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Comparison of Inflammation-Based Prognostic Scores Associated with the Prognostic Impact of Adenocarcinoma of Esophagogastric Junction and Upper Gastric Cancer

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ABSTRACT

Background. Several inflammation-based prognostic scores have a prognostic value in patients with various cancers. This study investigated the prognostic value of various inflammation-based prognostic scores in patients who underwent a surgery for adenocarcinoma of the esophagogastric junction (AEG) and upper gastric cancer (UGC).

Methods. We reviewed data of 206 patients who underwent surgery for AEG and UGC. We calculated neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), Glasgow Prognostic Score (GPS), modified GPS (mGPS), C-reactive protein (CRP)/albumin (Alb) ratio, prognostic index (PI), and prognostic nutritional index (PNI) and analyzed the relationship between these biomarkers and postoperative prognosis.

Results. In multivariate analyses for overall survival, mGPS ($P = 0.0337$, hazard ratio [HR] = 5.211), PI ($P = 0.0002$, HR = 21.20), and PNI ($P < 0.0001$, HR = 6.907) were identified as independent predictive factors. A multivariate analysis for recurrence-free survival showed that only PI ($P = 0.0006$, HR = 11.89) and PNI ($P = 0.0002$, HR = 4.972) were independent predictive factors among the above-mentioned inflammation-based prognostic scores.

Conclusions. In various inflammation-based prognostic scores, PI and PNI were more strongly associated with poor prognosis in patients who underwent surgery for AEG and UGC.

Morbidity and mortality rates of cancers are increasing globally. Gastric cancer is the fifth most common malignant disease and the third leading cause of cancer-related deaths in the world.[1] The treatment options for gastric cancer usually consist of surgical therapy, chemotherapy, and radiation therapy as the main axis, and the choice of treatment depends on the degree of tumor progression and the general condition of each patient. TNM classification is one of the indicators used for staging gastric cancers by assessing the depth of tumor, extent of lymph node metastasis, and distant metastasis.[2] The TNM classification is globally used as the most reliable prognostic indicator to predict the prognosis and to determine the treatment

strategy for gastric cancer.[2] However, even with the same TNM stage, the prognosis of each patient with gastric cancer is different, suggesting the influence of other factors on the prognosis. There are increasing data that factors, such as malnutrition, skeletal muscle loss, and systemic inflammatory response, are associated with poor outcomes in patients with various types of cancers.[3–10]

Several common inflammation-based prognostic scores, including neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), Glasgow Prognostic Score (GPS), modified GPS (mGPS), C-reactive protein (CRP)/albumin (Alb) ratio, prognostic index (PI), and prognostic nutritional index (PNI), have been reported to have a prognostic value in different cases of malignant, solid tumors.[3,11–22] These biomarkers can be evaluated easily by collecting blood from a peripheral vein and have great advantages, such as simplicity, minimal invasiveness, and low cost. However, it is still unclear as to which of these biomarkers is the most reliable prognostic predictor for cancer. Also, optimal cutoff values are not defined for each biomarker, and the most reliable biomarkers and cutoff values may be different according to the type of cancer.

We previously investigated the prognostic values of several inflammation-based prognostic scores, including NLR, PLR, GPS, and CRP/Alb ratio, in patients who underwent surgery for adenocarcinoma of the esophagogastric junction (AEG) and upper gastric cancer (UGC) and reported that the CRP/Alb ratio was an independent prognostic factor for overall survival (OS) [22] In the present study, we added three inflammation-based prognostic scores (mGPS, PI, and PNI) for the analyses and compared the prognostic values of these biomarkers in patients with AEG and UGC. In addition, we increased the number of patients by adding eligible cases from National Kyushu Medical Center. As a result, PI and PNI were strongly associated with the poor prognosis of AEG, and UGC and were independent prognostic factors for OS and recurrence-free survival (RFS).

METHODS

Patients

In this two-institute retrospective analysis, we reviewed the data of 157 patients with AEG or UGC who underwent surgical resection at the Department of Surgery and Science, Kyushu University, from January 2005 to March 2016, and 69 patients with AEG or UGC who underwent surgical resection at Department of Gastroenterological Surgery, National Kyushu Medical Center, from January 2010 to March 2019. All 226 patients were pathologically determined to have adenocarcinoma, and patients with squamous cell carcinoma or other tumors were excluded from this study.

