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ORIGINAL ARTICLE

The clinical utility of an mGPS and SII combined score in patients with advanced gastric cancer treated with nivolumab monotherapy

S. Udagawa, A. Ooki*, H. Osumi, K. Yoshino, M. Tamba, K. Shimozaki, S. Fukuoka, T. Wakatsuki, M. Ogura, E. Shinozaki, K. Chin & K. Yamaguchi

Department of Gastrointestinal Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

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Background: Several nutritional and inflammatory indices can predict the efficacy of immune checkpoint inhibitors and the prognosis in various cancers. However, indices that are useful for patients with advanced gastric cancer (AGC) remain unclear.

Materials and methods: This retrospective study was conducted at a single cancer center. Patients with AGC who received nivolumab as a third- or later-line treatment between June 2017 and May 2023 were selected. The association between nutritional and inflammatory indices and clinical outcomes was analyzed.

Results: In total, 277 patients were analyzed. Multivariate analysis revealed that several indices were significantly associated with time to treatment failure (TTF) and overall survival (OS) after adjustment for clinicopathological factors. The modified Glasgow prognostic score (mGPS) and systemic immune-inflammation index (SII) were identified as the most promising indices. A combined score (CS) developed by summing the SII and mGPS was associated with a shorter TTF and OS in CS 1 or 2 than in CS 0 [TTF: hazard ratio (HR) 1.39, 95% confidence interval (CI) 1.04-1.87, $P = 0.03$ for CS 1 and HR 2.04, 95% CI 1.49-2.80, $P < 0.01$ for CS 2; OS: HR 1.45, 95% CI 1.08-1.96, $P < 0.01$ for CS 1 and HR 2.81, 95% CI 2.06-3.82, $P < 0.01$ for CS 2]. CS 2 had a positive predictive value of 78.1% for detecting the first progressive disease. The clinical significance of CS was also confirmed in the first-line cohort.

Conclusion: CS may be useful for predicting treatment efficacy and prognosis in nivolumab-treated patients with AGC.

Key words: predictor, nutritional index, inflammatory index, immune checkpoint inhibitor

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the fifth leading cause of cancer-related death worldwide.[1] Although systemic therapies for unresectable or advanced gastric cancer (AGC) have been developed, the prognosis remains poor. Various chemotherapeutic agents such as cytotoxic chemotherapy and molecular targeting agents have been used for AGC, among which nivolumab has substantially advanced AGC treatment.[2] Nivolumab is an immunoglobulin G4 monoclonal antibody inhibitor of programmed cell-death protein 1. The ATTRACTION-2 trial showed that nivolumab as a third- or later-line agent improved the overall survival (OS) of heavily pretreated patients with AGC.[3] In addition, nivolumab combined with chemotherapy as a first-line treatment improved OS and progression-free survival (PFS) compared with chemotherapy alone in the CheckMate 649 trial; the ATTRACTION-4 trial also showed prolonged PFS.[2,4] However, biomarkers for predicting nivolumab efficacy are limited. In general, tumors with mismatch repair deficiency/microsatellite instability (dMMR/MSI) show notable benefit from immune checkpoint inhibitors (ICIs) in GC.[5] However, only ∼6% of patients with AGC have dMMR/MSI.[6] Thus, there is a need for easy-to-use biomarkers that can predict the efficacy of nivolumab in patients with AGC.

Recently, several nutritional and inflammatory indices have been investigated as biomarkers in patients with cancer receiving ICIs. These include neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP)-to-albumin ratio (CAR), the modified Glasgow prognostic score (mGPS), lung immune prognostic index (LIPI), prognostic nutrition index (PNI), advanced lung cancer inflammation index (ALI), systemic immune-inflammation index (SII), and so on.[7-20] Systemic inflammation is associated with tumorigenesis such as proliferation, cell survival, angiogenesis, migration, the tumor microenvironment, and local immune

*Correspondence to: Dr Akira Ooki, Department of Gastrointestinal Chemotherapy, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Ariake 3-8-3, Koto-ku, Tokyo, Japan. Tel: +81-3-3520-0111; Fax: +81-3-3520-0111

E-mail: akira.oki@jfcro.or.jp (A. Ooki).

