Inflammation-based prognostic markers in patients with advanced or recurrent gastric cancer treated with nivolumab: Tokushukai REAl-world Data project 02 (TREAD 02)

RAI SHIMOYAMA[1], YOSHINORI IMAMURA[2-4*], KIYOAKI URYU[5], TAKAHIRO MASE[6], MEGU OHTAKI[7], KEIKO OHTANI[7], MEGUMI SHIRAGAMI[8], YOSHIAKI FUJIMURA[8], MAKI HAYASHI[9], NOBUAKI SHINOZAKI[1] and HIRONOBU MINAMI[4,10]

[1]Department of General Surgery, Shonan Kamakura General Hospital, Kamakura, Kanagawa 247-8533, Japan; [2]Cancer Care Promotion Center, University of Fukui Hospital, Eiheiji, Fukui 910-1193, Japan; [3]Department of Hematology and Oncology, University of Fukui Hospital, Eiheiji, Fukui 910-1193, Japan; [4]Department of Medical Oncology and Hematology, Kobe University Graduate School of Medicine, Kobe, Hyogo 650-0017, Japan; [5]Department of Medical Oncology, Yao Tokushukai General Hospital, Yao, Osaka 581-0011, Japan; [6]Department of Breast Surgery, Ogaki Tokushukai Hospital, Ogaki, Gifu 503-0015, Japan; [7]deCult Co., Ltd., Hatsukaichi, Hiroshima 739-0413, Japan; [8]Development Division, Tokushukai Information System Inc., Osaka 530-0001, Japan; [9]Oncology Project Secretariat, Mirai Iryo Research Center Inc., Tokyo 102-0074, Japan; [10]Cancer Center, Kobe University Hospital, Kobe, Hyogo 650-0017, Japan

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Abstract. In addition to blood test data, inflammation-based prognostic markers have been used to predict the prognosis of various types of cancer. However, several of these previous studies may be outdated, as they were conducted prior to the widespread adoption of immune checkpoint inhibitors, leading to limited reports on their efficacy. The present study aimed to assess the accuracy of different inflammation-based prognostic markers in patients with advanced or recurrent gastric cancer undergoing nivolumab monotherapy as salvage-line chemotherapy. In a retrospective cohort study across Japan, a total of 159 patients with advanced or recurrent gastric cancer who were treated with nivolumab between September 2017 and March 2020 were selected. Blood test data were collected within 14 days of the start of chemotherapy and 17 inflammation-based prognostic markers were evaluated. Cox regression analysis was performed using all patient background factors. Subsequently, model selection was performed using backward elimination based on the Akaike information criterion (AIC) to obtain effective background factors which could be assessed for their impact on patient survival. For each marker, the magnitude of the impact on the survival rate, after adjusting for the background factors, was assessed using concordance and AIC analyses. A total of 159 patients (female, 30.2%; median age, 70 years) were included in the present study. Most patients received platinum, fluoropyrimidine and taxane treatment, with a median of three prior lines of systemic therapy. With a median follow-up of 3.3 months (95% CI, 2.5-3.8), median overall survival and time to treatment failure were 3.8 months (95% CI, 3.3-4.5) and 1.8 months (95% CI, 1.8-2.3), respectively. Amongst the 17 markers analyzed, the modified Glasgow prognostic score (mGPS) was classed as the most useful factor that affected the survival rate of patients. Real-world data showed that mGPS, an inflammation-based prognostic marker, had the strongest correlation with prognosis in patients with advanced or recurrent gastric cancer receiving nivolumab monotherapy. The present study was registered as a clinical trial with the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm) under the trial registration number UMIN000050590 on 15th March 2023.

Correspondence to: Dr Yoshinori Imamura, Cancer Care Promotion Center, University of Fukui Hospital, 23-3 Matsuoka-Shimoaizuki, Eiheiji, Yoshida, Fukui 910-1193, Japan
E-mail: yimamura@u-fukui.ac.jp

Abbreviations: AIC, Akaike information criterion; FTD/TPI, Trifluridine/tipiracil; GPS, Glasgow prognostic score; HR, hazard ratio; mGPS, modified GPS; MSI, micro satellite instability; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed death ligand 1; PS, performance status; TMB, tumor mutation burden; TTF, time to treatment failure

Key words: inflammation-based prognostic markers, gastric cancer, nivolumab, real-world data

Introduction

Globally, gastric cancer ranks fifth in terms of cancer incidence and fourth in terms of mortality (1) and it is the second most common cancer and third highest cause of deaths for patients with cancer in Japan (2). Although the 5-year survival rate for

all patients is >60%, the prognosis for patients with recurrent or metastatic disease remains poor, with a median overall survival (OS) of 6-13 months (2,3).

