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Neutrophil-to-lymphocyte ratio and risk of disease progression in patients with nivolumab-treated unresectable or recurrent gastric cancer

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Abstract. Studies have associated neutrophil-to-lymphocyte ratio (NLR) with overall survival (OS) and progression-free survival (PFS) in patients with gastric cancer (GC). The present study aimed to examine the relationship between dynamic changes in NLR during treatment and disease progression in patients with unresectable or recurrent GC treated with nivolumab monotherapy as a third-line or later regimen. Patients treated with nivolumab as a third-line or later therapy for unresectable or recurrent GC at Gifu University Hospital (Gifu, Japan) from April 2017 to December 2021 were included. Pretreatment data and those obtained every 2 weeks after the treatment commenced were evaluated. The association between all NLR values and disease progression for each patient was evaluated using a time-dependent Cox proportional hazards model and restricted cubic spline (RCS) curves. The study included 44 patients (23 men and 21 women). The response and disease control rates were 6.8 and 27.3%, respectively. The median PFS and OS of all patients were 1.84 months [95% confidence interval (CI), 1.32-2.14] and 5.93 months (95% CI, 3.75-10.75), respectively. The risk for progressive disease (PD) increased with higher NLR (hazard ratio, 2.25; 95% CI, 1.3-3.87). The RCS curves also indicated that the higher the NLR, the higher the risk for PD, especially if the NLR value was <3.0. NLR during treatment could predict the risk of PD, suggesting that NLR could be integrated with tumor markers, computed tomographic images and other modalities to enable treatment selection without delay.

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Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; GC, gastric cancer; RCS, restricted cubic spline; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ICI, immune checkpoint inhibitor

Key words: neutrophil-to-lymphocyte ratio, gastric cancer, nivolumab

Introduction

Nivolumab, a human immunoglobulin G4 monoclonal antibody against the immune checkpoint molecule programmed death-1 receptor, has demonstrated efficacy and safety in the treatment of a variety of cancer types (1-4). In 2017, the ATTRACTION-2 trial showed that nivolumab treatment significantly improved overall survival (OS) as a third-line or later therapy for unresectable or recurrent gastric cancer (GC) (5). In 2021, the combination of nivolumab and chemotherapy as a first-line therapy for HER2-negative unresectable or recurrent GC showed significantly improved progression-free survival (PFS) and OS in the CheckMate649 trial (6) and significantly improved PFS in the ATTRACTION-4 trial (7). Hence, nivolumab plus chemotherapy is one of the recommended first-line therapies; moreover, nivolumab monotherapy remains the recommended third-line or later therapy for HER2-negative unresectable or recurrent GC (8-10).

Evaluation of tumor activity during systemic chemotherapy is mainly conducted with tumor markers and computed tomography (CT) examination. Increased tumor markers correlate with increased tumor burden; however, depending on the histologic type, tumor markers may be negative or not elevated until the late phase of the disease course (11). CT imaging evaluation is performed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and is based on the objective assessment of changes in tumor size in solid tumors (12). Conversely, in unresectable

or recurrent GC, nonmeasurable lesion, such as peritoneal dissemination, is often observed. This made it important to comprehensively evaluate the clinical findings, hematologic data, and other imaging examinations, such as esophagogastroduodenoscopy, to evaluate the response of the primary lesion (13). Newer indicators that could be evaluated easily, less invasively, and reproductively could help in the evaluation of tumor progression and activity.

The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, reportedly reflects the systemic inflammatory response associated with cancer progression, invasion into surrounding tissues, and metastasis to distant organs (14). Higher pre-treatment NLR or increased NLR during treatment has been reported to worsen OS and PFS in patients with unresectable or recurrent GC on nivolumab monotherapy (14-17). Ogata *et al* (17). reported that advanced gastric cancer patients with NLR <5 had significantly longer median OS and PFS than did those with NLR >5 2 weeks after the first dose of nivolumab. Furthermore, Ota *et al* (14). reported that an increase of ΔNLR60, the NLR at 60 days after the first dose of nivolumab minus the NLR value prior to treatment initiation, of ≥2 was associated with significantly decreased OS. In previous reports, prognosis was predicted by the NLR value at a certain point in time. In other words, it is difficult to predict future clinical courses based on the NLR value at the time of examination and the amount of change. Therefore, whether the NLR can be a predictor of the timing of disease progression is a clinical question, and there are no reports on this subject. Moreover, there are few data on the correlation between NLR and immune checkpoint inhibitor (ICI). This study aimed to examine the relationship between dynamic changes in NLR during treatment and disease progression in patients with unresectable or recurrent GC treated with nivolumab monotherapy.