responses. It contributes to malignant tumor development and progression, thereby affecting response to treatment including immunotherapy and survival of cancer patients.[21-23] Although previous reports have suggested that nutritional and inflammatory indices are associated with PFS and OS in patients receiving ICI treatment, these studies were conducted on a limited number of patients.[7-20] Furthermore, various nutritional and inflammatory indices have been proposed; however, there are few reports indicating which of these indices is most useful in patients with AGC. Hence, the aim of this study was to identify the nutritional and inflammatory indices that are most useful in predicting treatment response and prognosis in patients with AGC who received nivolumab monotherapy, and to explore their optimal application in clinical practice.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR) in Japan. All data were obtained by reviewing the medical records. The inclusion criteria for the present study were as follows: (i) unresectable advanced or recurrent gastric/gastroesophageal junction cancer, (ii) histologically or cytologically confirmed adenocarcinoma, and (iii) nivolumab as a third- or later-line treatment or nivolumab with chemotherapy as first-line treatment between June 2017 and May 2024 at the JFCR. The exclusion criteria were as follows: (i) lack of laboratory data within 1 week before nivolumab administration, and (ii) multiple cancers. Tumor responses were retrospectively assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in patients with at least one measurable lesion. Time to treatment failure (TTF) was defined as the time between nivolumab treatment initiation and disease progression, treatment discontinuation, or death from any cause, whichever occurred first. OS was defined as the time from nivolumab treatment initiation to death from any cause. Hyperprogressive disease (HPD) was defined as tumor growth kinetics (TGK) ratio $\geq$2 and >50% increase in tumor burden: the sum of the longest diameters of the target lesions according to RECIST v1.1 at pre-baseline, baseline, and post-computed tomography (CT) scan were represented by S_{pre}, S_0, and S_{post}, respectively. Similarly, the timing of the CT scans was represented by T_{pre}, T_0, and T_{post}, respectively. TKG_{pre} and TKG_{post} were calculated as $(S_0 - S_{pre})/(T_0 - T_{pre})$ and $(S_{post} - S_0)/(T_{post} - T_0)$, respectively. The TGK ratio was defined as TGK_{post}/TGK_{pre}.[24] The data cut-off date for follow-up was September 2024. The study protocol (2024-GB-041) was approved by the JFCR ethics committee. All the procedures were carried out in accordance with the principles outlined in the Declaration of Helsinki of 1964 and its later version. Informed consent was not required because of the retrospective nature of the study.

Nutritional and inflammation index

In this study, we evaluated the following nutritional and inflammatory indices reported to be associated with ICIs: NLR, CAR, mGPS, LIPI, PNI, ALI, and SII. These indices were assessed within 1 week of treatment initiation. NLR was defined as neutrophil (/μl)/lymphocyte (/μl) ratio. The CAR was defined as the CRP (mg/dl)/albumin (g/dl) ratio. The mGPS was calculated as follows: patients with both elevated CRP (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl) were assigned a score of 2. Patients with elevated CRP (>1.0 mg/dl) were assigned a score of 1. Patients with a normal CRP ($\leq$1.0 mg/dl) and normal serum albumin ($\geq$3.5 g/dl) were allocated a score of 0. LIPI was calculated as follows: patients with derived NLR (dNLR), calculated as neutrophil count (/μl)/[white blood cell count (/μl) − neutrophil count (/μl)], >3 and high lactate dehydrogenase (LDH) (higher than the upper limit of LDH) were allocated a score of 2. Patients with either a dNLR >3 or a high LDH level were assigned a score of 1. Patients with dNLR $\leq$3 and normal LDH were assigned a score of 0. PNI was defined as 10 × serum albumin (g/dl) + 0.005 × lymphocyte count (/μl). ALI was defined as the body mass index [weight (kg)/height $(m)^2$] × albumin (g/dl)/NLR ratio. SII was defined as platelet (10^3/μl)/NLR ratio (Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2025.100177). The cut-off values for NLR, CAR, PNI, ALI, and SII remain unclear; therefore, the cut-off values were set at the medians during the preliminary screening for the nutritional and inflammation indices.

Statistical analyses

Categorical variables were compared using Fisher's exact test. TTF and OS were estimated using the Kaplan–Meier method, and the results were compared using the log-rank test. Multivariate analyses using the Cox proportional hazards model were carried out to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Logistic regression analysis was conducted to analyze the factors related to the objective variables. All reported *P* values were obtained using two-sided tests. Statistical significance was defined as $P < 0.05$. All statistical analyses were carried out using EZR version 1.41 statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[25]

RESULTS

Patient characteristics

A total of 289 patients who received nivolumab monotherapy as third- or later-line treatment were identified and nutritional and inflammatory indices of 277 patients with no missing data were assessed. The median age was 66 years (range 30-89 years), and 180 patients (65.0%) were male. Of these patients, 188 (67.9%) had diffuse-type AGC and 241 (87.0%) had a primary lesion in the stomach. A high degree of dMMR/MSI was observed in 4 patients (1.4%)

Table 1. Patient characteristics

No. of patients	Total, *n* (%) *n* = 277
Age, years	
Median (range)	66 (30-89)
≤65	137 (49.5)
Sex	
Male	180 (65.0)
Female	97 (35.0)
Performance status	
0-1	232 (83.8)
≥2	45 (16.2)
Lauren classification	
Intestinal	89 (32.1)
Diffuse	188 (67.9)
Location of primary site	
Stomach	241 (87.0)
EGJ	36 (13.0)
Microsatellite instability	
dMMR/MSI-high	4 (1.4)
pMMR/MSS	37 (13.4)
Unknown	236 (85.2)
HER2 status	
Negative	228 (82.3)
Positive	45 (16.2)
Unknown	4 (1.5)
Prior gastrectomy	
Yes	121 (43.7)
No	156 (56.3)
Treatment line	
Third	229 (82.7)
Fourth or later	48 (17.3)
Liver metastasis	
Yes	59 (21.3)
No	218 (78.7)
Peritoneum metastasis	
Yes	201 (75.6)
No	76 (24.4)
Lung metastasis	
Yes	33 (11.9)
No	247 (88.1)
No. of metastases sites	
<2	134 (48.4)
≥2	143 (51.6)
Tumor maker, median (range)	
CEA (ng/ml)	4.9 (0.5-7214.6)
CA19-9 (U/ml)	50.9 (2.0-50 000)