Immune checkpoint inhibitors have become the standard treatment option for recurrent or metastatic gastric cancer (4,5). Nivolumab is a fully humanized antibody drug active against programmed cell death-1 (PD-1). Nivolumab treatment increased survival in patients participating in the ATTRACTION-2 trial, which included placebo-controlled patients with advanced or recurrent gastric cancer who experienced standard second-line treatment failure (6). Nivolumab monotherapy was approved for use in Japan in September 2017 and was subsequently recommended as a third-line therapy for gastric cancer. (4,5). Trifluridine/tipiracil (FTD/TPI) was introduced as a salvage-line treatment option in August 2019 in Japan (7,8). Currently, nivolumab in combination with platinum and fluoropyrimidine is recommended as the first-line treatment for *HER2*-negative patients with gastric cancer based on the results of the CheckMate 649 and ATTRACTION-4 trials, following its approval in Japan in November 2021 (5,9,10).

Predicting the efficacy of immune checkpoint inhibitors is an important clinical challenge currently being explored. The Checkmate 649 and ATTRACTION-4 trials reported that programmed death ligand 1 (PD-L1) expression levels in tumor cells and tumor-associated immune cells, also known as the combined positive score, correlated with patient prognosis (9,10). However, the results from the ATTRACTION-2 trial, which evaluated nivolumab monotherapy as a third-line treatment, reported that PD-L1 expression did not correlate with patient prognosis (6). Pembrolizumab, a PD-1 antibody similar to nivolumab, has shown clinical benefits in solid tumors, including gastric cancer cases with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors, as well as those with high tumor mutation burden (TMB-H) (11-13). However, MSI-H/dMMR and TMB-H are relatively uncommon in gastric cancer, occurring in 6.7 and 5.2% of cases, respectively (14,15) Other therapeutic strategies, such as chemotherapy, also target the inflammatory micro-tumor environment, which suggests that the inflammatory micro-tumor environment may be a predictor of patient response to treatment with immune checkpoint inhibitors (16).

Several types of inflammation-based prognostic markers, based on a combination of blood-based parameters, have been studied for their association with clinical outcomes in patients with various types of cancer, including gastric cancer (17,18). In patients with cancer treated with immune checkpoint inhibitors, serum albumin levels (19), the Glasgow prognostic score (GPS) (20), neutrophil-lymphocyte ratio (NLR) (21) and lung immune prognostic index score (21,22) have been reported to be useful in predicting prognosis. These inflammation-based prognostic markers are readily accessible; however, numerous markers are in disarray, and it is unclear which markers should be prioritized in clinical decision making, particularly when using immune checkpoint inhibitors (23-38). In addition, while prognostic tools, such as the lung immune prognostic index (LIPI), have been developed in the era of immune checkpoint inhibitors (37), it has not been thoroughly reported whether they are superior to other existing markers.

Real-world data are the routine accumulation of specific information on patient health status and treatment through established mechanisms, such as the acquisition of electronic medical records (39). Although there are limitations in regard to the use of this type of data, due to incomplete datasets and heterogeneity in patient backgrounds, their utility in bridging the gap between clinical trials and routine clinical practice has been previously reported (40-44). The Tokushukai Group is the largest medical corporation in Japan and includes 75 hospitals. As all the hospitals in the Tokushukai Group use electronic medical records and are connected by a closed network, it is possible to simultaneously collect information from all of these hospitals. The present real-world clinical study aimed to utilize data from the Tokushukai Group medical database to assess and compare correlations between inflammation-based prognostic markers reported in patients with advanced or recurrent gastric cancer who received nivolumab monotherapy.

Materials and methods

Ethical approval and clinical trial registration. The Tokushukai Real-World Data project is a nationwide retrospective cohort study conducted across the Tokushukai Medical Group hospitals in Japan. It encompasses 46 hospitals equipped with a chemotherapy protocol system and Diagnosis Procedure Combination, totaling ~15,000 beds. The methodology of the present study has been outlined in our previously published study (45). The present protocol adhered to ethical guidelines for medical and biological research involving human subjects in Japan (46), as well as the principles of the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024) and was registered with the UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm) under the trial registration number UMIN000050590 on 15th March 2023. Patients were informed about the present study using the opt-out patient consent method.

Patients. The present study evaluated patients with pathologically or radiologically confirmed advanced or recurrent gastric cancer who were treated with nivolumab monotherapy as a late-line chemotherapy, at Tokushukai Medical Group hospitals using the same medical record system (e-Karte; version 2.2 and Newtons2; version 2.2; Software Service Inc.) and chemotherapy protocol system (srvApmDrop; version 3.0.522; Software Service Inc.), between September 1, 2017 and March 31, 2020.

Patients with histological diagnoses other than adenocarcinoma were excluded from further analysis. Additional key exclusion criteria were the presence of active secondary cancer, inadequate treatment history and missing fundamental patient data, such as body weight and height.

