The upper limits of reference ranges for CRP level (0.1 mg/dL) and white blood cell count ($11\,000/\text{mm}^3$) were used as cut-off values.^{13,22} PI was 0 if both values were below the cut-offs, 1 if either value was elevated, and 2 if both were above the cut-offs. PNI was calculated using the following formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$.¹⁶

Combined index. The NLR, PLR, PI, and PNI values were used for calculating the new combined index. Each factor was scored according to the cut-off values. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cut-off values of NLR and PLR. The PI value was obtained from the original score. Based on previous reports, the tendency of a cut-off value of the PNI was investigated. Although the cut-off values differed from one study to another, to the best of our knowledge, 40 and 45 were generally used as the cut-off values of PNI.^{16,22–24} We classified a score in each IBPS based on the hazard ratio calculated in multivariate analyses.

Statistical analyses. Differences in characteristics between groups were evaluated using Fisher's exact test or an unpaired *t*-test. Kaplan–Meier survival curves were plotted, and differences were analyzed using the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazard model to identify independent prognostic factors. All *P*-values were two-sided, and $P < 0.05$ was considered to be statistically significant. ROC curve analysis was used to determine the predictive value of the NLR and PLR. All analyses were performed using JMP PRO 11 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. The clinicopathological characteristics of the 635 patients (417 [65.7%] men and 218 [34.3%] women) are summarized in Table 1. The mean patient age was 68.5 (range 30–97) years. Regarding TNM classification, 401 (63.2%), 112 (17.6%), and 122 (19.2%) patients had Stage I, II, and III disease, respectively. Distal, total, and proximal gastrectomy (PG) were performed in 410 (64.6%), 182 (28.7%), and 43 (6.8%) patients, respectively. Pathological features such as

Table 1 Characteristics of patients with gastric cancer

Characteristic	No. of patients <i>n</i> (%)
Sex	
Male	417 (65.7)
Female	218 (34.3)
Age	68.5 (30-97)
Tumor location	
EGJ	13 (2.0)
U	124 (19.5)
M	241 (38.0)
L	257 (40.5)
Macroscopic type	
0-I	16 (2.5)
0-IIa	69 (10.9)
0-IIb	6 (0.9)
0-IIc	293 (46.1)
0-III	2 (0.3)
1	9 (1.4)
2	102 (16.1)
3	88 (13.9)
4	17 (2.7)
5	33 (5.2)
Dissection of lymph nodes	
D1	95 (15.1)
D1+	288 (45.6)
D2	248 (39.3)
Pathological feature	
tub1	159 (25.0)
tub2	167 (26.3)
por1	73 (11.5)
por2	160 (25.2)
sig	51 (8.0)
muc	15 (2.4)
pap	7 (1.1)
others	3 (0.5)
Stage	
I	401 (63.2)
II	112 (17.6)
III	122 (19.2)
Surgical procedure	
DG	410 (64.6)
TG	182 (28.7)
PG	43 (6.8)
Surgical approach	
Open	254 (40.0)
Laparoscopic	381 (60.0)
Adjuvant chemotherapy	
No	475 (74.8)
Yes	160 (25.2)
NLR	
<2.75	431 (67.9)
≥2.75	204 (32.1)
PLR	
<178	413 (65.0)
≥178	222 (35.0)
PI	
0	579 (91.2)
1	52 (8.2)
2	4 (0.6)

(Continues)

Table 1 (Continued)

Characteristic	No. of patients <i>n</i> (%)
PNI	
≥45	469 (73.9)
40 ≤ PNI < 45	100 (15.7)
<40	66 (10.4)
Recurrence	
No	547 (86.1)
Yes	88 (13.9)
Prognosis	
Survival	447 (70.4)
Death	188 (29.6)

Data are presented as *n* (%) with the exception of age, which is presented as mean (range).

