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The new prognostic score for unresectable or recurrent gastric cancer treated with nivolumab: A multi-institutional cohort study

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Abstract

Background: Real-world outcomes of nivolumab treatment for gastric cancer and associated prognostic factors remain unclear; the present study aimed to evaluate both items.

Methods: A total of 278 consecutive patients treated with nivolumab for gastric cancer during 2017-2019 were enrolled in this multi-institutional retrospective cohort study. The impact of laboratory findings, immune-related adverse events (irAEs), and clinicopathological factors on long-term survival was evaluated using the Cox proportional hazards model.

Results: The response rate was 11.7% in patients with measurable lesions. The overall and progression-free survival estimates were 6.77 and 2.53 months, respectively. The incidence of irAEs was 30.6% (6.8% for grade ≥3). There were no treatment-related deaths. Multivariate analysis revealed that C-reactive protein level of ≤0.5 mg/dL (hazard ratio = 0.476, $P < .001$), irAE occurrence (hazard ratio = 0.544, $P < .001$), albumin level of >3.5 g/dL (hazard ratio = 0.688, $P = .045$), performance status 0 (hazard ratio = 0.711, $P = .028$), lymphocyte count >1000/μL (hazard ratio = 0.686, $P = .027$), and differentiated histological type (hazard ratio = 0.740, $P = .046$) were independently associated with improved survival. The median survival of patients with four or more good prognostic factors was 18.3 months.

Conclusion: Nivolumab showed safety and survival benefits in patients with previously treated unresectable or recurrent gastric cancer. Low C-reactive protein level, irAE occurrence, high albumin level, high lymphocyte count, and differentiated histological type may affect outcomes. The presence of four or more good prognostic factors may help identify likely long-term survivors.

Funding information
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KEYWORDS
antineoplastic agents, adenocarcinoma, immunotherapy, nivolumab, stomach neoplasms

1 | INTRODUCTION

Despite improvements in chemotherapy for unresectable or recurrent gastric cancer (GC), the median overall survival (OS) remains within 11-14 months.[1–4] In the last two decades, while the median OS associated with advanced colorectal adenocarcinoma exceeded 30 months,[5] the development of GC chemotherapy didn't make that much progress. Immune checkpoint inhibitors have been recently introduced for GC and are expected to improve the prognosis of unresectable or recurrent GC in later-line chemotherapy.[6,7]

A randomized phase 3 trial (ATTRACTION-2) has demonstrated a significant survival benefit associated with nivolumab, a humanized IgG4 monoclonal antibody of programmed cell death protein 1 (PD-1), in unresectable or recurrent GC.[7,8] In response, the Japanese gastric cancer treatment guidelines recommend the use of nivolumab in third-line chemotherapy.[9] However, real-world therapeutic effects of nivolumab remain unclear, as do factors associated with prognosis. Herein, we performed a multi-institutional retrospective cohort study aimed at evaluating the real-world therapeutic effects and prognostic factors associated with unresectable or recurrent GC treated with nivolumab.

2 | MATERIALS AND METHODS

2.1 | Study design

Between October 2017 and December 2019, a total of 282 patients with initially unresectable or recurrent GC underwent nivolumab treatment as a later-line chemotherapy across 11 institutions around Tokyo Bay. Four patients with other simultaneous active malignancies were excluded; a total of 278 patients were enrolled in this study.

Data were collected retrospectively. In every case, the tumor was histologically confirmed as adenocarcinoma with distant metastasis using imaging techniques or exploratory laparotomy. Tumor response was assessed using computed tomography, magnetic resonance imaging, and gastroscopy, according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1.[10] Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.0.[11]

2.2 | Treatment

Patients received 3 mg/kg or 240 mg/body nivolumab intravenously every 2 weeks. Nivolumab treatment was continued until the evidence of progressive disease or onset of severe adverse effects were observed by the attending physician. Three patients with initially unresectable distant metastasis underwent conversion surgery after nivolumab treatment. Treatment after discontinuation of nivolumab was determined by the attending physician.

2.3 | Immune-related adverse events

The present study was retrospective, precluding definitive conclusions regarding the relationship between adverse events and nivolumab treatment. Therefore, we defined the following adverse events as immune-related adverse events (irAEs): diarrhea (grade 2 or above), pruritus (any grade), rash (any grade), arthritis (any grade), myositis (any grade), intestinal lung disease (any grade), aspartate aminotransferase level increase (grade 2 or above), alanine aminotransferase level increase (grade 2 or higher), renal disorder (any grade), hypothyroidism (any grade), hyperthyroidism (any grade), adrenal deficiency (any grade), diabetes mellitus (any grade), thrombocytopenia (any grade), myocarditis (any grade), myasthenia gravis (any grade).