CA19-9, carbohydrate cancer antigen; CEA, carcinoembryonic antigen; dMMR/MSI, mismatch repair deficiency/microsatellite instability; EGJ, esophagogastric junction; *HER2*, human epidermal growth factor receptor 2; pMMR/MSS, mismatch repair proficiency/microsatellite stability.

and MSI was not evaluated in 236 patients (85.2%). A total of 201 (75.6%) patients had peritoneal metastases. Nivolumab was administered as third-line treatment in 229 patients (82.7%). The characteristics of the 277 patients are summarized in Table 1. A total of 255 and 248 events were observed for TTF and OS, respectively. Median TTF and OS for the 277 assessed patients were 1.8 months (95% CI 1.63-1.97 months) and 5.8 months (95% CI 4.87-6.63 months), respectively (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmogo.2025.100177). Among the 126 patients with target lesions, the best overall response was complete response (4 patients, 3.2%), partial response (14 patients, 11.1%), stable disease (30 patients, 23.8%), progressive disease (PD; 65 patients, 51.6%), and not evaluable (13 patients, 10.3%). Disease control and objective response rates (ORRs) were 38.1% and 14.3%, respectively (Table 2). First progressive disease (FPD), which included clinical PD until the first follow-up CT scan, was observed in 177 (63.9%) of the 277 assessed patients. TTF <1 month was observed in 63 patients (22.7%). HPD was observed in 13 patients (11.5%) (Table 3). Of the 277 patients who received nivolumab, 13 (4.7%) developed grade 3-4 immune-related adverse events (irAEs) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100177).

TTF and OS according to the nutritional and inflammatory indices

The median NLR, CAR, PNI, ALI, and SII values were 2.79, 0.0839, 39.8, 24.1, and 638, respectively. LIPI and NLR were divided into two groups: 0 or 1,2. We calculated the HRs for TTF and OS adjusted for sex, age, performance status (PS), Lauren classification, primary site, human epidermal growth factor receptor 2 status, prior gastrectomy, treatment line of nivolumab, liver metastasis, and peritoneal metastasis for each nutritional and inflammatory index. The HRs for TTF in LIPI, NLR, CAR, mGPS, PNI, ALI, and SII were 1.19 (95% CI 0.91-1.56), 1.75 (95% CI 1.34-2.28), 1.38 (95% CI 1.04-1.85), 1.81 (95% CI 1.35-2.42), 1.40 (95% CI 1.07-1.84), 1.64 (95% CI 1.26-2.15), and 1.84 (95% CI 1.42-2.37), respectively. The HRs for OS in LIPI, NLR, CAR, mGPS, PNI, ALI, and SII were 1.22 (95% CI 0.94-1.60), 2.05 (95% CI 1.57-2.69), 1.78 (95% CI 1.32-2.39), 2.37 (95% CI 1.77-3.19), 1.82 (95% CI 1.38-2.39), 1.93 (95% CI 1.47-2.52), and 1.98 (95% CI 1.52-2.57), respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.esmogo.2025.100177).

mGPS, SII, and their combined score

Following a preliminary screening of the nutritional and inflammatory indices, we selected the mGPS and SII as the most suitable indices for assessing nutrition and inflammation. This decision was based on the highest HR for TTS and OS, taking into account the components of these indices, such as CRP, albumin, platelet, neutrophil, and lymphocyte counts. To determine the optimal cut-off value of the SII, we plotted the HR and *P* values at different cut-off points to confirm the trend of the HR and *P* values for TTF and OS. Of the variable cut-off points, we adopted 1810 as the optimal cut-off, where the HR was the highest for both TTF and OS (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmogo.2025.100177). The median TTF was shorter in patients with mGPS 1,2 and SII high (>1810) than in those with mGPS 0 (HR 1.75, 95% CI 1.34-2.29, $P < 0.01$) and SII low (≤1810) (HR 1.91, 95% CI 1.37-2.66, $P < 0.01$) (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmogo.2025.100177). The median OS was shorter in patients with mGPS 1,2 and SII higher than in those with mGPS 0 (HR 2.38, 95% CI 1.82-3.12, $P < 0.01$) and SII low (HR 2.07, 95% CI 1.50-2.85, $P < 0.01$). We calculated the combined score (CS) of mGPS and SII as follows: CS was 0 if mGPS 0 and SII low, CS was 1 if mGPS 1,2 or SII high, and CS was 2 if mGPS 1,2 and SII high. When compared with CS 0,