DG, distal gastrectomy; EGJ, esophagogastric junction; NLR, neutrophil/lymphocyte ratio; PG, proximal gastrectomy; PI, prognostic index; PLR, platelet/lymphocyte ratio; PNI, prognostic nutritional index; TG, total gastrectomy.

tumor location, tumor macroscopic features, and histological type are also summarized in Table 1. The overall survival (OS) rate in all patients was 70.4%, and the recurrence rate was 13.9%. NLR, PLR, PI, and PNI scores were calculated based on laboratory data, which were obtained by sampling peripheral venous blood. ROC curve analysis was performed to identify the optimal cut-off values of the NLR and PLR related to OS. The optimal cut-off values of the NLR and PLR were identified as 2.75 and 178. The area under the curve (AUC) was 0.60166 and 0.60570, respectively (Fig. S1, Supporting information). The number of patients according to the cut-off values of the NLR, PLR, PI, and PNI is shown in Table 1.

Prognostic factors for OS. To evaluate the relationship between gastric cancer prognosis and each variable, univariate and multivariate analyses with a Cox proportional hazard model were performed. Univariate analyses revealed sex, age, surgical procedure (total gastrectomy [TG] vs distal gastrectomy [DG] or proximal gastrectomy [PG]), surgical approach (open vs laparoscopic), TNM stage (Stage II–III vs Stage I), and individual NLR, PLR, PI, and PNI scores that were associated with poor OS in patients with gastric cancer (Table 2). Multivariate analyses revealed that male sex ($P = 0.0026$), age ≥65 years ($P < 0.0001$), Stage II–III ($P < 0.0001$), and PNI score <40 ($P = 0.0021$) were independent poor prognostic factors of OS in patients with gastric cancer (Table 2).

Postoperative prognosis based on the combined index. In defining the combined index, correlation coefficients in each pair of NLR, PLR, PI, and PNI were estimated (Fig. S2, Supporting information). Based on the hazard ratio calculated in multivariate analyses, a score in each IBPS was assigned as shown in Table 3. Finally, the combined index was calculated for each patient as the sum of all IBPSs, ranging from 0 to 6. Kaplan–Meier curves were plotted for each score of the combined index (Fig. 1a) and showed three tendencies. Patients whose combined index was 0 had good long-term outcomes,

Table 2 Univariate and multivariate analyses for overall survival

Factor	Univariate analysis		Multivariate analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Male (vs female)	1.683 (1.223-2.355)	0.0012	1.648 (1.187-2.327)	0.0026
Age ≥65 years (vs <65 years)	2.593 (1.834-3.761)	<0.0001	2.214 (1.544-3.248)	<0.0001
TG (vs DG or PG)	1.785 (1.329-2.387)	0.0001	1.218 (0.892-1.655)	0.2132
Open (vs laparoscopic)	1.737 (1.291-2.352)	0.0003	1.168 (0.846-1.619)	0.3465
Stage II-III (vs Stage I)	3.493 (2.601-4.724)	<0.0001	2.549 (1.854-3.525)	<0.0001
NLR ≥ 2.75 (vs <2.75)	2.359 (1.763-3.151)	<0.0001	1.271 (0.875-1.838)	0.2070
PLR ≥ 178 (vs <178)	1.795 (1.342-2.395)	<0.0001	1.054 (0.743-1.489)	0.7669
PI (ref: 0)				
1	2.240 (1.446-3.331)	0.0006	1.208 (0.749-1.885)	0.4285
2	10.27 (2.524-27.31)	0.0036	1.953 (0.456-5.745)	0.3229
PNI (ref: ≥45)				
40 ≤ PNI < 45	1.933 (1.324-2.766)	0.0009	1.236 (0.823-1.823)	0.3008
<40	4.619 (3.179-6.585)	<0.0001	2.079 (1.312-3.243)	0.0021

CI, confidence interval; DG, distal gastrectomy; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; PG, proximal gastrectomy; PI, prognostic index; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; ref, reference; TG, total gastrectomy.

while those with a combined index between 4 and 6 had poor prognosis. The prognosis of patients whose combined index ranged from 1 to 3 was better than that of patients with a higher combined index, but the long-term OS rates were poor, especially over 5 years (Fig. 1a). Patients were subsequently categorized into the following three groups according to the combined index: low OS, score 0; medium OS, score 1–3; high OS, score 4–6. Kaplan–Meier survival curves for the OS between the three groups are shown in Figure 1b. Five-year OS rates in the low, medium, and high groups were 82.0, 67.6, and 29.6%, respectively ($P < 0.0001$).