2.4 | Statistical analysis

Continuous variables were expressed as median values (interquartile ranges). We measured OS from the start of nivolumab administration to the date of the last follow-up. Progression-free survival (PFS) was measured from the date of nivolumab administration to the date of progressive disease or death. OS and PFS were calculated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. The optimal cut-off values of neutrophil count, lymphocyte count, monocyte count, platelet count, albumin level, and C-reactive protein (CRP) level were determined using receiver operating characteristic curve analyses to predict the survival for 1 year. Univariate and multivariate survival analyses of OS were performed using the Cox proportional hazards regression. Multivariate analysis included covariates with *P*-values of <.05 in univariate analyses. After identifying factors independently associated with improved OS in multivariate analysis, we calculated the prognostic score based on the overall number of prognostic factors present and overall survival time. All statistical analyses were performed using JMP® 13 (SAS Institute Inc). *P*-values of <.05 were considered indicative of a statistically significant difference.

3 | RESULTS

3.1 | Patient characteristics

Table 1 summarizes the demographic and clinical characteristics of 278 patients that received nivolumab treatment. The sample included 185 (66.6%) men, and the median age was 68.5 (interquartile range, 61-74) years. Thirteen (4.7%) patients were diagnosed with Eastern Cooperative Oncology Group Performance Status (PS) 2 when nivolumab treatment was started. There were 133 (47.8%) primary unresectable cases and 145 (52.1%) post-gastrectomy recurrence cases. The most frequent metastatic site was the peritoneum (n = 117, 42.1%). A total of 147 (52.9%) patients had an undifferentiated histological type, and 59 (21.2%) patients were positive for human epidermal growth factor receptor 2. A total of 242 (87.1%) patients had received taxane-based regimens, and 216 (77.7%) patients had received ramucirumab regimens prior to nivolumab administration. Post-treatment, 14 (5.0%) patients continued nivolumab treatment, 104 (37.4%) patients received other regimens, and 160 (57.6%) patients received supportive care.

3.2 | Short-term results

Table 2 summarizes short-term outcomes of nivolumab treatment. Among 163 patients with measurable lesions, 6 (3.6%), 13 (8.0%) and 26 (16.0%) patients showed complete and partial response and stable disease, respectively. The response and disease control rates were 11.7% and 27.6%, respectively. The overall disease control rate was 27.0% (n = 278), and the median number of treatment cycles was four (interquartile range, 3-8).

3.3 | Adverse events

Table 3 summarizes all adverse events associated with nivolumab treatment. The most common adverse event was appetite loss (15.8%). Meanwhile, irAEs occurred in 85 (30.6%, including overlaps) patients. The most frequent irAEs were pruritus (6.8%), hypothyroidism (6.8%), skin rash (5.4%), and renal disorder (2.9%). Intestinal lung disease occurred in seven (0.4%, all grades) patients. Grade 3 or above irAEs occurred in 19 (6.8%) patients. One (0.4%) patient had grade 4 myocarditis, and another (0.4%) patient suffered from myasthenia gravis. There were no treatment-related deaths.

3.4 | Long-term results

The median OS was 6.77 months (95% confidence interval [CI]: 5.33-9.30 months) (Figure 1A). The median PFS was 2.53 months (95% CI = 2.10-2.83 months) (Figure 1B).