Materials and methods

This retrospective observational study was approved by the Institutional Review Board of Gifu University Hospital (approval numbers:2021-B185) and was conducted in compliance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. Informed consent was obtained in the form of opt-out on the web-site. Those who did not provide consent were excluded.

The medical records of patients treated at Gifu University Hospital were obtained and retrospectively analyzed. Patients with unresectable or recurrent GC who received nivolumab monotherapy in third-line or later between April 2017 and December 2021 were identified from the database. The patients received standard doses of nivolumab 3 mg/kg or 240 mg/body intravenously over 30 min every 2 weeks until disease progression, unacceptable toxicity, or the patient refused to continue treatment. There was no concomitant use of antiemetic drugs or steroids as part of the regimen.

To evaluate the association between NLR changes and disease condition during treatment with nivolumab, tumor response was evaluated using RECIST v1.1 for CT examination. In patients whose disease progression was not diagnosed with CT examination but with clinical symptoms and blood examinations, including tumor markers and non-CT examinations such as endoscopy, their events of disease progression were defined as clinical progressive disease (PD). These clinical and objective PDs diagnosed through CT examinations were set as events of disease progression, and their correlations with NLR, which was calculated based on data from routine blood examinations, were analyzed. Hematological data were analyzed every 2 weeks. Tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were evaluated once a month. CT examination was performed at 6-8 weeks. NLR was defined as the number of neutrophils divided by the number of lymphocytes. NLR was analyzed at the initiation of nivolumab monotherapy and every 2 weeks during treatment.

Patient characteristics such as age, sex, Eastern Cooperative Oncology Group performance status, histology, HER2 status, history of gastric resection, site of metastasis, treatment regimen, and blood cell count were collected. Tumor histology was classified according to Lauren's classification into intestinal (well-differentiated, moderately differentiated, papillary adenocarcinoma) and diffuse (poorly differentiated, mucinous adenocarcinoma, signet-ring cell carcinoma) types. In the safety analysis of nivolumab therapy, adverse events were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

The primary outcome is PFS, while the secondary outcome is OS and the best overall response and immunorelated adverse events (IrAEs). PFS was defined as the time from the initiation of nivolumab monotherapy to the disease progression date with objective PD or clinical PD, the date of death from any cause, or the last date of contact. OS was defined as the time from the initiation of nivolumab monotherapy to death from any cause or the last date of contact.

Statistical analysis. Patient characteristics were summarized using medians and interquartile ranges for continuous variables and counts and proportions for categorical variables. The PFS and OS rates after the initiation of nivolumab monotherapy were estimated using the Kaplan-Meier method. The median survival month was calculated, and 95% confidence interval was estimated using the Brookmeyer and Crowley method.

In analyzing the association between NLR and disease progression, blood examinations within 2 weeks from disease progression were linked with progressive disease. NLR was used as a time-dependent variable in the analysis because it was collected as repeated data from the start of nivolumab treatment to the last observation. The association between PFS and NLR was evaluated using a time-dependent Cox proportional hazards model. Nonlinearity was considered using restricted cubic spline (RCS) curves to accurately estimate the association between NLR and disease progression. The RCS curve can express nonlinear relationships more strongly as the number of knots is increased, though overfitting is more likely to occur. The number of knots in RCS was set to 3 to avoid overfitting. Moreover, the hazard ratios (HRs) predicted from the time-dependent Cox model were plotted using the median NLR as a reference. Separate from the model in the primary analysis described above, an interaction term between the NLR at each measurement time point and the baseline NLR was included in the model to assess the modifying effect of NLR at the start of nivolumab monotherapy. A multivariable

Table I. Clinical characteristics of patients.