Data collection. The present study evaluated eligible patients identified using electronic medical record data. Patient information, such as age, sex, body height, body weight, body surface area, BMI, Brinkman Index and the latest data on confirmation of survival or death (registration of survival or death in the electronic medical record), survival outcomes and

diagnosis on medical receipt, which is a document that outlines the medical treatments received, costs incurred and insurance coverage applied in Japan, were extracted from the medical record system. Blood test data within 14 days of nivolumab treatment initiation were extracted from the electronic medical records. Information related to previous chemotherapy regimens, the start and end dates of chemotherapy and Eastern Cooperative Oncology Group performance status (PS) score (on a scale of 0-5, with higher scores indicating greater disability) were extracted from the chemotherapy protocol system. The linked cancer registry information, including diagnostic information (tumor site, pathology and stage), treatment details (surgery, endoscopic procedure, radiotherapy and systemic therapy) and prognosis (final date of survival confirmation, date of death and cause of death) were extracted from the National Cancer Registry Data of Japan (2,47). The date of the last confirmed survival was extracted from both the cancer registry and electronic medical records and the later date was used. Patients with an inadequate treatment history, such as previous or subsequent cancer treatment outside of Tokushukai Medical Group hospitals or whose records reported no detailed treatment information, were excluded from the study. Patients with missing laboratory data were also excluded.

Statistical analysis. Basic statistics, such as absolute and relative frequencies for categorical variables, maximum and minimum values and medians for continuous and discrete variables, were obtained to summarize the distribution of variables related to patient background factors, complications and other prognostic factors.

The primary endpoint evaluated in the present study was OS, which was defined as the time from the date of nivolumab treatment initiation to the date of death or final survival confirmation. Censored cases included patients who were alive at the study end-date or dropped out of the study for any reason. The secondary endpoint was time to treatment failure (TTF), which was defined as the duration from the start of nivolumab treatment to discontinuation of the treatment for any reason. For each prognostic marker tested, Kaplan-Meier curves for the occurrence of events associated with the study endpoint were obtained and log-rank and chi-squared tests were performed.

Cox regression analysis was performed using all prognostic factors at the start of nivolumab treatment (such as age, sex, BMI, Brinkman Index, PS, location of the primary site, stage, histology, HER2 status, previous surgery and previous radiotherapy) to examine their degree of impact on OS. Estimated hazard ratios (HRs) and 95% CI for each prognostic factor in association with OS were calculated using univariate and multivariate analyses. Subsequently, variable selection was performed using the Akaike information criterion (AIC) to identify useful background factors. A total of 17 inflammation-based prognostic markers were evaluated (Table SI). For each of these markers, the impact on the survival rate, after adjusting for background factors, was compared using concordance and AIC analyses. The concordance and AIC of each marker on TTF were also examined.

Survival analyses were performed using OS and TTF. A stratified Cox proportional model was used to obtain adjusted Kaplan-Meier survival curves for each prognostic marker, and its significance was obtained using a likelihood ratio test.

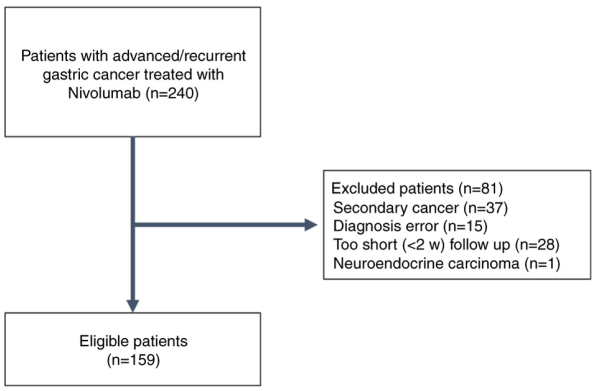


Figure 1. Flow chart of the patient recruitment and enrollment process in the present study. W, weeks.

The null hypothesis was that the item was not involved in the goodness-of-fit of the model.

All analyses were performed using R (version 4.2.2; R Foundation for Statistical Computing). All statistical assessments were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. The present study was an exploratory study and did not consider multiplicity.

Results

Patient characteristics. According to the aforementioned protocol, a total of 240 patients were identified, of whom 159 met the inclusion criteria (Fig. 1; Table SII). Of the patients included in the present study, 25% were aged >75 years and almost 60% had primary metastatic cancer. Most patients received platinum, fluoropyrimidine and taxane treatment, with a median of three prior lines of systemic therapy (Table SIII).

Survival. The OS and TTF were calculated using Kaplan-Meier curves (Fig. 2). The median follow-up period was 3.3 months (95% CI, 2.5-3.8) and the median OS and TTF were 3.8 months (95% CI, 3.3-4.5) and 1.8 months (95% CI, 1.8-2.3), respectively. The 1- and 2-year survival rates were 19.5% (95% CI, 13.0-29.2) and 15.6% (95% CI, 8.6-28.3), respectively. Sequential systemic therapy was administered in 21.4% of patients, which included taxanes (11.9%) and irinotecan (5.7%) (Table SIII). None of the patients received FTD/TPI.

Cox regression analyses. Cox regression analyses demonstrated that no factors that significantly affected patient prognosis were identified in the univariate analysis (Table SIV). As a substantial proportion of patient data were not available (N/A), excluding these data could have affected the accuracy of the analysis. Therefore, N/A data was treated as a separate treatment group and included in the analyses.. The multivariate analysis showed an improved prognosis in patients who had received prior radiation therapy (HR, 0.22; 95% CI, 0.05-0.98). Age, sex, tumor location, tumor stage and previous radiotherapy treatment were selected as adjusting factors based on AIC criterion.