TABLE 1 Baseline patient characteristics

Variables	n = 278 (%)
Age	68.5 (61-74)
Sex	
Male	185 (66.6)
Female	93 (33.5)
Eastern cooperative oncology group performance status (ECOG PS)	
0	143 (51.4)
1	122 (43.9)
2	13 (4.7)
Type of cancer	
Primary	133 (47.8)
Recurrence	145 (52.1)
Esophagogastric junction cancer (Siewert type)	
Type 1	6 (2.2)
Type 2	29 (10.4)
Type 3	12 (4.3)
Metastatic site	
Peritoneum	117 (42.1)
Liver	82 (29.5)
Lung	23 (8.3)
Lymph node	89 (32.0)
Pathological type	
Differentiated	130 (46.8)
Undifferentiated	147 (52.9)
Unknown	1 (0.4)
Human epidermal growth factor 2 (HER2) status	
Positive	59 (21.2)
Negative	184 (66.2)
Unknown	35 (12.6)
Number of prior regimens[a]	
≤2	183 (65.8)
3	72 (25.9)
≥4	23 (8.3)
Prior regimens	
Taxane agents	242 (87.1)
Irinotecan	33 (11.9)
Ramucirumab	216 (77.7)
Post nivolumab treatment	
Nivolumab continuation	14 (5.0)
Irinotecan[b]	61 (21.9)
Trifluridine/Tipiracil[b]	25 (9.0)
Taxane agents[b]	6 (2.2)
Other regimens[b]	17 (6.1)
Best supportive care	160 (57.6)

[a]Includes treatments received in the adjuvant setting.
[b]Including overlap.

3.5 | Factors associated with overall survival

The cut-off values of laboratory findings were as follows: neutrophil count of 2850/μL, lymphocyte count of 1000/μL, monocyte count of 400/μL, platelet count of 20×10^4/μL, albumin level of 3.5 g/dL, and CRP level of 0.5 mf/dL, respectively (Figure S1).

Univariate analysis of OS showed that low CRP level, irAEs, high albumin level, PS 0, high lymphocyte count, low platelet count, low neutrophil count, and differentiated histological type were associated with improved OS. However, human epidermal growth receptor 2 status, monocyte count, age, type of cancer (recurrence or primary), number of non-curable factors, sex, number of prior regimens, and prior use of ramucirumab had no impact on OS. Multivariate analysis showed that low CRP level (hazard ratio = 0.476, 95% CI: 0.336-0.675, $P < .000$), irAE occurrence (hazard ratio = 0.544, 95% CI: 0.384-0.770, $P < .001$), high albumin level (hazard ratio = 0.688, 95% CI: 0.478-0.991, $P = .045$), PS 0 (hazard ratio = 0.711, 95% CI: 0.525-0.964, $P = .028$), high lymphocyte count (hazard ratio = 0.686, 95% CI: 0.492-0.958, $P = .027$), and differentiated histological type (hazard ratio = 0.740, 95% CI: 0.550-0.995, $P = .046$) were independently associated with improved OS (Table 4).

OS estimates, stratified by CRP level, irAEs, albumin level, PS, lymphocyte count, and histological type are shown in Figure 2. There were significant differences between groups, as follows: CRP level of ≥0.5 mg/dL and CRP level of <0.5 mg/dL ($P < .001$), irAE "yes" and "no" ($P < .001$), albumin level of >3.5 g/dL and albumin of ≤3.5 g/dL ($P < .001$), PS 0 and PS 1, 2 ($P < .001$), lymphocyte count of >1000/μL and lymphocyte of ≤1000/μL ($P = .004$), and undifferentiated and differentiated histological types ($P = .006$). Except for irAEs, these factors can be assessed ahead of treatment initiation and were thus used to calculate the pre-treatment prognostic score. The median OS was significantly different between pre-treatment prognostic score groups; pre-treatment prognostic scores of 0 (n = 12), 1 (n = 51), 2 (n = 70), 3 (n = 71), 4 (n = 56), and 5 (n = 18) points were

TABLE 2 Summary of response and treatment cycle of nivolumab treatment

Patients with measurable lesions	**n = 163 (%)**
Complete response	6 (3.6)
Partial response	13 (8.0)
Stable disease	26 (16.0)
Progressive disease	115 (70.6)
Not evaluated	3 (1.8)
Overall response rate	19 (11.7)
Disease control rate	45 (27.6)
All patients	**n = 278 (%)**
Disease control rate	75 (27.0)
Median treatment cycles (Interquartile range)	4 (3-8)