Among the 226 patients, 13 who underwent palliative or noncurative surgery were excluded. In addition, seven patients who underwent neoadjuvant chemotherapy were excluded, leaving 206 patients with AEG and UGC eligible for analysis. We adopted the Siewert classification regarding tumor location.[23] We defined Siewert type I, II, and III tumors as AEG, and tumors in which the center was located > 5 cm below the esophagogastric junction in the upper third of the stomach as UGC.[10] According to this classification, 96 and 110 patients were categorized as having AEG and UGC, respectively.

Permission to perform this retrospective cohort study was provided by the Institutional Review Board of Kyushu University (2019-395) and National Kyushu Medical Center (19C066).

Inflammation-Based Prognostic Scores

The NLR, PLR, GPS, mGPS, CRP/Alb ratio, PI, and PNI were calculated. The baseline blood data were obtained by collecting blood from the peripheral vein of each patient before surgery. The NLR and PLR were defined as absolute neutrophil count and platelet count, respectively, divided by the absolute lymphocyte count.[13,18,21] The GPS and mGPS were calculated by CRP and albumin using standard thresholds (> 1.0 mg/dl for CRP and < 3.5 g/dl for albumin)[16] The CRP/Alb ratio was defined as the serum CRP level divided by the serum albumin level.[22] Calculation of the PI was based on the CRP level and the white blood cell count. The upper limits of reference ranges for the CRP level (0.1 mg/dL) and the white blood cell count ($11,000/mm^3$) were used as cutoff values.[11] The PI was zero if both values were < the cutoff values, and the PI was one if one of the two markers was elevated. The PNI was calculated using the following formula: $10 \times$ serum albumin (g/dL) $+ 0.005 \times$ total lymphocyte count (per mm^3)[19] Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff values of these inflammation-based prognostic scores (Supplementary Fig. 1). Time-dependent ROC curve analysis also was performed to identify prognostic factors associated with poor outcomes of AEG and UGC among various inflammation-based prognostic scores (Supplementary Fig. 2).

Statistical Analysis

Differences in characteristics between the groups were evaluated using Fisher's exact test or unpaired t test. Survival curves were plotted according to Kaplan–Meier method, and any differences were analyzed using log-rank

test. Univariate and multivariate analyses were performed with a Cox proportional hazard model to clarify the independent prognostic factors. All P values were two-sided, and a $P < 0.05$ was considered statistically significant. ROC curve analysis was used to determine the predictive value of the inflammation-based prognostic scores. All analyses were performed with JMP PRO 13 software (SAS Institute Inc., https://www.jmp.com/ja_jp/home.html).

RESULTS

Characteristics of Patients and Overall Survival according to Inflammation-based Prognostic Scores

The clinicopathological characteristics of 206 patients (151 [73.3%] male, 55 [26.7%] female) and their association with overall survival (OS) are summarized in Table 1. The median patient age was 66 (range, 35–92) years. Based on the tumor location, 96 and 110 patients were categorized as having AEG and UGC, respectively. Among the 206 patients, 161 (78.2%) patients underwent total gastrectomy and remaining 45 (21.8%) underwent proximal gastrectomy. D1 + lymphadenectomy was performed for tumors clinically diagnosed as T1, while D2 lymphadenectomy was performed for tumors clinically diagnosed as T2-4 tumors. The NLR, PLR, GPS, mGPS, CRP/Alb ratio, PI, and PNI were calculated based on laboratory data obtained by sampling peripheral blood. ROC curve analysis was performed to identify the optimal cutoff values of these inflammation-based prognostic scores related to the overall survival of patients with AEG and UGC. The optimal cutoff values of the NLR, PLR, GPS, mGPS, CRP/Alb ratio, PI, and PNI were identified as 2.20, 170, 1, 1, 0.017, 1, and 44.7; the area under the curve (AUC) values were 0.60213, 0.52591, 0.60714, 0.58587, 0.65948, 0.57390, and 0.67218, respectively. The AUC of the CRP/Alb ratio and PNI tended to be higher than that of the other biomarkers (Supplementary Table 1; Supplementary Fig. 1). The patients were divided into two groups according to the cutoff values of inflammation-based prognostic scores, and the number of patients in each group is summarized in Table 1. Time-dependent ROC curve analyses for OS and RFS were performed, and each AUC value of PNI was the highest among inflammation-based prognostic scores (0.7436 [OS] and 0.6756 [RFS], respectively) (Supplementary Table 2; Supplementary Fig. 2).