Table 2. Tumor response in patients with target lesion

Tumor response	*n* = 126 *n* (%)	mGPS 0 *n* = 84 *n* (%)	mGPS 1,2 *n* = 42 *n* (%)	SII low *n* = 107 *n* (%)	SII high *n* = 19 *n* (%)	CS 0 *n* = 80 *n* (%)	CS 1 *n* = 31 *n* (%)	CS 2 *n* = 15 *n* (%)
Complete response	4 (3.2)	3 (3.6)	1 (2.4)	3 (2.8)	1 (5.3)	2 (2.5)	2 (6.5)	0
Partial response	14 (11.1)	12 (14.3)	2 (4.8)	12 (11.2)	2 (10.5)	12 (15.0)	0	2 (13.3)
Stable disease	30 (23.8)	20 (23.8)	10 (23.8)	27 (25.2)	3 (15.8)	19 (23.8)	9 (29.0)	2 (13.3)
Progressive disease	65 (51.6)	46 (54.8)	19 (45.2)	57 (53.3)	8 (42.1)	44 (55.0)	15 (48.4)	6 (40.0)
Non-evaluable	13 (10.3)	3 (3.6)	10 (23.8)	8 (7.5)	5 (26.3)	3 (3.8)	5 (16.1)	5 (33.3)
Disease control rate	48 (38.1)	35 (41.7)	13 (31.0)	42 (39.3)	6 (31.6)	33 (41.3)	11 (35.5)	4 (26.7)
Objective response rate	18 (14.3)	15 (17.9)	3 (7.1)	15 (14.0)	3 (15.8)	14 (17.5)	2 (6.5)	2 (13.3)

CS, combined score; mGPS, modified Glasgow prognostic score; SII, systemic immune-inflammation index.

the HR for TTF in CS 1,2 increased from 1.51 (CS 1, 95% CI 1.13-2.03) to 2.56 (CS 2, 95% CI 1.72-3.82), and that for OS increased from 2.04 (CS 1, 95% CI 1.51-2.76) to 2.98 (CS 2, 95% CI 2.03-4.38) (Figure 1). Moreover, CS 1,2 was an independent significant factor for shorter TTF and OS in the multivariate analysis (Table 4). However, the positive predictive values (PPVs) of mGPS 0, SII low, and CS 0 for ORR were 17.9% (15/84), 14.0% (15/107), and 17.5% (14/80), respectively, which were similar to the ORR of 14.3% (18/126) in all patients (Table 2). The incidence and characteristics of irAEs did not differ according to the mGPS, SII, and CS (Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100177).

Clinicopathological features of mGPS, SII, and CS

The characteristics of the patients according to mGPS, SII, and CS are shown in Supplementary Table S4, available at https://doi.org/10.1016/j.esmogo.2025.100177. Patients with mGPS 1,2, SII high, and CS 2 were more likely to have a PS of 2-3. Logistic regression analysis for mGPS and SII showed that both mGPS [odds ratio (OR) 6.40, 95% CI 3.03-13.50, $P < 0.01$] and SII (OR 3.63, 95% CI 1.67-7.91, $P < 0.01$) were associated with PS 2-3 (Supplementary Table S5, available at https://doi.org/10.1016/j.esmogo.2025.100177). Moreover, among patients with PS 2-3, the median TTF was significantly shorter in patients with SII high and CS 1,2 than in those with SII low (HR 2.48, 95% CI 1.24-4.97, $P = 0.01$) and CS 0 (HR 2.29, 95% CI 1.14-4.63, $P = 0.02$). The median OS was significantly shorter in patients with mGPS 1,2, high SII, and CS 1,2 than in those with mGPS 0 (HR 2.48, 95% CI 1.25-4.91, $P < 0.01$), SII low (HR 2.33, 95% CI 1.23-4.42, $P < 0.01$), and CS 0 (HR 3.10, 95% CI 1.51-6.37, $P < 0.01$) (Figure 2).

Short-term value of mGPS, SII, and CS

We evaluated the short-term value of mGPS, SII, and CS. The PPVs of mGPS 1,2 and SII high for FPD were 72.0% (59/82) and 74.5% (35/47), respectively, which were higher than the 63.9% (177/277) PPV observed in all patients. Moreover, the PPV of CS 2 for the FPD increased to 78.1% (25/32). Similarly, the PPVs of mGPS 1,2 and SII high for TTF $\leq$1 month were 45.1% (37/82) and 51.0% (24/47), respectively. The PPV of CS 2 for TTF $\leq$1 month increased to 59.4% (19/32) in CS 2, which was higher than the 22.7% (63/277) PPV observed in all patients. However, the PPVs for mGPS 1,2, SII high, and CS 2 for HPD were 15.2% (5/33), 0% (0/14), and 0% (0/10), respectively, which were not useful (Table 3).