Comparison of markers. The concordance and AIC of the markers tested were analyzed after adjusting for background

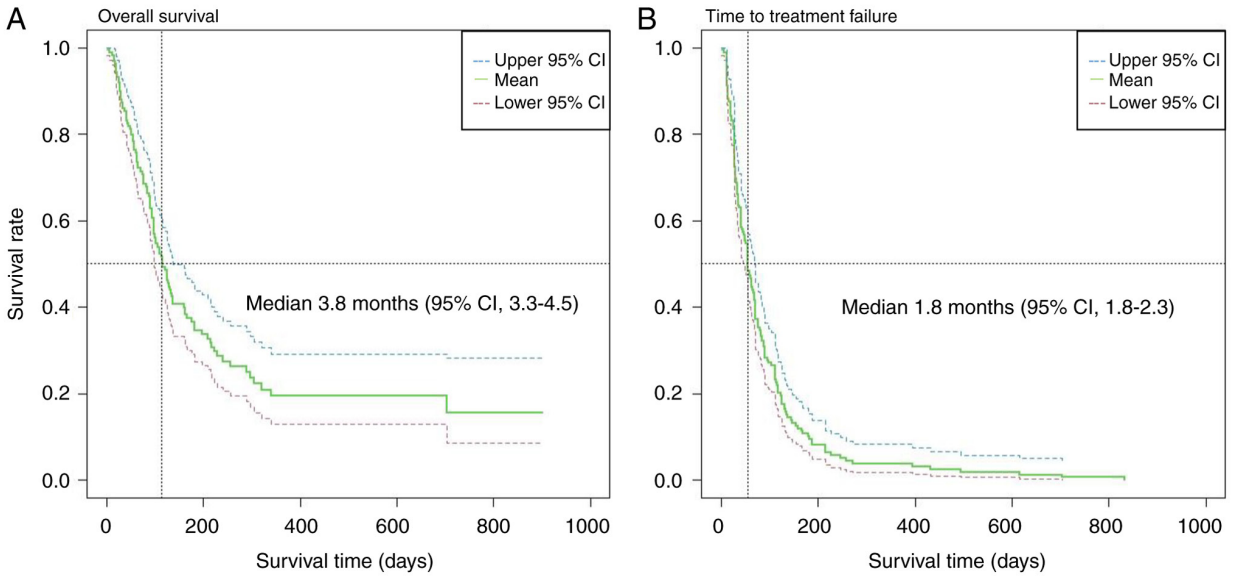


Figure 2. Kaplan-Meier curves. (A) overall survival and (B) and time to treatment failure.

factors, such as age, sex, tumor location, tumor stage and previous radiotherapy, in relation to both OS (Fig. 3; Table SV) and TTF (Fig. S1; Table SVI). Most of the markers tested demonstrated a significant correlation with patient prognosis. The marker modified GPS (mGPS) showed the strongest correlation with prognosis, followed by GPS, which also exhibited a dose-response relationship. The Cox model involving mGPS showed the highest concordance and lowest AIC among all of the markers analyzed. The marker that demonstrated the highest correlation with TTF was also mGPS.