TABLE 3 Treatment-related adverse events

	Grade (%)				
Adverse event	**Any**	**1**	**2**	**3**	**4**
Appetite loss	44 (15.8)	26 (9.4)	15 (5.4)	3 (1.1)	0 (0)
Fatigue	42 (15.1)	31 (11.2)	10 (3.6)	1 (0.4)	0 (0)
AST increased	41 (14.7)	30 (10.8)	9 (3.2)	2 (0.7)	0 (0)
Diarrhea	28 (10.1)	22 (7.9)	4 (1.4)	2 (0.7)	0 (0)
Nausea	27 (9.7)	17 (6.1)	8 (2.9)	2 (0.7)	0 (0)
Pruritus	19 (6.8)	15 (5.4)	3 (1.1)	1 (0.4)	0 (0)
Hypothyroidism	19 (6.8)	15 (5.4)	3 (1.1)	1 (0.4)	0 (0)
ALT increased	17 (6.1)	13 (4.7)	3 (1.1)	1 (0.4)	0 (0)
Rash	15 (5.4)	9 (3.2)	5 (1.8)	1 (0.4)	0 (0)
Renal disorder	8 (2.9)	3 (1.1)	4 (1.4)	1 (0.4)	0 (0)
Intestinal lung disease	7 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)	0 (0)
Arthritis	5 (1.8)	2 (0.7)	2 (0.7)	1 (0.4)	0 (0)
Pyrexia	4 (14.4)	2 (0.7)	2 (0.7)	0 (0)	0 (0)
Hyperthyroidism	4 (1.4)	3 (1.1)	0 (0)	1 (0.4)	0 (0)
Diabetes mellitus	3 (1.1)	0 (0)	0 (0)	3 (1.1)	0 (0)
Adrenal deficiency	2 (0.7)	0 (0)	0 (0)	2 (0.7)	0 (0)
Thrombocytopenia	2 (0.7)	1 (0.4)	1 (0.4)	0 (0)	0 (0)
Myocarditis	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)
Myasthenia gravis	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)
Myositis	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0 (0)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

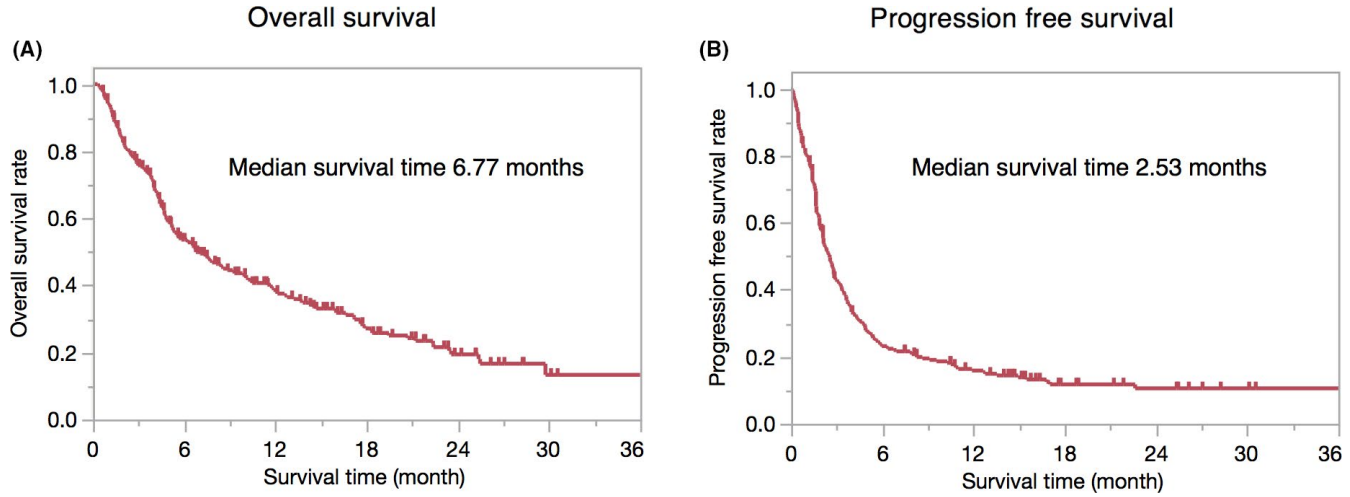

FIGURE 1 Kaplan-Meier curve for overall survival and progression free survival. (A) median overall survival was 6.77 (95% confidence interval of 5.33-9.30) months, (B) median progression-free survival was 2.53 (95% confidence interval of 2.10-2.83) months

associated with OS of 4.7, 2.87, 5.53, 10.1, 17.6, and 22.4 months, respectively ($P < .001$) (Figure 3A). Patients were divided into low (n = 63, score of 0 and 1 points), medium (n = 141, score of 2 and 3 points), and high (n = 74, score of 4 and 5 points) pre-treatment prognostic score groups, obtaining median OS estimates of 2.97, 6.63, and 18.3 months, respectively ($P < .001$) (Figure 3B).