Factors associated with Poor Prognosis of AEG and UGC

To identify independent prognostic factors for OS, univariate and multivariate analyses with a Cox

TABLE 1 Characteristics of AEG and UGC patients

Characteristic	No. of patients n (%)
Sex	
Male	151 (73.3)
Female	55 (26.7)
Age (yr)	66.3 (35–92)
Tumor location	
AEG	96 (46.6)
UGC	110(53.4)
pStage	
I	113 (54.9)
II	52 (25.2)
III	41 (19.9)
pT	
T1	97 (47.1)
T2	25 (12.1)
T3	55 (26.7)
T4	29 (14.1)
pN	
N0	136 (66.0)
N1	33 (16.0)
N2	13 (6.3)
N3	24 (11.7)
Surgical procedure	
TG	161 (78.2)
PG	45 (21.8)
All postoperative complications	
No	141 (68.4)
Yes	65 (31.6)
Severe complications (CD grade $\geq$ IIIa)	
No	185 (89.8)
Yes	21 (10.2)
Adjuvant chemotherapy	
No	155 (75.2)
Yes	51 (24.8)
Serum albumin (g/dl)	4.09 (2.6-5.0)
NLR	
< 2.20	103 (50.0)
$\geq$ 2.20	103 (50.0)
PLR	
< 170	141 (68.4)
$\geq$ 170	65 (31.6)
GPS	
< 1	182 (88.3)
$\geq$ 1	24 (11.7)
mGPS	
< 1	190 (92.2)
$\geq$ 1	16 (7.8)
CRP/Alb ratio	
< 0.017	92 (44.7)

TABLE 1 continued

Characteristic	No. of patients *n* (%)
≥ 0.017	114 (55.3)
PI	
0	191 (92.7)
1	15 (7.3)
PNI	
< 44.7	167 (81.1)
≥ 44.7	39 (18.9)

EG adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *TG* total gastrectomy; *PG* proximal gastrectomy; *CD* Clavien-Dindo classification; *NLR* neutrophil–lymphocyte ratio; *PLR* platelet-lymphocyte ratio; *GPS* Glasgow prognostic score; *mGPS* modified Glasgow prognostic score; *CRP* C-reactive protein; *Alb* albumin; *PI* prognostic index; *PNI* prognostic nutritional indexData are presented as n (%) with the exception of age and serum albumin, which are presented as mean (range)

proportional hazard model was done. The univariate analyses revealed that age ≥ 65 years (vs. < 65 years; $P = 0.0030$), T-stage (T3-4 vs. T1-2; $P < 0.0001$), N-stage (N1-3 vs. N0; $P < 0.0001$), postoperative complication (yes vs. no; $P = 0.0386$), NLR ≥ 2.20 (vs. < 2.20; $P = 0.0001$), PLR ≥ 170 (vs. < 170; $P = 0.0129$), GPS ≥ 1 (vs. < 1; $P = 0.0003$), mGPS ≥ 1 (vs. < 1; $P = 0.0006$), CRP/Alb ≥ 0.017 (vs. < 0.017; $P = 0.0046$), PI $= 1$ (vs. 0; $P < 0.0001$), and PNI < 44.7 (vs. ≥ 44.7; $P < 0.0001$) were associated with OS in patients with AEG and UGC (Supplementary Table 3). In the multivariate analyses, GPS, mGPS, and CRP/Alb ratio were analyzed individually because of their strong associations with each other; these scores are dependent on values of serum albumin and CRP in common. GPS ($P = 0.0125$, hazard ratio [HR] $= 4.373$), mGPS ($P = 0.0337$, HR $= 5.211$), PI ($P < 0.0001$, HR $= 13.58$), and PNI ($P < 0.0001$, HR $= 8.946$) were independent predictive factors of OS in patients with AEG and UGC among the above-mentioned, inflammation-based, prognostic scores (Table 2). We also performed univariate and multivariate analyses on RFS. In the univariate analysis, the same factors used in the OS analysis, except for age ≥ 65 years, were extracted (Supplementary Table 4). The multivariate analysis for RFS showed that only GPS ($P = 0.0150$, HR $= 3.774$), PI ($P < 0.0001$, HR $= 10.33$), and PNI ($P < 0.0001$, HR $= 6.416$) were independent predictive factors among the above-mentioned inflammation-based prognostic scores (Table 3).