Subgroup analyses, classifying the disease into early stage (Stage I) and advanced stage (Stage II and III), were also performed. Kaplan–Meier survival curves for OS according to the

combined index in patients with early or advanced stages are shown in Figure 2. Five-year OS rates of patients with early-stage disease in the low, medium, and high groups were 90.2, 80.9, and 39.3% ($P < 0.0001$) and those of patients with advanced-stage disease were 57.4, 52.2, and 25.5%, all in respective order ($P < 0.0001$). The five-year OS rate of patients with Stage I disease in the medium group was relatively good. However, the 8-year OS was poorer than that of the low group (50.5 vs 78.7%, $P = 0.0017$) (Fig. S3, Supporting information).

Postoperative survival based on the combined index after categorization by surgical procedure was also analyzed. Patients were categorized into two groups: those who underwent DG or PG, and those who underwent TG. Kaplan–Meier survival curves showed 5-year OS rates of patients who underwent DG or PG in the low, medium, and high groups to be 85.5, 74.6, and 27.2% ($P < 0.0001$) and those of patients who underwent TG to be 73.0, 52.9, and 32.3%, respectively ($P = 0.0001$) (Fig. 3).

Discussion

We created a new index combining four IBPSs (i.e. NLR, PLR, PI, and PNI) and verified its effectiveness by analyzing data from patients who underwent surgical resection for gastric cancer. A higher value of the combined index was strongly associated with poor prognosis in patients with gastric cancer, so this combined index can predict long-term outcomes of gastric cancer after surgery.

Factors included in this combined index are neutrophil count, lymphocyte count, platelet count, CRP level, and serum albumin level. Neutrophil count and CRP level usually increase during systemic inflammation, which may occur as a result of tumor progression. Serum albumin level is an indicator of nutritional status. Hypoalbuminemia may occur because of the systemic inflammatory response and reflects malnutrition or cachexia due to tumor progression.²⁰ The significance of lymphocytes in antitumor immunity is evident from lymphopenia, a state of immunosuppression, promoting cancer progression.^{25,26}

Table 3 Calculation of the combined index

Factor	Score
NLR	
<2.75	0
≥2.75	1
PLR	
<178	0
≥178	1
PI	
CRP ≤1.0 mg/dL and WBC ≤11 000/mm ³	0
CRP >1.0 mg/dL or WBC >11 000/mm ³	1
CRP >1.0 mg/dL and WBC >11 000/mm ³	2
PNI	
≥45	0
40 ≤ PNI < 45	1
<40	2
Combined index	
=total value of each score of five IBPSs	0–6

CRP, C-reactive protein; IBPS, inflammation-based prognostic score; NLR, neutrophil/lymphocyte ratio; PI, prognostic index; PLR, platelet/lymphocyte ratio; PNI, prognostic nutritional index; WBC, white blood cell count; .