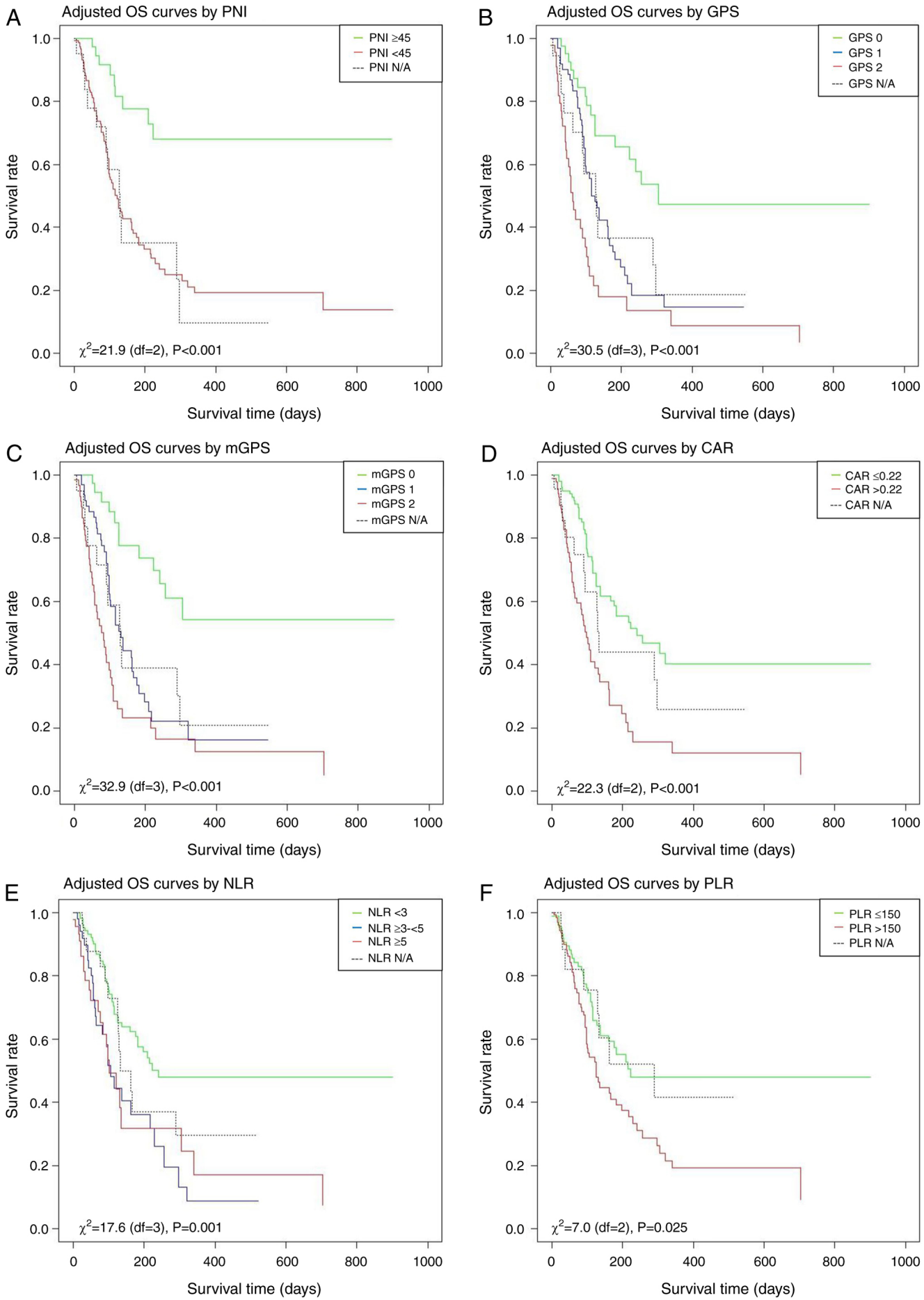
Discussion

The present study investigated the outcomes of late-line nivolumab monotherapy in patients with advanced or recurrent gastric cancer. The main aim of the present study was to analyze 17 inflammation-based prognostic markers to identify factors that correlated best with prognosis, thereby potentially contributing to the future use of prognostic factors in clinical practice. These findings demonstrated that mGPS exhibited the most robust correlation with prognosis among the markers assessed, which was consistent with our previous study in patients with chemotherapy-naive metastatic pancreatic cancer (48). A strength of the present study was the simultaneous evaluation of real-world data for the presence of various inflammation-based markers in patients with advanced or recurrent gastric cancer in the era of immune checkpoint inhibitors. While previous studies have examined the accuracy of similar markers (32,33), the present study included and compared novel markers whenever possible. In addition, many of the markers were reported prior to the use of immune checkpoint inhibitors, and the efficacy of the markers in treatment with immune checkpoint inhibitors was unclear.

In the ATTRACTION-2 trial, the median progression-free survival and median OS for nivolumab as third-line treatment were reported to be 1.6 and 5.3 months, respectively (6). The 1- and 2-year survival rates were 27.3 and 11.6%, respectively (49). In the present study, the median OS was 3.8 months, with 1- and 2-year survival rates of 19.5 and 15.6%, respectively. The trends observed between these two studies were similar; however, differences in the outcomes reported in clinical trials may be attributed to variations in patient characteristics and backgrounds between controlled trials and real-world clinical practice. For example, the median age was 62 years in the ATTRACTION-2 trial, compared with 70 years in the present study. In addition, patients were limited to PS 0 and 1 in the ATTRACTION-2 study, whereas 12.6% of the patients in the present study had PS 2. In the ATTRACTION-2 trial, 35.0% of the patients received subsequent systemic therapy, compared with 21.4% in the present study. Thus, patient conditions, including performance status and comorbidities, were often poorer in actual clinical practice compared with in clinical trials. Therefore, median OS in the present study may have been shorter compared with that reported in clinical trials. However, these findings suggest that the results of the present study reflected actual clinical practice (6).

In the present analysis, the only prognostic factor that remained in the multivariate analysis was prior radiotherapy treatment. The synergistic effects of radiotherapy and immune checkpoint inhibitors has previously been reported in preclinical studies (50,51). In addition, prior radiation therapy has been reported to be an independent prognostic factor in patients treated with nivolumab for non-small cell lung cancer (52). Potential synergistic mechanisms have been proposed between radiotherapy and immune checkpoint inhibitors, with several key factors contributing to this synergy. These include increased tumor immunogenicity, enhanced infiltration of T cells into tumors and reversal of immune suppression within the tumor microenvironment (53). In the present study, prior radiotherapy had a protective effect in patients with gastric cancer receiving nivolumab.