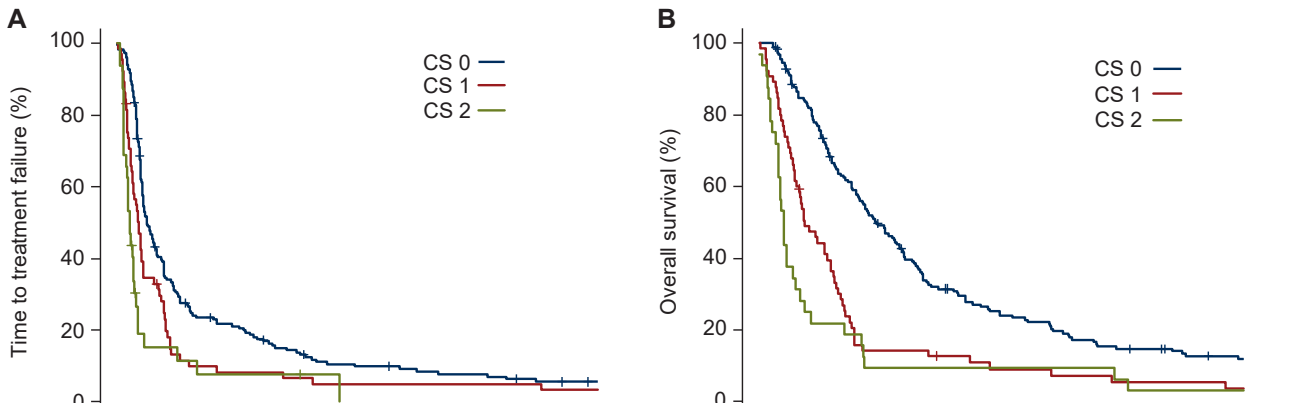
mGPS, SII, and CS in first-line cohort

Based on the phase III CheckMate 649 trial, nivolumab in combination with chemotherapy had been established as a standard first-line treatment for AGC. Since then, most patients with AGC have received nivolumab with chemotherapy. In this study, 230 patients received nivolumab monotherapy as third-line or later treatment before nivolumab with chemotherapy was available in Japan, while 47 patients received nivolumab monotherapy after that. Therefore, we evaluated the validity of CS in 150 patients who received first-line nivolumab in combination with chemotherapy. Patient characteristics of the first-line cohort are summarized in Supplementary Table S6, available at https://doi.org/10.1016/j.esmogo.2025.100177. When compared with CS 0, adopting a

Table 3. Short-term value of mGPS, SII, and CS

	FPD (+)	FPD (−)	PPV	TTF ≤ 1	TTF > 1	PPV	HPD (+)	HPD (−)	PPV
All	177	100	63.9% (177/277)	63	214	22.7% (63/277)	13	100	11.5% (13/113)
mGPS 0	118	77		26	169		8	72	
mGPS 1,2	59	23	72.0% (59/82)	37	45	45.1% (37/82)	5	28	15.2% (5/33)
SII low	142	88		39	191		13	86	
SII high	35	12	74.5% (35/47)	24	23	51.0% (24/47)	0	14	0% (0/14)
CS 0	108	72		21	159		8	68	
CS 1	44	21		23	42		5	22	
CS 2	25	7	78.1% (25/32)	19	13	59.4% (19/32)	0	10	0% (0/10)

CS, combined score; FPD, first progressive disease; HPD, hyperprogressive disease; mGPS, modified Glasgow prognostic score; PPV, positive predictive value; SII, systemic immune-inflammation index; TTF, time to treatment failure.



	TTF (95% CI)	HR (95% CI)	*P* value
CS 0	2.10 (1.80-2.73)	Ref	
CS 1	1.50 (1.10-1.83)	1.51 (1.13-2.03)	<0.01
CS 2	0.88 (0.47-1.23)	2.56 (1.72-3.82)	<0.01

	OS (95% CI)	HR (95% CI)	*P* value
CS 0	8.10 (6.87-9.77)	Ref	
CS 1	3.13 (2.50-5.00)	2.04 (1.51-2.76)	<0.01
CS 2	1.70 (1.33-2.53)	2.98 (2.03-4.38)	<0.01

Figure 1. Kaplan–Meier plots by CS of mGPS and SII. Kaplan–Meier plots of (A) TTF and (B) OS by the CS of mGPS and SII.
CI, confidence interval; CS, combined score; HR, hazard ratio; mGPS, modified Glasgow prognostic score; OS, overall survival; SII, systemic immune-inflammation index; TTF, time to treatment failure.