Postoperative Prognosis Based on PI and PNI

The results of multivariate analyses in this study suggest that PI and PNI may be strongly correlated with the poor

prognosis of AEG and UGC among the above inflammation-based prognostic scores. Therefore, patients were divided into two groups according to the cutoff values of these two scores, and the Kaplan–Meier method was performed for comparison of 5-year RFS and OS. This revealed that poorer 5-year RFS and OS rates in patients with AEG and UGC were associated with both PI = 1 (vs. PI = 0) (RFS: 23.5% vs. 76.9%, HR = 7.048, $P < 0.0001$; OS: 22.8% vs. 79.7%, HR = 7.605, $P < 0.0001$) and PNI < 44.7 (vs ≥ 44.7) (RFS: 42.0% vs. 80.7%, HR = 4.058, $P < 0.0001$; OS: 41.7% vs. 84.5%, HR = 5.460, $P < 0.0001$; Figs. 1 and 2).

Subgroup analyses also were performed. First, the same analyses were performed with the subjects limited to patients diagnosed with Stage II or III disease as tumor progression might affect general condition and nutritional status. ROC curve analysis was performed again to identify the optimal cutoff values of PI and PNI in patients with only Stage II and III. As a result, the optimal cutoff values of the PI and PNI were identified as 1 and 44.7, which were the same values as those of all patients; the AUC values were 0.58842 and 0.65172, respectively. Both PI = 1 (vs. PI = 0) and PNI < 44.7 (vs. ≥ 44.7) were significantly associated with poor prognosis in patients with Stage II and III disease (Fig. 3).

Next, patients were categorized according to tumor location as biological properties differed between AEG and UGC. The Kaplan–Meier method performed separately according to location showed that both PI = 1 (vs. PI = 0) and PNI < 44.7 (vs. ≥ 44.7) were significantly associated with poor prognosis, regardless of tumor location (Supplementary Figs. 3 and 5). Especially in AEG patients, the prognosis of the PI = 1 group was extremely poor (5-year RFS and OS: 0.0%; Supplementary Fig. 3). We also categorized patients according to Siewert classification and performed the Kaplan–Meier method separately by Siewert types I, II, and III. Because of subdivision of patients, the analyses for Siewert types I and III groups were a small sample size especially, but a similar tendency was observed in each group (Supplementary Figs. 4 and 6).

DISCUSSION

In this study, the prognostic value of the common inflammation-based prognostic scores, including NLR, PLR, GPS, mGPS, CRP/Alb ratio, PI, and PNI, in patients who underwent surgery for AEG and UGC was compared. We found that GPS, PI, and PNI were more strongly associated with the poor prognosis of AEG and UGC than the other biomarkers and that they were independent prognostic factors for OS and RFS in patients who underwent surgical treatment of AEG and UGC.

TABLE 2 Evaluation of each inflammation-based prognostic score in multivariate analyses for overall survival

Factors	Multivariate analysis			Multivariate analysis			Multivariate analysis		
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
Male (vs female)	1.346	(0.610–3.140)	0.4675	1.462	(0.653–3.470)	0.3614	1.395	(0.630–3.272)	0.4180
Age ≥ 65 y (vs < 65 y)	2.438	(1.191–5.353)	0.0141	2.221	(1.083–4.867)	0.0291	2.317	(1.131–5.072)	0.0210
AEG (vs UGC)	1.352	(0.697–2.685)	0.3746	1.731	(0.872–3.517)	0.1171	1.443	(0.744–2.864)	0.2797
T-Stage (T3-4 vs T1-2)	1.981	(0.715–5.619)	0.1907	1.905	(0.682–5.416)	0.2206	2.256	(0.855–6.173)	0.1013
N-Stage (N1-3 vs N0)	6.403	(2.262–20.92)	0.0002	5.117	(1.879–15.86)	0.0009	4.365	(1.674–12.80)	0.0019
PG (vs TG)	3.881	(1.397–10.48)	0.0104	3.791	(1.381–10.03)	0.0109	3.467	(1.244–9.365)	0.0185
Postoperative complication	2.689	(1.337–5.489)	0.0057	2.583	(1.291–5.251)	0.0075	2.295	(1.152–4.623)	0.0184
NLR ≥ 2.20 (vs < 2.20)	1.555	(0.697–3.644)	0.2851	1.538	(0.688–3.600)	0.2978	1.743	(0.777–4.100)	0.1797
PLR ≥ 170 (vs < 170)	0.931	(0.353–2.308)	0.8815	0.875	(0.327–2.192)	0.7818	0.863	(0.317–2.221)	0.7651
GPS ≥ 1 (vs < 1)	4.373	(1.363–15.70)	0.0125	–			–		
mGPS ≥ 1 (vs < 1)	–			5.211	(1.127–26.71)	0.0337	–		
CRP/Alb ≥ 0.017 (vs < 0.017)	–			–			1.046	(0.482–2.407)	0.9107
PI = 1 (vs PI = 0)	13.58	(3.838–50.51)	<0.0001	21.20	(4.191–106.2)	0.0002	5.231	(1.917–13.50)	0.0018
PNI < 44.7 (vs PNI ≥ 44.7)	8.946	(3.432–23.73)	<0.0001	6.907	(2.791–17.43)	<0.0001	4.593	(1.949–11.02)	0.0005