Among the 17 inflammation-based prognostic markers analyzed, mGPS and GPS were most effective in predicting outcomes in patients with gastric cancer undergoing nivolumab treatment. The mGPS scores used in the present study were



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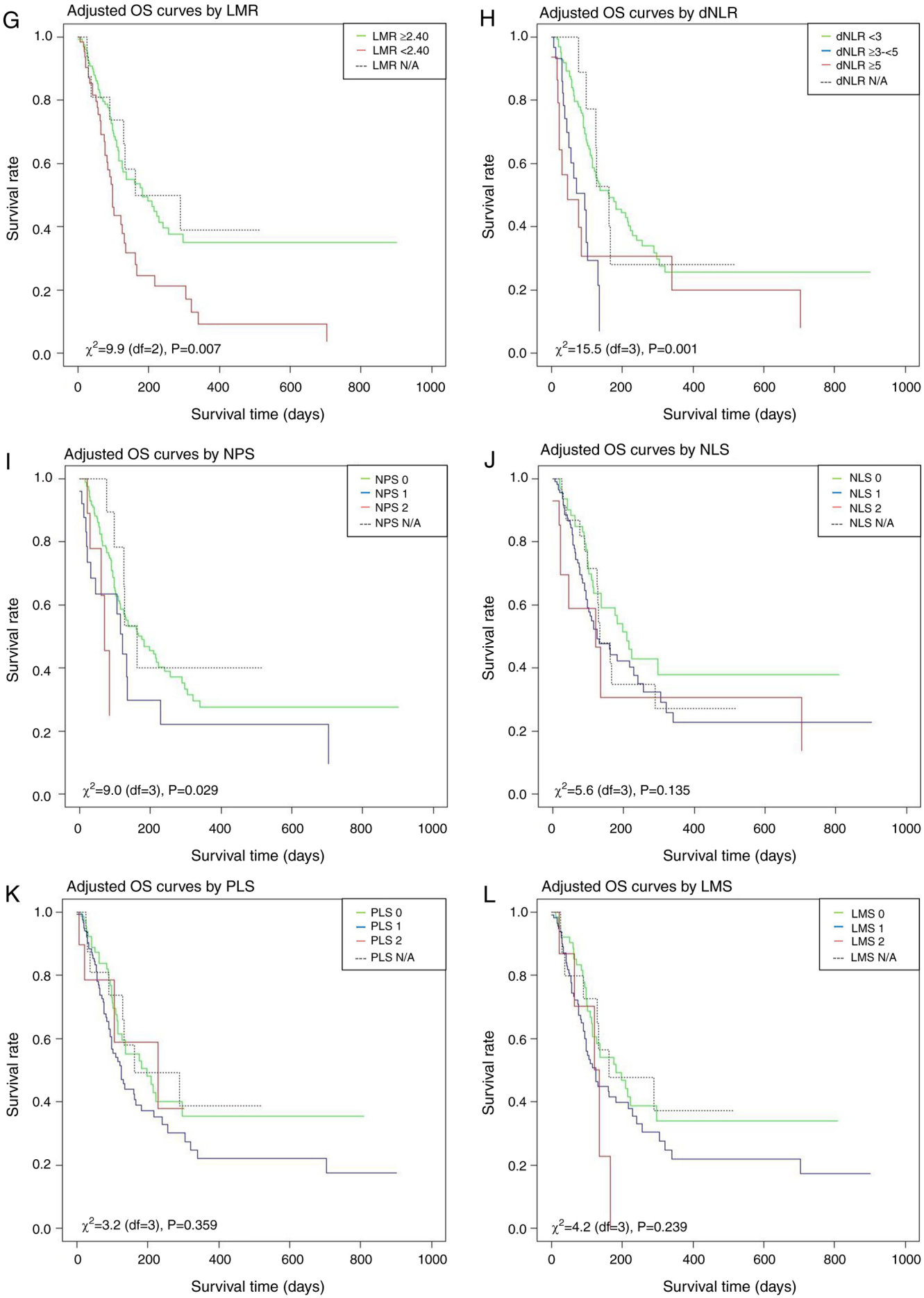