cut-off value of 1810 in SII, the HR for TTF in CS 1,2 increased from 1.42 (CS 1, 95% CI 0.76-2.66) to 2.64 (CS 2, 95% CI 1.56-4.47), and that for OS increased from 1.71 (CS 1, 95% CI 0.83-3.50) to 3.73 (CS 2, 95% CI 1.99-7.02), although CS 1 was not statistically significant (Supplementary Figure S4A and B, available at https://doi.org/10.1016/j.esmogo.2025.100177). SII cut-off value in the first-line cohort was recalculated using the same method as in the third-line or later cohort and was calculated to be 1900. Once the cut-off was adopted, the HR for TTF in CS 1,2 increased from 1.89 (CS 1, 95% CI 1.02-3.49) to 2.59 (CS 2, 95% CI 1.51-4.44) and HR for OS increased from 2.13 (CS 1, 95% CI 1.06-4.27) to 3.59 (CS 2, 95% CI 1.88-6.84) compared with CS 0 (Supplementary Figure S4C and D, available at https://doi.org/10.1016/j.esmogo.2025.100177). Moreover, six patients with PS 2-3 and CS 1-2 had very poor outcomes. Median TTF and OS were 2.62 months (95% CI 2.1 months-not reached) and 3.60 months (95% CI 2.1 months-not reached), respectively. The rates of subsequent therapy in CS 0, CS 1, and CS 2 were 86.2% (50/58), 69.2% (9/13), and 61.1% (11/18), respectively.

DISCUSSION

In the present study, nutritional and inflammatory indices, except LIPI, were associated with TTF and OS in patients with AGC treated with nivolumab monotherapy. Among these indices, the CS of mGPS and SII-stratified TTF and OS may be more useful in predicting clinical outcomes. To the best of our knowledge, this is the first report demonstrating the predictive utility of CS, especially for predicting poor short-term outcomes, in patients with AGC treated with nivolumab.

Our findings are consistent with those of previous studies and indicate that several nutritional and inflammatory indices are prognostic factors and predictive markers of ICI efficacy.[7-20] However, most of these studies involved a relatively limited number of patients. One strength of this study is that it evaluated the value of nutritional and inflammatory indices not only in combination with ICIs and chemotherapy but also in nivolumab monotherapy without the influence of chemotherapy, using a larger sample size than those in previous reports. To increase the clinical value of the SII and mGPS, we combined them. In addition, the factors comprising the nutritional and inflammatory indices overlapped, and the CS was considered reasonable because of the differences in component factors. The combination of the SII and mGPS is associated with clinical outcomes and may provide a stratification of clinical outcomes compared with using a single index. In addition, the association between CS and both TTF and OS was also evaluated based on MSI status. Although the patient sample was limited, the significance of CS was confirmed in patients with microsatellite stability (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmogo.2025.100177). A similar trend was observed in patients with MSI-high: among four patients with MSI-high, the median TTF for the two patients with CS 0 was 29.37 months, compared with 1.83 months for the two patients with CS 1. For OS, the median for the

Table 4. Multivariate analysis for TTF and OS

	HR	Lower 95% CI	Upper 95% CI	*P* value
TTF				
Sex (female[a] or male)	1.10	0.83	1.47	0.50
Age (≤65[a] or >65 years)	0.62	0.48	0.82	<0.01
Performance status (0,1[a] or 2,3)	1.72	1.22	2.44	<0.01
Lauren classification (intestinal[a] or diffuse)	1.30	0.96	1.75	0.09
Location of primary site (stomach[a] or EGJ)	1.11	0.74	1.68	0.61
Prior gastrectomy (no[a] or yes)	1.00	0.77	1.29	0.99
Treatment line (third[a] or fourth or later)	0.91	0.65	1.29	0.59
Liver metastasis (no[a] or yes)	1.36	0.98	1.88	0.07
Peritoneal metastasis (no[a] or yes)	1.62	1.15	2.27	<0.01
No. of metastases sites (<2[a] or ≥2)	1.36	1.02	1.82	0.04
Combined score (0[a] or 1,2)	1.87	1.44	2.43	<0.01
OS				
Sex (female[a] or male)	1.08	0.81	1.44	0.60
Age (≤65[a] or >65 years)	0.96	0.73	1.25	0.75
Performance status (0,1[a] or 2,3)	2.10	1.45	3.03	<0.01
Lauren classification (intestinal[a] or diffuse)	1.55	1.14	2.10	<0.01
Location of primary site (stomach[a] or EGJ)	1.45	0.97	2.17	0.07
Prior gastrectomy (no[a] or yes)	0.97	0.74	1.27	0.83
Treatment line (third[a] or fourth or later)	0.97	0.68	1.37	0.84
Liver metastasis (no[a] or yes)	1.58	1.13	2.21	<0.01
Peritoneal metastasis (no[a] or yes)	2.03	1.43	2.87	<0.01
No. of metastases sites (<2[a] or ≥2)	1.19	0.88	1.60	0.26
Combined score (0[a] or 1,2)	2.08	1.59	2.71	<0.01

CI, confidence interval; EGJ, esophagogastric junction; HR, hazard ratio; OS, overall survival; TTF, time to treatment failure.
[a]Reference.