HR hazard ratio; *CI* confidence interval; *AEG* adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *PG* proximal gastrectomy; *TG* total gastrectomy; *NLR* neutrophil–lymphocyte ratio; *PLR* platelet-lymphocyte ratio; *GPS* Glasgow prognostic score; *mGPS* modified Glasgow prognostic score; *CRP* C-reactive protein; *Alb* albumin; *PI* prognostic index; *PNI* prognostic nutritional index

TABLE 3 Evaluation of each inflammation-based prognostic score in multivariate analyses for recurrence-free survival

Factors	Multivariate analysis			Multivariate analysis			Multivariate analysis		
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
Male (vs female)	1.948	(0.885–4.554)	0.0986	1.936	(0.869–4.598)	0.1075	1.940	(0.881–4.554)	0.1014
Age ≥ 65 y (vs < 65 y)	1.260	(0.667–2.457)	0.4811	1.183	(0.621–2.318)	0.6117	1.244	(0.655–2.436)	0.5086
AEG (vs UGC)	1.222	(0.653–2.327)	0.5326	1.437	(0.762–2.757)	0.2633	1.285	(0.687–2.445)	0.4334
T-Stage (T3-4 vs T1-2)	2.449	(1.017–6.179)	0.0457	2.474	(1.033–6.204)	0.0420	2.740	(1.171–6.745)	0.0195
N-Stage (N1-3 vs N0)	5.474	(2.208–14.89)	0.0001	4.400	(1.846–11.40)	0.0006	3.978	(1.715–9.963)	0.0010
PG (vs TG)	2.466	(0.970–5.819)	0.0575	2.482	(0.978–5.833)	0.0554	2.439	(0.946–5.868)	0.0640
Postoperative complication	2.489	(1.295–4.827)	0.0064	2.320	(1.219–4.450)	0.0106	2.050	(1.091–3.872)	0.0260
NLR ≥ 2.20 (vs < 2.20)	1.403	(0.679–2.992)	0.3639	1.426	(0.684–3.061)	0.3470	1.649	(0.789–3.545)	0.1852
PLR ≥ 170 (vs < 170)	1.182	(0.499–2.677)	0.6975	1.049	(0.439–2.392)	0.9125	1.046	(0.433–2.428)	0.9191
GPS ≥ 1 (vs < 1)	3.774	(1.287–11.86)	0.0150	–			–		
mGPS ≥ 1 (vs < 1)	–			3.484	(0.883–14.24)	0.0754	–		
CRP/Alb ≥ 0.017 (vs < 0.017)	–			–			0.879	(0.442–1.803)	0.7175
PI = 1 (vs PI = 0)	10.33	(3.292–33.03)	< 0.0001	11.89	(2.875–47.22)	0.0006	4.418	(1.810–10.08)	0.0017
PNI < 44.7 (vs PNI ≥ 44.7)	6.416	(2.703–15.23)	<0.0001	4.972	(2.186–11.32)	0.0002	3.730	(1.746–7.884)	0.0008

HR hazard ratio; *CI* confidence interval; *AEG* adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *PG* proximal gastrectomy; *TG* total gastrectomy; *NLR* neutrophil–lymphocyte ratio; *PLR* platelet-lymphocyte ratio; *GPS* Glasgow prognostic score; *mGPS* modified Glasgow prognostic score; *CRP* C-reactive protein; *Alb* albumin; *PI* prognostic index; *PNI* prognostic nutritional index