3.6 | Conversion surgery

Among 133 patients with initially unresectable GC, three (2.3%) underwent conversion surgery (Table 5). One patient presented with a grade 3 pathological response and the pre-treatment prognostic score of 4 points. Two patients remained alive for >2 years after conversion surgery without recurrence. One patient died 6 months after conversion surgery due to tumor recurrence.

4 | DISCUSSION

This retrospective multi-institutional study of patients with unresectable or recurrent GC treated with nivolumab as a late-line chemotherapy revealed the median OS and PFS estimates of 6.77 and 2.53 months, respectively. The overall response rate was 11.7%. Low CRP level, irAEs, high albumin level, PS 0, high lymphocyte count, and differentiated histological type were prognostic factors associated with improved OS. We found that the pre-treatment prognostic score, which accounted for all pre-treatment prognostic factors, was significantly associated with OS. To the best of our knowledge, this study is the first to show the pre-treatment prognostic score in unresectable or recurrent GC treated by nivolumab.

The present median OS (6.77 months) and PFS (2.53 months) estimates were relatively higher than those reported by the ATTRACTION-2 trial (corresponding values of 5.26 and 1.61, respectively).[7] This discrepancy might be accounted for by the rates of post-nivolumab chemotherapy, which were comparable overall (34.8% vs 37.4%, respectively), while trifluridine/tiperacil was administered in 25 cases in the present study.[12] As a result, relatively greater survival estimates may have been achieved. Another reason behind this between-study discrepancy in estimates may be sample heterogeneity. The rate of PS 0 patients was significantly higher in our study than in the nivolumab group in the ATTRACTION-2 trial (51.4% vs 29%, $P = .001$). As PS is associated with survival, the good general condition of the present study patients may have resulted in relatively good prognosis. Third, conversion surgery may have affected survival. Two of three patients undergoing surgery survived for >2 years. Conversion surgery may be paramount to the treatment of unresectable GC; surgery during nivolumab treatment may further improve outcomes in patients with a good response.[13,14]

The incidence of irAEs may affect the prognosis of patients with GC treated with nivolumab; in the present study, irAEs were more common than they were in a previous study (30.6% vs 21.5%).[15] This discrepancy may be due to the differences in irAE definitions used. As this was a retrospective study, the relationship between irAEs and nivolumab was difficult to confirm. Although intestinal lung disease, endocrine disorder, skin disease, and neuromuscular disease are specific to immune checkpoint inhibitors, liver enzyme elevation and diarrhea are common adverse events during any kind of systemic chemotherapy. Slight liver enzyme elevation often occurs in patients that were heavily pre-treated with systemic chemotherapy; mild diarrhea often occurs after gastrectomy. Therefore, in the present study, irAEs were defined as grade 2 or higher liver enzyme elevation and diarrhea. Overall, irAEs occurred more frequently in PS 0 patients than in PS 1 or 2 patients (40.6% vs 20.0%, $P < .001$); overall, irAEs were common in the present study. PS has been reported as an important prognostic factor in other malignancies treated with immune checkpoint inhibitors. PS 0 may help predict survival in patients with unresectable or recurrent GC.[16–18]

TABLE 4 Univariate and multivariate analysis of clinicopathological factors for predicting overall survival in the gastric cancer patients who received nivolumab

	Univariate		Multivariate		
Variables	**Hazard ratio**	***P*-value**	**Hazard ratio**	**95% confidence interval**	***P*-value**
C-reactive protein					
≤0.5	0.358	**<.001**	0.476	0.336-0.675	**<.001**
>0.5	1		1		
Immune related adverse events					
Yes	0.501	**<.001**	0.544	0.384-0.770	**<.001**
No	1		1		
Albumin					
>3.5	0.536	**<.001**	0.688	0.478-0.991	**.045**
≤3.5	1		1		
Performance status					
0	0.590	**<.001**	0.711	0.525-0.964	**.028**
1, 2	1		1		
Lymphocyte count					
≥1000	0.631	**.005**	0.686	0.492-0.958	**.027**
<1000	1		1		
Platelet count					
$<20 \times 10^4$	0.636	**.003**	0.851	0.608-1.190	.346
$\geq 20 \times 10^4$	1		1		
Neutrophil count					
≤2850	0.663	**.007**	0.922	0.655-1.298	.643
>2850	1		1		
Histological type					
Differentiated	0.668	**.007**	0.740	0.550-0.995	**.046**
Undifferentiated	1		1		
Human epidermal growth receptor 2 status					
Positive	0.722	.079			
Negative	1				
Monocyte count					
≤400	0.779	.091			
>400	1				
Age					
≥75	0.810	.234			
<75	1				
Type of cancer					
Recurrence	0.859	.301			
Primary	1				
Number of non-curable factors					
2 or more	0.861	.415			
1	1				
Sex					
Male	0.882	.419			
Female	1				