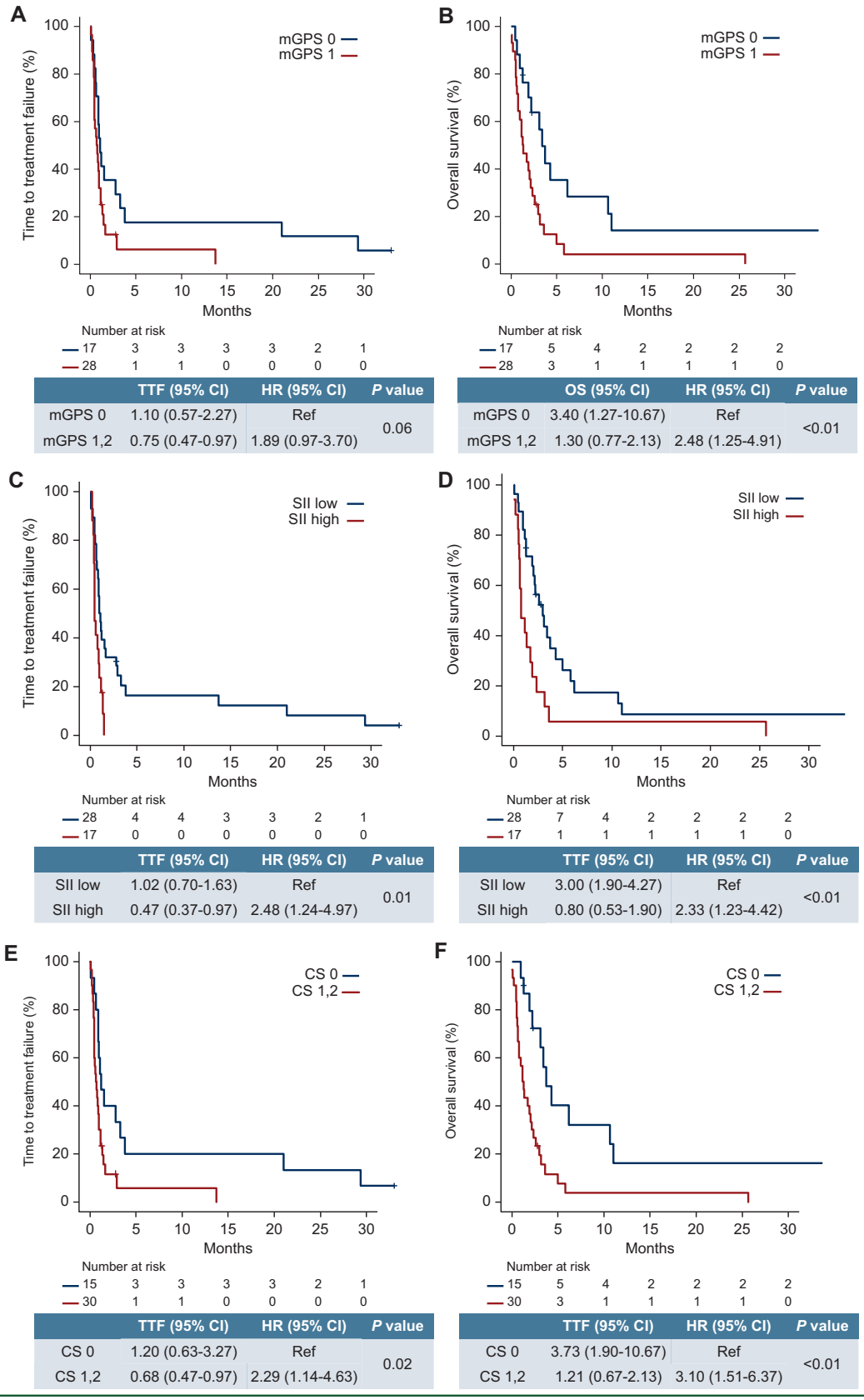
two patients with CS 1 was 2.90 months, while no events occurred in patients with CS 0.

The clinical significance of CS was also confirmed in the first-line cohort and further clarified by adjusting the recalculated cut-offs in the first-line cohort. In the first-line cohort, the rate of subsequent therapy may have an impact on OS. Patients with CS 2 have a shorter TTF and a lower rate of subsequent chemotherapy, and patients with CS 1 have a TTF and rate of subsequent chemotherapy intermediate between CS 0 and 2. As a result, TTF and OS are stratified by CS.

Nakazawa et al. showed that the best response was PD in AGC patients with low albumin levels and high dNLR scores who received nivolumab monotherapy.[7] In a subset analysis of the ATTRACTION-2 phase III trial, the median PFS in patients with high NLR was similar in the nivolumab and placebo groups, with a median value of 1.4 months.[8] These findings indicated that patients with poor nutritional and inflammatory scores may not benefit from nivolumab monotherapy. The current study included a relatively large cohort of patients, some of whom had poor general conditions, such as those classified as having a PS of 2-3, which are often considered borderline chemotherapy indications. This is primarily due to the high prevalence of patients with peritoneal metastases. Notably, CS of 1,2 was associated with significantly poorer clinical outcomes, even in patients with a PS of 2-3, and was an independent prognostic factor for poor outcomes. Patients with PS 2-3 and CS 1-2 had very short TTF and OS, even in the first-line cohort, which was similar to patients in the third- or later-line cohort. Six patients had PS of 2-3 in the first-line cohort, while 45 patients had PS of 2-3 in the third-line or later cohort because of nivolumab monotherapy without chemotherapy. Patients with PS of 3 are generally considered candidates for best supportive care and are typically excluded from clinical trials. However, we believe that data including patients with poor PS in clinical practice are also important. When shared decision making, including the option for best supportive care, was implemented, nivolumab monotherapy without cytotoxic chemotherapy was considered acceptable for some patients with PS of 3 due to its lower toxicity and the potential for a durable response. Therefore, when considering nivolumab treatment for patients with a PS of 2-3, the CS may serve as an important factor in treatment decision making. However, SII, mGPS, and CS were unable to effectively predict HPD, despite HPD being a part of treatment failure. One potential explanation for this discrepancy is that disease progression in patients without target lesions, such as peritoneal metastasis or ascites, is not included in HPD, whereas TTF and FPD include patients without target lesions and clinical PD.