The above-mentioned biomarkers have been reported to have prognostic value in patients with various types of cancers, including gastrointestinal tumors, such as esophageal cancer, gastric cancer, and colorectal cancer.[3,11–22] However, few studies about the relationship among these biomarkers with respect to prognosis in patients with AEG have been published. In patients with AEG, pre-albumin, BMI, NLR, and CRP/Alb ratio were
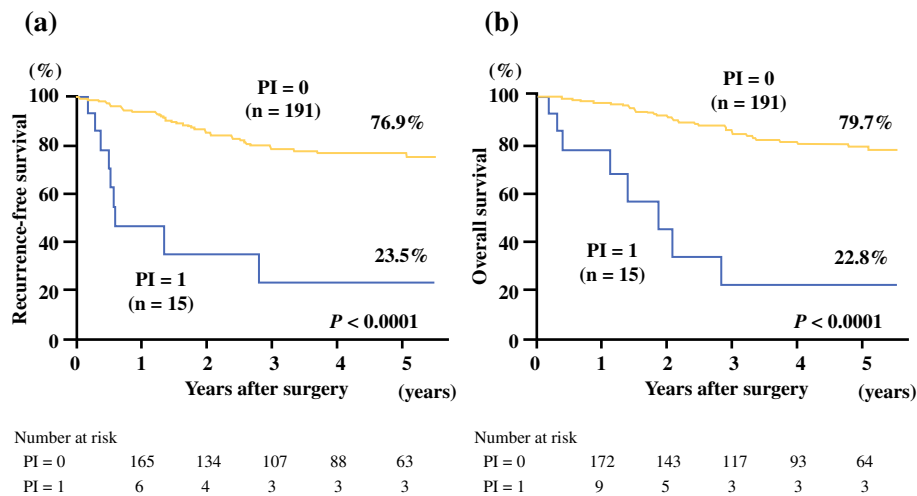
(a)

(b)

Number at risk
PI = 0	165	134	107	88	63
PI = 1	6	4	3	3	3

Number at risk
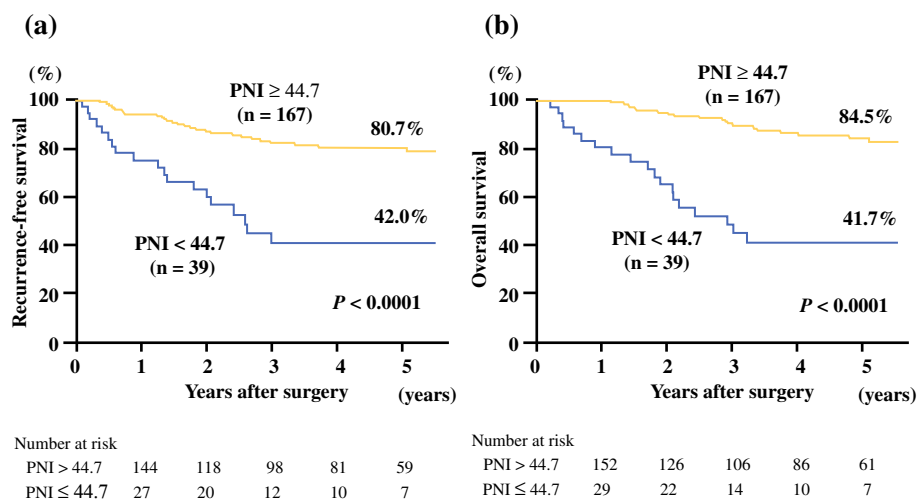| PI = 0	172	143	117	93	64
PI = 1	9	5	3	3	3

FIG. 1 Postoperative survival in patients with AEG and UGC based on prognostic index (PI): (**a**) recurrence-free survival and (**b**) overall survival of all studied patients. Patients were categorized according to PI (PI = 0 or PI = 1). The 5-year recurrence-free and overall survival rates were significantly lower in patients with PI = 1 than those in patients with PI = 0 (RFS: $P < 0.0001$, HR = 7.048; OS: $P < 0.0001$, HR = 7.605). *AEG* adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *PI* prognostic index; *HR* hazard ratio

(a)

(b)