(Continues)

TABLE 4 (Continued)

Variables	Univariate		Multivariate		
	Hazard ratio	*P*-value	Hazard ratio	95% confidence interval	*P*-value
Number of prior regimens					
≥3	0.919	.592			
≤2	1				
Prior ramucirumab					
Yes	0.950	.751			
No	1				

P-values of <.05 were shown in bold type.

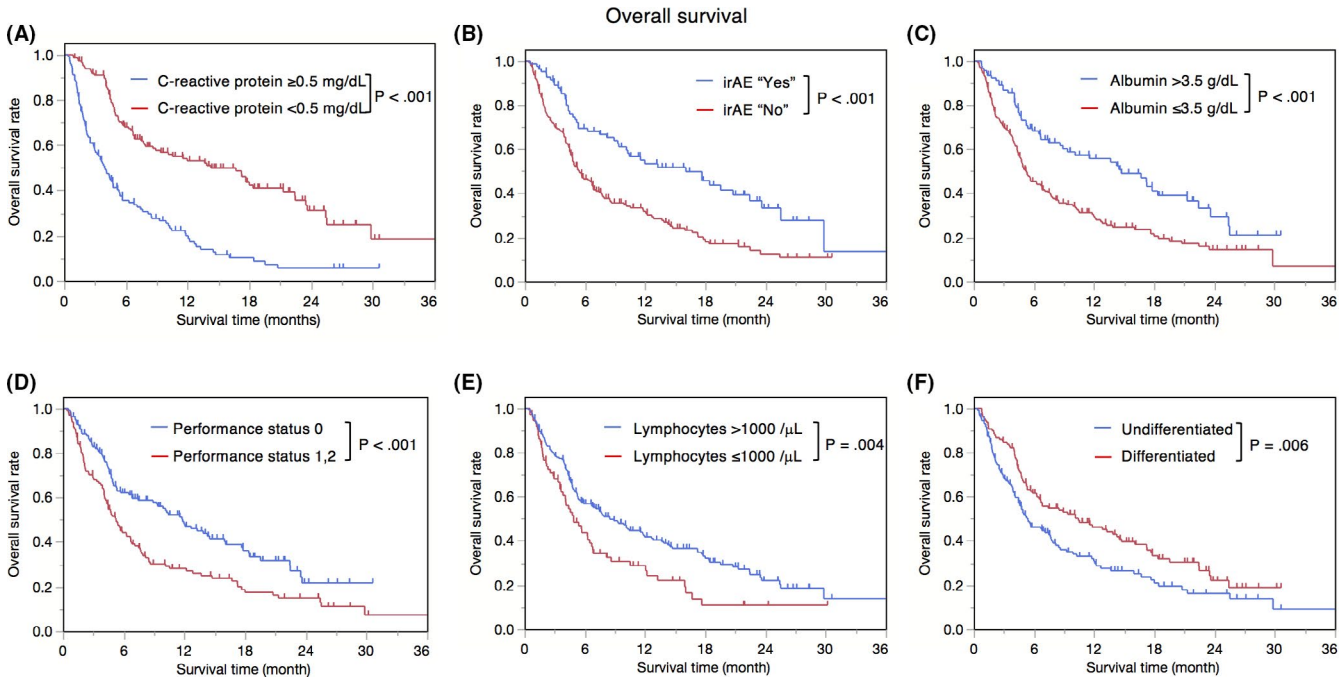

FIGURE 2 Kaplan-Meier overall survival for all registered patients, stratified by C-reactive protein level, immune-related adverse events occurrence, albumin level, performance status, lymphocyte count, histological type. (A) CRP ≥0.5 vs CRP <0.5 (MST (months) 3.93 vs 16.63, $P < .001$), (B) irAE "Yes" vs irAE "No" (MST 16.00 vs 5.37, $P < .001$), (C) Alb >3.5 vs Alb ≤3.5 (MST 14.67 vs 5.20, $P < .001$), (D) PS 0 vs PS 1, 2 (MST 11.77 vs 5.20, $P < .001$), (E) Lym >1000 vs Lym ≤1000 (MST 8.43 vs 4.83, $P = .004$), (F) Undifferentiated vs Differentiated (MST 5.33 vs 10.37, $P = .006$). CRP, C-reactive protein; MST, median survival time; irAE, immune-related adverse event; Alb, albumin; PS, performance status