In this study, LIPI alone was not associated with TTF or OS. The difference between the LIPI and other nutritional and inflammatory indices is that the LIPI is calculated using LDH, whereas the others do not include LDH. LIPI has been used to predict the efficacy and prognosis of ICIs in patients with non-small-cell lung cancer (NSCLC).[26,27] High LDH levels are associated with a high tumor burden in NSCLC.[28] However, in AGC, patients with more advanced PD often have peritoneal metastasis and ascites, which do not necessarily correlate with the tumor burden. Peritoneal metastases and ascites are closely associated with cachexia, particularly in AGC.[29,30] However, the relationship between cachexia and tumor burden is complex.[31] There are instances where a correlation between the two is not evident. Therefore, LDH values may not reflect the prognosis of patients with AGC with advanced disease compared with other inflammatory indices. Indeed, it has been reported that LIPI is well correlated with the outcomes of patients with AGC treated with ICIs, including early-line treatment and neoadjuvant chemotherapy.[13,14]

This study has several limitations. Firstly, it was a retrospective study conducted at a single cancer center. Secondly, programmed death-ligand 1 (PD-L1) status was not assessed in this study. An exploratory analysis of the ATTRACTION-2 trial showed that PD-L1 status was not a predictive factor for the efficacy of nivolumab monotherapy. Consequently, in Japan, nivolumab has been approved for use as a third- or later-line treatment, regardless of PD-L1 status. Thirdly, some patients were not evaluated using CT at the time of PD and were evaluated based on clinical symptoms and laboratory data. We included these cases because a real-world analysis would be important. Therefore, the efficacy of short-term treatment was assessed using the definitions of FPD and TTF of ≤1 month including clinical PD, in addition to HPD. Fourthly, tumor mutation burden (TMB) was not evaluated in



	TTF (95% CI)	HR (95% CI)	*P* value
mGPS 0	1.10 (0.57-2.27)	Ref	0.06
mGPS 1,2	0.75 (0.47-0.97)	1.89 (0.97-3.70)	

	OS (95% CI)	HR (95% CI)	*P* value
mGPS 0	3.40 (1.27-10.67)	Ref	<0.01
mGPS 1,2	1.30 (0.77-2.13)	2.48 (1.25-4.91)	

	TTF (95% CI)	HR (95% CI)	*P* value
SII low	1.02 (0.70-1.63)	Ref	0.01
SII high	0.47 (0.37-0.97)	2.48 (1.24-4.97)	

	TTF (95% CI)	HR (95% CI)	*P* value
SII low	3.00 (1.90-4.27)	Ref	<0.01
SII high	0.80 (0.53-1.90)	2.33 (1.23-4.42)	

	TTF (95% CI)	HR (95% CI)	*P* value
CS 0	1.20 (0.63-3.27)	Ref	0.02
CS 1,2	0.68 (0.47-0.97)	2.29 (1.14-4.63)	

	TTF (95% CI)	HR (95% CI)	*P* value
CS 0	3.73 (1.90-10.67)	Ref	<0.01
CS 1,2	1.21 (0.67-2.13)	3.10 (1.51-6.37)	

Figure 2. Kaplan—Meier plots by CS of mGPS and SII in patients with a PS of 2-3. Kaplan—Meier plots of (A) TTF by mGPS, (B) OS by mGPS, (C) TTF by SII, (D) OS by SII, (E) TTF by CS, and (F) OS by CS in patients with a PS of 2-3.
CI, confidence interval; CS, combined score; HR, hazard ratio; mGPS, modified Glasgow prognostic score; OS, overall survival; PS, performance status; SII, systemic immune-inflammation index; TTF, time to treatment failure.

most patients, making evaluation by TMB status difficult. Fifthly, nutritional and inflammatory indices could be affected by previous treatments. However, due to the wide variety of previous treatments and lack of methods to adjust for them, this factor was not considered in this study.

In conclusion, the present study suggests that the CS of mGPS and SII may be more useful for predicting clinical outcomes in patients with AGC treated with nivolumab. Furthermore, the CS is particularly useful for predicting poor short-term outcomes.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The data presented in this study are available from the corresponding author upon request.

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