Number at risk
PNI > 44.7	144	118	98	81	59
PNI ≤ 44.7	27	20	12	10	7

Number at risk
PNI > 44.7	152	126	106	86	61
PNI ≤ 44.7	29	22	14	10	7

FIG. 2 Postoperative survival in patients with AEG and UGC based on prognostic nutritional index (PNI): (**a**) recurrence-free survival and (**b**) overall survival of all studied patients. The optimal cutoff value of PNI was determined to be 44.7. The 5-year recurrence-free and overall survival rates were significantly lower in patients with PNI < 44.7 than in those with PNI ≥ 44.7 (RFS: $P < 0.0001$, HR = 4.058; OS: $P < 0.0001$, HR = 5.460). *AEG* adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *PNI* prognostic nutritional index; *HR* hazard ratio

reported as independent prognostic factors.[22,24,25] On the other hand, to the best of our knowledge, no studies compare the relationship among various inflammation-based prognostic scores and prognosis in patients with AEG who underwent surgery.

A few studies have compared the validity of several inflammation-based prognostic scores to predict the prognosis of gastrointestinal malignancies. Toyokawa et al. evaluated the prognostic value of CRP/Alb ratio, NLR, PLR, PNI, GPS, and PI in patients with stage II gastric cancer.[26] They concluded that CRP/Alb ratio and PNI were independent prognostic factors and superior to the other biomarkers.[26] Wen et al. also compared various inflammation-based prognostic scores, such as mGPS, NLR, PLR, PI, and PNI, in patients with esophageal and gastric carcinoma and concluded that only PLR and PNI were the significant predictors of patient survival.[27] They also performed a subgroup analysis and indicated that mGPS was predictive of patient survival only in esophagectomies.[27] In our analysis, seven prognostic scores were compared, and GPS, PI, and PNI were identified as the independent prognostic factors for both OS and RFS in patients with

FIG. 3 Postoperative survival in patients diagnosed with Stage II and III AEG and UGC based on prognostic index (PI) ((**a**) recurrence-free survival and (**b**) overall survival) or prognostic nutritional index (PNI) ((**c**) recurrence-free survival and (**d**) overall survival). Kaplan–Meier analyses were performed according to the same criteria as in Figs. 1 and 2. *AEG* adenocarcinoma of esophagogastric junction; *UGC* upper gastric cancer; *PI* prognostic index; *PNI* prognostic nutritional index
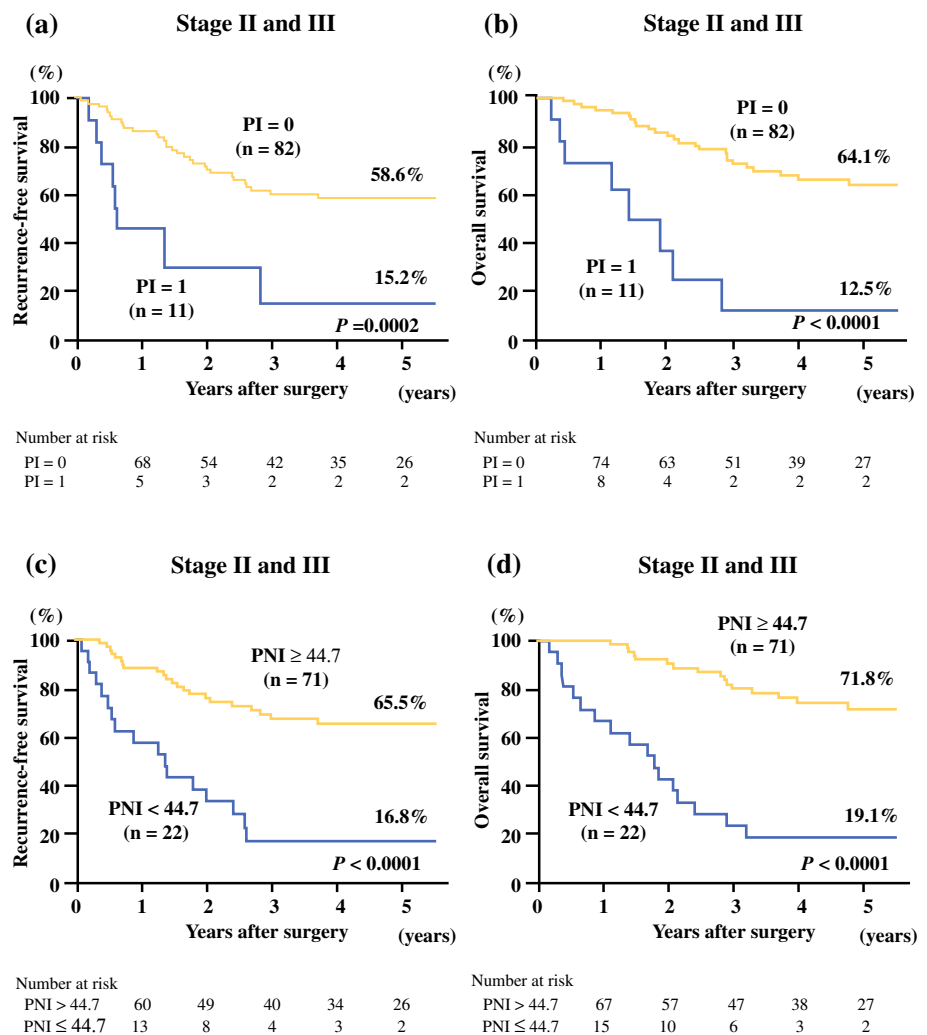
AEG and UGC. Although there were differences in cancer type and cutoff values for prognostic scores among these studies, all of them suggest that PNI is a significant predictive biomarker common to above studies. Therefore, PNI may be the most reliable biomarker to predict the prognosis of gastrointestinal tumors among inflammation-based prognostic scores.