CRP and albumin levels reflect local and systemic inflammation associated with cancer progression and nutritional status. Namikawa et al demonstrated that GPS, which is a score that combines CRP and albumin levels, is independently associated with survival in patients with GC treated with nivolumab; the present study findings are consistent with those of this previous study.[19] Lymphocytes play a critical role in the host immune response and may suppress cancer progression.[20] Peripheral PD-1 positive CD4 T-lymphocyte count has been associated with PFS in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Peripheral lymphocyte count may be a biomarker of nivolumab treatment efficacy against unresectable or recurrent GC.[21]

Differentiated histological type was another factor independently associated with good survival. The direct relationship between histological type and efficacy of nivolumab treatment remains unclear; however, programmed cell death ligand 1 (PD-L1) expression may account for this suspected link. Yamashita et al reported that the combined positive score—which consists of the number of PD-L1-positive tumor cells, lymphocytes, and macrophages—was significantly higher in patients with the differentiated type than in their counterparts.[22] Hagi et al reported that combined positive score was an independent biomarker for nivolumab treatment efficacy in unresectable or recurrent GC; in the present study, the differentiated type was positively associated with survival.[23]

In the sub-analysis of Japanese patients in ATTRACTION-2 study, patients with prior ramucirumab showed better response rate than those without; however, there were no differences in response rate, disease control rate, OS, and PFS between the two groups in