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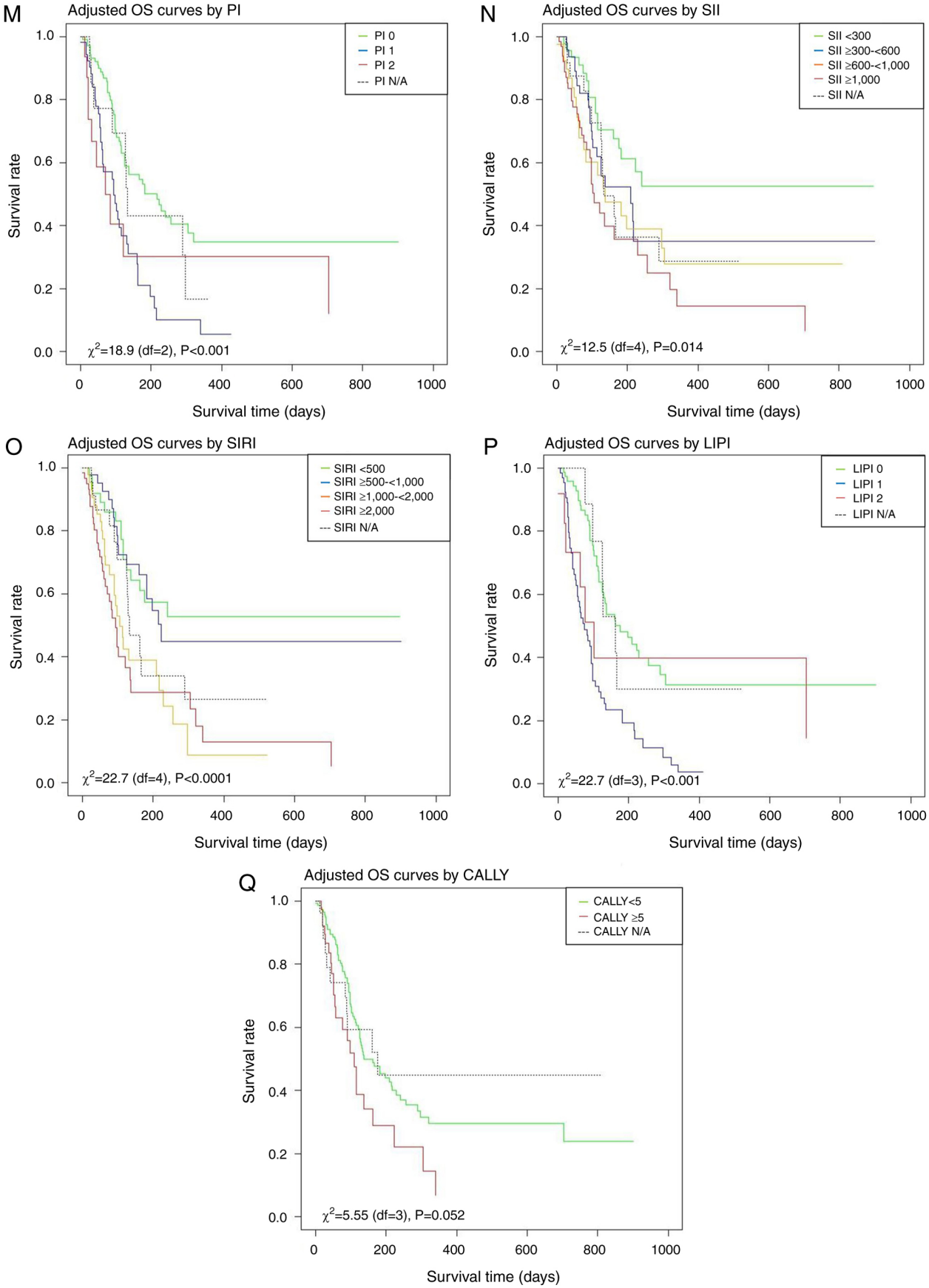

Figure 3. OS based on different scores and ratios. A log-rank test was used to calculate statistical significance. (A) PNI, (B) GPS, (C) mGPS, (D) CAR, (E) NLR, (F) PLR, (G) LMR, (H) dNLR, (I) NPS, (J) NLS, (K) PLS, (L) LMS, (M) PI, (N) SII, (O) SIRI, (P) LIPI and (Q) CALLY. CRP, C-reactive protein, df; degrees of freedom; OS, overall survival; PNI, prognostic nutritional index; GPS, Glasgow prognostic score; mGPS, modified GPS; CAR, CRP-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; dNLR, derived NLR; NPS, neutrophil-platelet score; NLS, neutrophil-lymphocyte score; PLS, platelet-lymphocyte score; LMS, lymphocyte-monocyte score; PI, prognostic index; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; LIPI, lung immune prognostic index; CALLY, CRP albumin lymphocyte index.

obtained from Japan, where the cutoff value for C-reactive protein was reduced from 1.0-0.5 mg/dl. In a previous study, receiver operating characteristic curves for serum C-reactive protein (CRP) and albumin were generated to calculate the diagnostic cutoff point at which survival could be most accurately assessed (25). The results showed that CRP had a sensitivity of 79.5% and specificity of 51.1% when the cutoff value was set at 0.5 mg/dl, and albumin had a sensitivity of 80.7% and specificity of 36.7% when the cutoff value was set at 3.5 mg/dl. In the present study, the mGPS had a HR of 3.28 (95% CI, 1.68-6.38) for score 1 and a HR of 5.60 (95% CI, 2.90-10.80) for score 2, which indicated that the HR increased with increasing mGPS score. Similar associations were shown between GPS, HR and mGPS. The utility of the GPS for predicting patient prognosis has been previously reported. In the early 2010s, the Glasgow Inflammation Outcome study examined the utility of the GPS and reported its success compared with various biochemical tests and other major inflammation-based prognostic markers, including the NLR (54-56). In addition, in a previous systematic review, GPS was identified as an independent prognostic factor in various types of cancers, both operable and inoperable (57,58). However, the evidence showing that GPS is superior to other markers is primarily based on operable cases from the 2010s. Therefore, to date, there has not been sufficient investigation into its effectiveness in inoperable cancers treated with immune checkpoint inhibitors. The present study demonstrated that GPS was useful in patients receiving immune checkpoint inhibitors, and that the mGPS developed in Japan is as useful as conventional GPS.