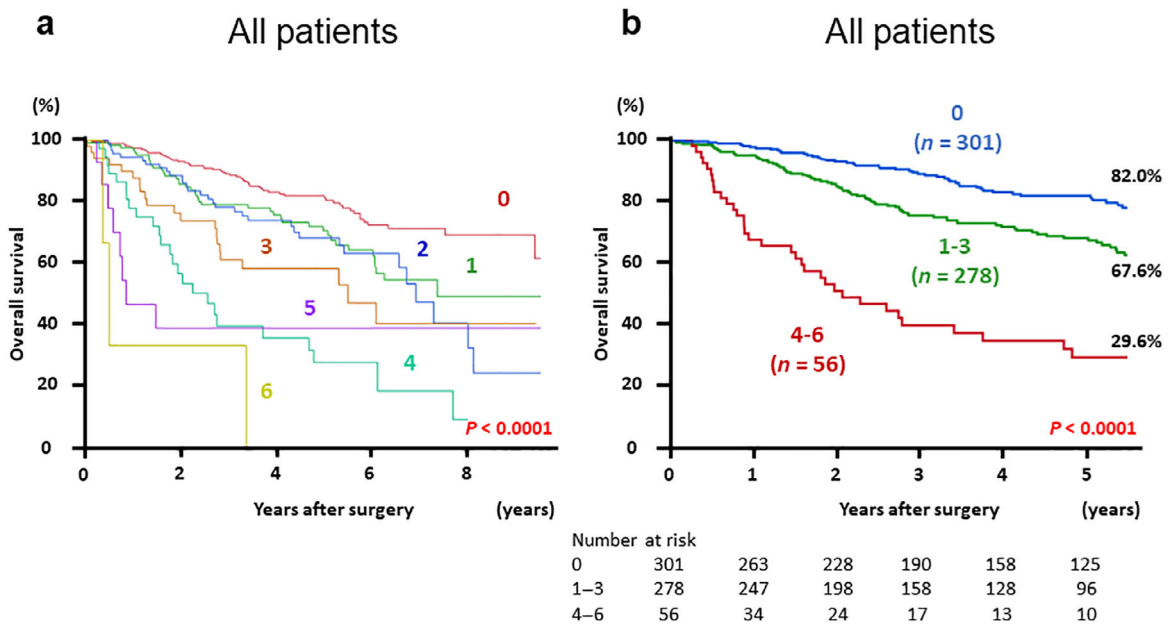


Figure 1 (a) Kaplan–Meier survival curves for overall survival (OS) in patients with gastric cancer based on each score of the combined index of inflammation-based prognostic scores. (b) Kaplan–Meier survival curves for OS by dividing patients into three groups according to the value of combined index: Low (score 0), medium (score 1–3), and high (score 4–6).

Platelets contribute to tumor growth, angiogenesis, and tumoral neovascularization by secreting platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor-beta

in the tumor microenvironment.^{27,28} These mechanisms explain why these biomarkers can be indicators of cancer prognosis. The combined index covers more indicators than a single IBPS.