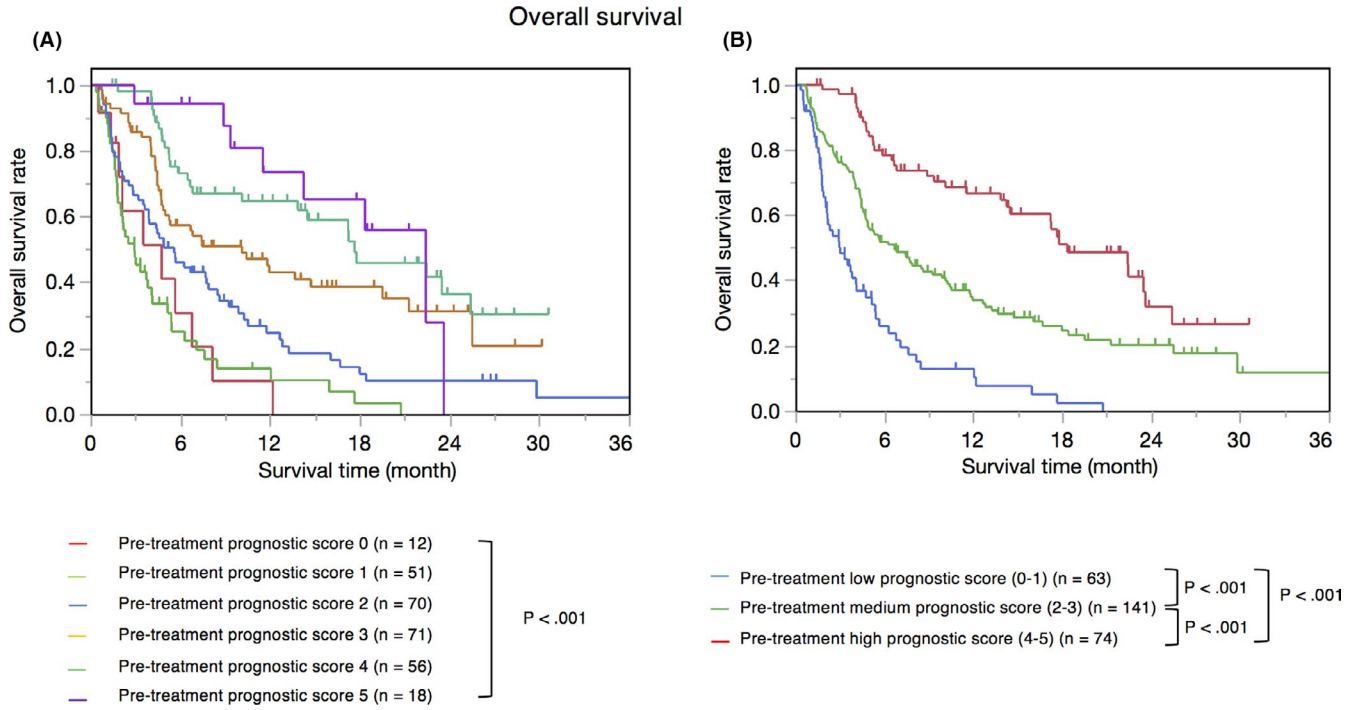

FIGURE 3 Kaplan-Meier overall survival according to pre-treatment prognostic score. (A) Pre-treatment prognostic score 0 (n = 12) 4.7 months, pre-treatment prognostic score 1 (n = 51) MST 2.87 months, pre-treatment prognostic score 2 (n = 70) MST 5.53 months, pre-treatment prognostic score 3 (n = 71) MST 10.1 months, pre-treatment prognostic score 4 (n = 56) MST 17.6 months, pre-treatment prognostic score 5 (n = 18) MST 22.4 months. (B) Pre-treatment low prognostic score (0-1) (n = 63) MST 2.97 months, pre-treatment medium prognostic score (2-3) (n = 141) MST 6.63 months, pre-treatment high prognostic score (4-5) (n = 74) MST 18.3 months. Pre-treatment high prognostic score group showed significantly better OS compared with pre-treatment medium prognostic score group ($P < .001$). Pre-treatment medium prognostic score group showed significantly better OS compared with low pre-treatment prognostic score group ($P < .001$). MST, median survival time; OS, overall survival

the current study (data not shown).[24] These results may be explained by the frequency of prior ramucirumab between the two studies. In the current study, 77.7% of the patients received ramucirumab prior to nivolumab; however, only 22.3% did in nivolumab group of Japanese patients in ATTRACTION-2 study.

In multivariate analysis, the prognostic score was significantly associated with OS (Figure S2). IrAEs were absent before nivolumab treatment; thus, they were not accounted for in the pre-treatment prognostic scores. The high pre-treatment prognostic score group showed relatively good survival, suggesting this approach to prognostication may be useful in clinical practice.

This study has some limitations. First, this was a retrospective study that may have been subject to selection bias. Although 278 patients treated across 11 institutions were included, nivolumab treatment was mainly performed by surgeons; therefore, recurrent cases were frequently observed. Second, irAE occurrence was evaluated retrospectively; therefore, the relationship between nivolumab and the observed adverse events was difficult to confirm. Third, due to the lack of data, the present study did not account for immunohistochemical analysis. Combined positive score and mismatch repair deficiency have been reported as effective efficacy biomarkers for unresectable or recurrent GC treated with nivolumab; therefore, future studies should account for immunohistochemical analysis.[23]

In conclusion, this multi-institutional study revealed real-world therapeutic effects of nivolumab in patients with unresectable or recurrent GC. Low CRP level, irAEs, high albumin level, PS 0, high lymphocyte count, and differentiated histological type may help predict good OS. Patients with the pre-treatment prognostic score of ≥4 points may be suitable for nivolumab treatment as later-line chemotherapy.

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DISCLOSURE

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TABLE 5 The clinicopathological factors of the three cases who underwent conversion surgery after nivolumab treatment

Case	Sex	Age	PS	Metastatic site	Before nivolumab			After nivolumab			Treatment cycles	Survival	Survival time (months)
					cT	cN	Pre-treatment prognostic score	ypT	ypN	ypStage			
1	Male	63	0	Peritoneum, Lung	4b	1	4	0	0	0	17	Alive	27.07
2	Female	65	2	Peritoneum, Lymph node	3	1	1	4b	3a	IV	4	Dead	17.60
3	Male	67	1	Peritoneum	4b	1	2	3	0	IIA	3	Alive	26.17

Abbreviation: PS, performance status.

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Ethics: All procedures in this retrospective study were performed following the ethical standards of each institution's committee on human experimentation and were in compliance with the Helsinki Declaration of 1964 and its later versions. Following personal information protection laws, patients were given an opportunity to opt-out of this study through public announcements published by each institution. The study protocol was approved by the Toho University School of Medicine Institutional Review Board (approval number of the study: A20043_A20007_A19017_A16084). All institutions applied for and obtained study approval from their respective institutional review boards.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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