Notably, LIPI is a novel indicator that has shown usefulness for predicting prognosis in patients treated with immune checkpoint inhibitors (37). In the present study, LIPI ranked fourth among 17 markers in terms of concordance and AIC; however, it did not surpass mGPS or GPS. LIPI was initially developed for lung cancer and has been validated through a previous meta-analysis (59). Additionally, it has shown prognostic value in metastatic renal cell carcinoma (60). However, its applicability to other types of cancer, such as gastric cancer, has not yet been reported. Nonetheless, the comprehensive comparison of these markers in the era of immune checkpoint inhibitors, as conducted in the present study, provided important insights that showed GPS as most useful prognostic marker, out of the 17 analyzed. The findings of the present study, which indicated that mGPS and GPS were the most accurate predictors of prognosis in patients with advanced or recurrent gastric cancer receiving nivolumab monotherapy, were consistent with previous reports prior to the era of immune checkpoint inhibitors (32,33). These markers could potentially be used as prognostic tools in routine clinical practice in the future.

The present study had a number of limitations. First, although the study was designed to examine prognostic factors in late-line nivolumab treatment, the results were of limited value in clinical practice because nivolumab is now often used as first-line therapy in patients with HER2-negative gastric cancer. Therefore, the usefulness of this marker in patients receiving concomitant chemotherapy as first-line therapy would necessitate a separate study. Second, the present study did not provide PD-L1 expression data because its utility in a late-line setting has not yet been reported and it is not typically measured in clinical practice (6). MSI, MMR and TMB status were also unavailable, as testing for these factors is not mandatory prior to drug administration (5). Therefore, the association between these status and inflammatory markers could not be analyzed. Third, several patient records did not show blood test results for C-reactive protein and albumin levels, which are not essential for chemotherapy induction. Accordingly, the full-set analysis included fewer patients than the total number of patients enrolled, which resulted in a moderate sample size being included in the final analyses. Finally, data on concomitant medications, including steroids and immunosuppressive drugs, which could affect the inflammatory markers tested, were not collected in the present study. This was due to the present study's moderate sample size of 159 patients, which limited the ability to assess the impact of the presence or absence of such relatively infrequently used concomitant medications. Despite these limitations, the comprehensive assessment of multiple inflammation-based prognostic markers for immune checkpoint inhibitor monotherapy using real-world data could be considered clinically valuable. Although the results of the present study may not significantly impact the choice of treatment regimen, these markers are useful for predicting patient prognosis with immune checkpoint inhibitor treatment, similar to their role with conventional cytotoxic anticancer drugs. These results may also help clinicians to navigate decisions on treatment adjustments for patients with advanced or recurrent gastric cancer.

In conclusion, the present study analyzed real-world data and demonstrated a strong prognostic value of various inflammation-based markers in patients with advanced or recurrent gastric cancer, treated with nivolumab as late-line chemotherapy. mGPS exhibited the most robust correlation with patient prognosis. Future studies should aim to collect and analyze data to assess the potential utility of these inflammatory markers for first-line treatment and preoperative treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RS, YI and MO contributed to study design and conception. RS, YF, MS and MH performed data acquisition. RS, YI and

MS confirm the authenticity of all the raw data.RS and YI interpreted data and drafted the manuscript. KU, TM, KO, NS and HM offered advice on the research design and contributed to the interpretation of the study content. NS and HM reviewed and approved the final version of the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

The project rigorously followed ethical guidelines for medical and biological research involving human subjects in Japan, in accordance with the principles of The Declaration of Helsinki. Approval for the study was obtained from the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024). The study was registered in the UMIN Clinical Trial Registry under the number UMIN000050590. Patients were informed about the study using opt-out methods and all chose to participate.

Patient consent for publication

Not applicable.

Competing interests

RS received speaker bureau fees/honoraria from Daiichi-Sankyo, Ono Pharm, Taiho Pharma and Chugai outside the scope of the submitted work. YI received speaker bureau fees/honoraria from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer and Ono Pharm outside of the submitted work. HM received speaker bureau fees/honoraria from Daiichi-Sankyo and Ono Pharm, research funding from Astellas-Amgen Biopharma, Bayer, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Incite, Novartis, Ono Pharm, Pfizer and Rakuten Medical and scholarship donations from Bayer, Chugai, Daiichi-Sankyo, Eisai, Kyowa-Kirin, Lilly, Ono Pharmaceutical, Pfizer, Taiho Pharma and Takeda outside the scope of the submitted work. However, these organizations were not involved in the design, conduct or reporting of the present study.

Authors' information

ORCID IDs: RS, 0000-0001-8601-0442; YI, 0000-0002-5202-531X; and HM, 0000-0001-8630-9145.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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