The value of PNI is determined by serum albumin and total lymphocyte count. Serum albumin is used as an indicator of nutritional status, and it has been reported that hypoalbuminaemia is associated with cancer progression and poor survival outcomes in various types of cancers.[28–33] Possible mechanisms are as follows: first, chronic inflammation exhausts nutrition and energy in cancer patients, and hypoalbuminemia may occur because of the systemic inflammatory response; and second, hypoalbuminemia reflects malnutrition or cachexia, which is associated with poor outcomes.[27] Moreover, decrease in the number of lymphocytes can be a factor that deteriorates the value of PNI. Ray-Coquard et al. found that

lymphopenia was an independent prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas.[34] Precise mechanisms of the relationship between lymphopenia and poor prognosis remains unclear. The possible mechanisms are as follows: first, lymphopenia reflects the presence of immunosuppression, which promotes cancer progression. This condition suggests that the host tends to have an inadequate immunological reaction. Second, the low lymphocyte count may be a consequence of lympholytic cytokines produced by lymphoma cells, and such a lymphoma may itself be resistant; and third, a combination of both or other factors.[34] The mechanisms of lymphopenia in cancer patients may be multifactorial.

As described above, inflammation-based prognostic scores represented by PNI may reflect patient nutritional and immune status. Nutrition disorders result in skeletal muscle loss. Recent studies have shown that some myokines secreted by muscle cells can regulate cancer cell growth. Aoi et al. reported that a novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppressed

colon tumor growth via exercise by increasing apoptosis.[35] Hojman et al. have reported that exercise-induced, muscle-derived cytokines inhibit mammary cancer cell growth.[36] These results suggest that nutritional support and increased muscle mass may contribute to tumorigenesis prevention via myokine secretion. Therefore, enhanced perioperative nutritional support and physical exercises may improve long-term outcomes after surgery, especially in AEG and UGC patients with poor inflammation-based prognostic scores.

A limitation of our previous study was that it had a small sample size and was a single-institution retrospective study. Therefore, we increased the number of patients by adding eligible cases from National Kyushu Medical Center in this study. Although these results may not be generalizable to other patient cohorts, few studies have focused on the relationships between patients with AEG or UGC and inflammation-based prognostic scores. Accumulation of the findings obtained from retrospective studies from various institutes would be meaningful. The findings from the current study offer useful information regarding the clinical value of GPS, PI, and PNI.

CONCLUSIONS

The GPS, mGPS, PI, and PNI were strongly associated with a poor prognosis in patients who underwent surgery for AEG and UGC. These predictive scores for the prognosis of AEG and UGC were superior to the other inflammation-based prognostic scores. PNI tended to be the most relevant score for the prognosis of gastrointestinal tumors, which is consistent with that reported in previous studies. These biomarkers may be useful for evaluating high-risk patients with AEG and UGC easily and noninvasively.

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