Characteristic	N (%)
Sex	
Male	23 (52.3)
Female	21 (47.7)
Age, years	70 (35-84)
ECOG performance status	
0	21 (47.7)
1	16 (36.4)
2	1 (2.3)
3	6 (13.6)
Histological type (Lauren classification)	
Intestinal type	13 (29.5)
Diffuse type	31 (70.5)
HER2 status	
Positive	2 (4.5)
Negative	37 (84.1)
Unknown	5 (11.4)
Organs with metastases	
<2	30 (68.2)
≥2	14 (31.8)
Previous gastrectomy	
No	13 (29.5)
Yes	31 (70.5)
Previous treatment regimens	
2	40 (90.9)
3	4 (9.1)
Previous therapies	
Pyrimidine analogues	44 (100)
Platinum	36 (81.8)
Taxane	42 (95.5)
Ramucirumab	40 (90.9)
Irinotecan	3 (6.8)
Trastuzumab	2 (4.5)

ECOG, Eastern Cooperative Oncology Group.

Table II. Clinical responses of patients to nivolumab therapy.

Best overall response	N (%)	Objective PD	Clinical PD
CR	0 (0)		
PR	3 (6.8)	2	
SD	2 (4.5)	2	
Non-CR/non-PD	6 (13.6)	6	
PD	24 (54.5)	24	
NE	9 (20.5)		9

PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease; NE, not evaluable.

Table III. Categorization of immune-related adverse events.

	Grade, n (%)	
Adverse event	1/2	3≤
Diarrhea	5 (11.4)	0
Pruritus	4 (9.1)	0
Fatigue	4 (9.1)	0
Appetite loss	3 (6.8)	0
Hypothyroidism	3 (6.8)	0
Adrenal insufficiency	1 (2.3)	0
Colitis	1 (2.3)	0
Liver dysfunction	1 (2.3)	0
Renal dysfunction	1 (2.3)	0
Colonic perforation	0	1 (2.3)
Interstitial pneumonia	0	1 (2.3)

time-dependent Cox proportional hazards regression model was used to simultaneously assess the independent association between NLR, CEA, and CA19-9 levels with disease progression. A two-sided P-value <0.05 was considered statistically significant. All analyses were performed using the R software version 4.2.2 (www.r-project.org).

Results

Table I summarizes the clinical characteristics of the patients who received nivolumab monotherapy for unresectable or recurrent GC. The most frequent metastatic site was the peritoneum in 23 patients (52.3%), followed by the lymph node in 14 patients (31.8%), liver in 9 patients (20.1%), bone in 6 patients (13.6%), and others in 6 patients (13.6%). Pretreatment regimens included S-1 plus oxaliplatin (n=19), capecitabine plus oxaliplatin (n=8), S-1 plus cisplatin (n=5), S-1 plus docetaxel (n=5), fluorouracil plus oxaliplatin (n=3), capecitabine plus cisplatin (n=1), and S-1 (n=3) as the first-line regimen. The second-line regimen included ramucirumab plus paclitaxel (n=19), ramucirumab plus nab-paclitaxel (n=19), ramucirumab plus trastuzumab (n=2), paclitaxel (n=2), ramucirumab plus irinotecan (n=1), and ramucirumab (n=1). The third-line regimen included irinotecan (n=2). Table II shows the patients' clinical responses to nivolumab therapy. The response and disease control rates were 6.8 and 27.3%, respectively. The median number of cycles administered per patient was 3 (range, 1-29). Only one patient maintained partial response (PR), and the others developed PD. None of the patients continued nivolumab monotherapy after disease progression. The median PFS of all included patients was 1.84 months [95% confidence interval (CI), 1.32-2.14], and the median OS was 5.93 months (95% CI, 3.75-10.75) (Fig. 1). IrAEs of any degree were observed in 36.4% of the patients (Table III). Patients with grade ≤2 irAE were restarted on nivolumab treatment after symptomatic improvement. Among patients with grade 3 irAEs, intestinal perforation occurred in one patient after four cycles of treatment requiring surgery, and the other patient presented with interstitial pneumonia