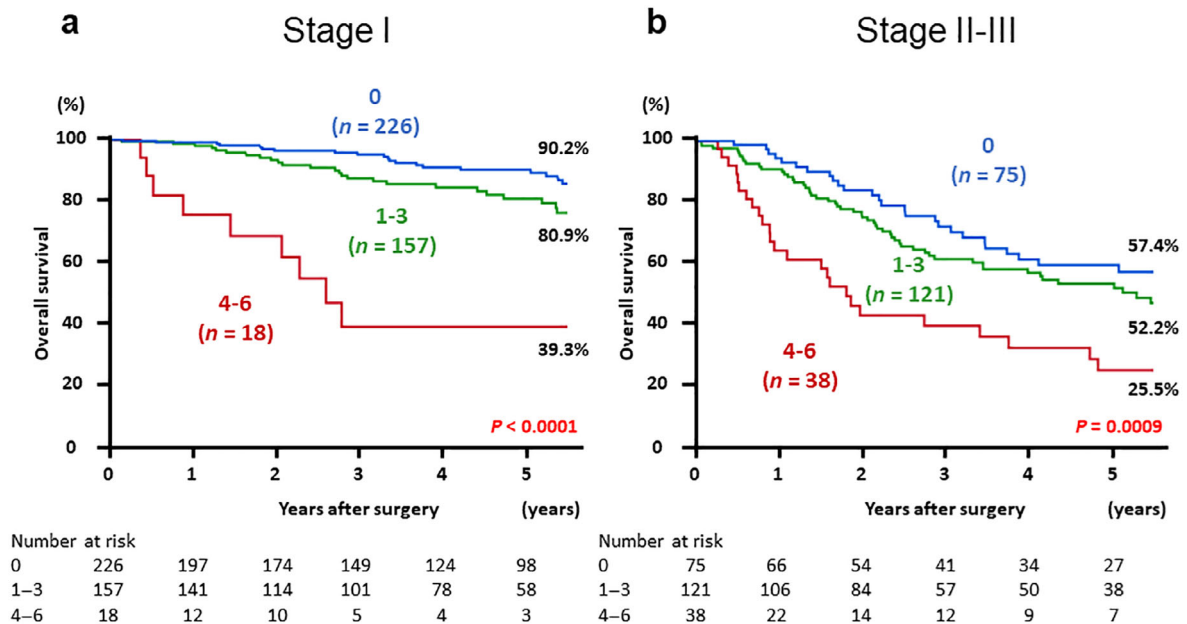


Figure 2 Postoperative overall survival in patients with gastric cancer based on the three groups according to the value of combined index: low (score 0), medium (score 1–3), and high (score 4–6). The Kaplan–Meier method was performed separately by the tumor-node-metastasis stage. (a) Patients diagnosed with Stage I, and (b) patients diagnosed with Stages II and III.

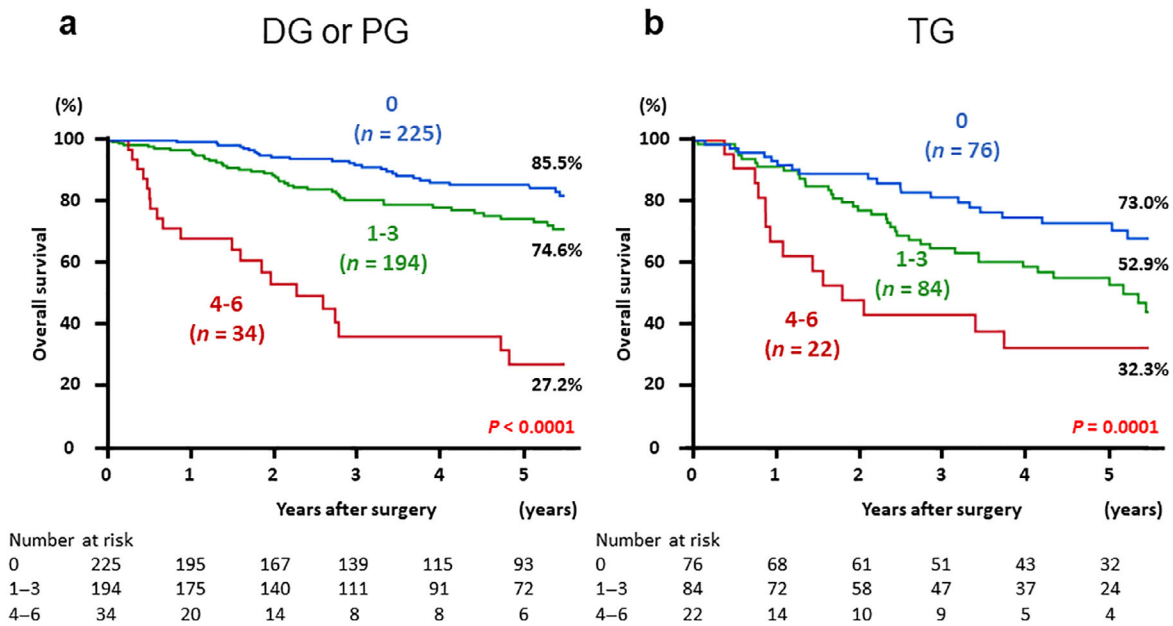


Figure 3 Postoperative overall survival in patients with gastric cancer based on the three groups according to the value of combined index: low (score 0), medium (score 1–3), and high (score 4–6). The Kaplan–Meier method was performed separately by surgical procedure. (a) Patients who underwent distal gastrectomy or proximal gastrectomy, and (b) patients who underwent total gastrectomy. DG, distal gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy.