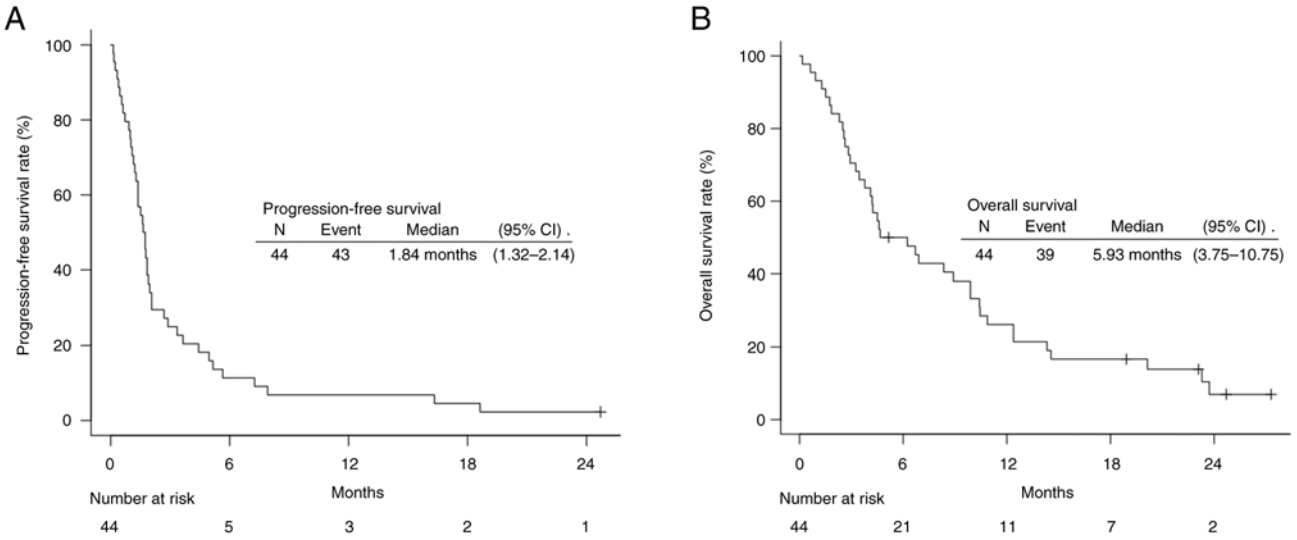

Figure 1. Kaplan-Meier survival analysis for all patients. (A) Progression-free survival and (B) overall survival progression-free survival. CI, confidence intervals.

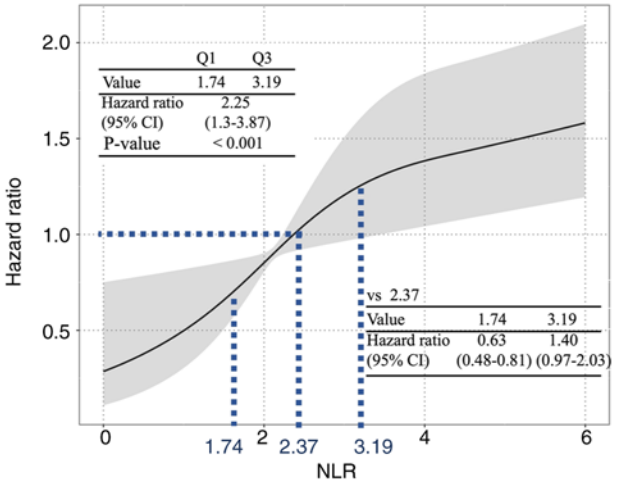

Figure 2. Time-dependent Cox proportional hazards regression analysis. CI, confidence intervals.

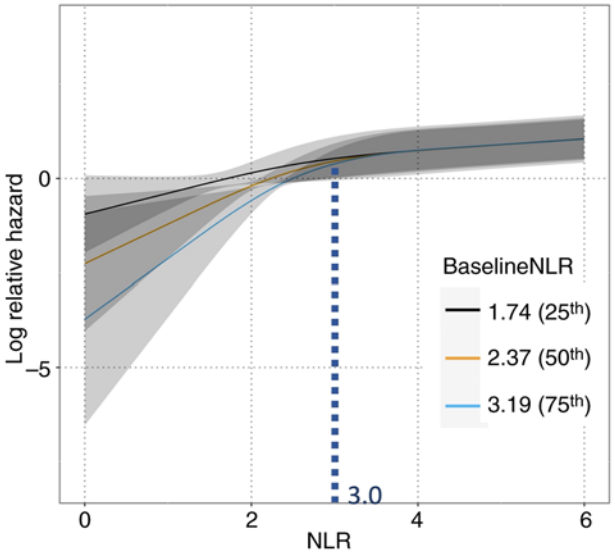

Figure 3. Restricted cubic spline curves. Three baseline NLR values were supplemented as the 25, 50 and 75th percentile points. NLR, neutrophil-to-lymphocyte ratio.

after three cycles of treatment requiring steroid therapy. Those two patients subsequently survived after treatment for those adverse events. A paired-sample t-test confirmed that there was no significant difference in NLR values 2 or 4 weeks prior to the onset of irAEs compared to NLR values at the onset of irAEs (P=0.200, P=0.247).