Previous reports and our study indicate that even a single IBPS can be correlated with the prognosis of various solid tumors, including gastric cancer. However, setting a cut-off value for each IBPS can lead to the contradiction of the prognostic value of one IBPS being poor but that of another IBPS being good in some patients. The cut-off values of IBPSs also differ among studies. To reduce these discrepancies, we created a more reliable stratification by combining scores of four IBPSs. We categorized patients into three groups according to the combined index value: low (score 0), medium (score 1–3), and high (score 4–6). Kaplan–Meier survival curves for OS showed that the prognosis of patients in the low-score group was good, while that of patients in the high-score group was remarkably poor. Regarding patients in the medium-score group, the 5-year OS rates were better than those of patients in the high-score group, especially for Stage I disease, but poorer than those of patients in the low-score group according to the follow-up survey. These results suggest that the combined index may be correlated with long-term survival, even when gastric cancer is cured. Also, these patients’ classification according to the combined index may be useful in considering the indications for surgery and predicting the postoperative prognosis of patients with gastric cancer. In particular, patients in the medium-score group should undergo radical surgery for gastric cancer because they can be expected to have long-term survival beyond 5 years. However, indications for surgery in patients in the low-score group may be considered more carefully because the 5-year OS rates were very poor even though curative surgery was accomplished.

Subgroup analyses based on surgical procedures showed a higher combined index, which was significantly correlated with poor prognosis in the DG or PG group. Generally, TG is a more invasive surgery than DG or PG. It is unclear why the prognosis of patients with high combined index values was poor, especially in the DG or PG group. However, we speculate that some patients who need TG as standard surgery might undergo DG or PG because of their poor general condition.

A few studies have investigated the prognostic significance of the combination of multiple IBPSs or other biomarkers. Guo *et al.* showed that the combination of CRP and NLR could function as an independent prognostic factor in gastric cancer and provide a more accurate prediction than NLR or CRP alone.²⁹ Sun *et al.* reported that preoperative NLR and PLR could predict survival in patients with Stage I–II gastric cancer.³⁰ However, to the best of our knowledge and as evidenced by literature review, no reports discussing a combination of four IBPSs to predict gastric cancer prognosis exist. Our combined index may be useful because it can categorize patients into good and poor prognosis groups based on one cut-off value and it can be stratified by a score from 0 to 6.

This study has some limitations. First, it is limited in that it was a retrospective, single-institution study. However, the accumulation of findings from retrospective studies could be valuable. Moreover, this study may play an important role in proposing a new combined index and presenting its effectiveness. Second, our combined index includes NLR, PLR, and PNI scores, which have common components such as lymphocytes. Thus, we calculated correlation coefficients in each pair of NLR,

PLR, PI, and PNI. As a result, all four IBPSs were not correlated with each other (Fig. S2). Based on these analyses, we included four IBPSs in the combined index. Our new combined index, through its clear stratification, can express the degree of poor prognosis more reliably than a single IBPS. There may still be room for improvement in the reliability of this combined index, but we sought both the strength of correlation with prognosis and simplicity of calculation, and as a result, established such an index.

The new combined index was strongly associated with poor prognosis in patients who underwent surgery for gastric cancer. It is inferred that it can predict prognosis after surgical resection for gastric cancer with a strong correlation and clearer stratification than a single IBPS.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Comparison of the predictive ability of the NLR and PLR by receiver operating characteristic (ROC) curve analyses. AUC, area under the curve; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Figure S2. Analyses of correlation coefficients in each pair of NLR, PLR, PI, and PNI. NLR, neutrophil/lymphocyte ratio;

PLR, platelet/lymphocyte ratio; PI, prognostic index; PNI, prognostic nutritional index.

Figure S3. Postoperative overall survival in patients who were diagnosed with Stage I gastric cancer based on the three groups according to the value of combined index: low (score 0) and medium (score 1–3). This figure is related to Figure 2 but specifically indicates long-term survival curves of 5 years or longer. OS, overall survival.