Fig. 2 shows the results of the time-dependent Cox proportional hazards regression analysis on the relationship between NLR and disease progression. A median NLR of 2.37 was used as a reference to analyze the risk for disease progression. The risk for disease progression was higher when the NLR was above the reference value, and the risk was lower when the NLR was below the reference value. The 25 and 75th percentile NLR values (1.74 and 3.19, respectively) were used to calculate the representative HR for disease progression, and the risk was increased with higher NLR (HR 2.25; 95% CI, 1.3-3.87; P<0.001).

Fig. 3 shows the three models of relationships between NLR and relative hazard for disease progression, which were stratified based on the baseline NLR values. Nonlinearities were considered using an RCS curve. There was a significant difference in the interaction between the NLR at each time point and the baseline NLR (P=0.009). Using the NLR values (25% value: 1.74, 50% value: 2.37, and 75% value: 3.19) as baseline NLR, the relative hazard of disease progression at each NLR value during treatment was calculated. When the NLR value was below 3.0, the risk of disease progression showed a more strongly positive correlation to NLR in all three models. When the NLR value increased compared to prior blood examination, the risk of disease progression also increased. Furthermore, the baseline NLR values stratified the relative risk each patient owed for their values of NLR. The smaller the baseline NLR value, the larger the risk of progressive disease, especially if

Table IV. Multivariable time-dependent Cox proportional hazards regression analysis.

Variable	Q1	Q3	HR	95% CI	P-value
NLR	1.79	3.16	1.16	1.04, 1.29	0.006
CEA	2.1	7.25	1.25	1.12, 1.39	<0.001
CA19.9	9.05	203.85	0.99	0.98, 1	0.163

NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19.9, carbohydrate antigen 19-9.

the values and increments were the same in all three models. Conversely, when the NLR value exceeded 3.0, there were few differences in risk for subsequent disease progression regardless of the NLR value and the baseline NLR value.

Table IV shows the analysis of correlations between NLR and tumor markers and disease progression. The multivariable time-dependent Cox proportional hazards regression analysis showed that NLR (HR 1.16; 95% CI, 1.04-1.29; P=0.006) and CEA (HR 1.25; 95% CI, 1.12-1.39; P<0.001) correlated with disease progression.

Discussion

In this study, the relationship between NLR and the risk of disease progression was examined in patients with unresectable or recurrent GC treated with nivolumab monotherapy as a third-line or later regimen. As shown in Figures 2 and 3, NLR, which was calculated from daily blood examinations, positively correlated with disease progression. The higher the NLR, the higher the risk for disease progression, especially if the NLR value is <3.0. If the NLR value is higher compared to prior blood examination, the risk of disease progression also increases. The multivariable time-dependent Cox proportional hazards regression analysis showed that NLR was correlated with disease progression. These findings suggested that NLR, as a dynamic and convenient indicator of tumor condition, could be better than tumor markers or imaging examinations in predicting the risk of developing PD. We believe our results are novel because previous literature has examined the NLR value prior to treatment initiation or at some point in treatment for prognosis but has not examined NLR dynamics and the risk of developing PD (14-17).

Cancers are known to induce inflammatory responses that affect the survival of patients with cancer (14-18). Transcription factors, such as nuclear factor κB, in tumor cells are activated to produce inflammatory mediators, such as cytokines and chemokines (18). Cytokines activate inflammatory cells, including neutrophils, to produce more inflammatory mediators. This results in a cancer-associated inflammatory microenvironment that increases cancer aggressiveness in terms of cancer invasiveness, immune system resistance, enhanced angiogenesis, and resistance to treatment (19,20). Furthermore, cytokines and chemokines produced by neutrophils can suppress lymphocyte immune activity, which plays an important role in antitumor immunity which plays an important role in antitumor immunity (21). Increased infiltration of lymphocytes into tumors has been associated with better response to cytotoxic therapy in *patients with cancer (22). In this way, cancer activates neutrophils, lymphocytes are suppressed, and the values of NLR are elevated in case the disease progresses. In contrast, if the cancers are controlled by systemic chemotherapy, the inflammation is suppressed, and the values of NLR will decrease. Ohashi reported that responders tend to have decreased neutrophils and increased lymphocytes, while within 6 weeks after anti-PD-1 therapy for advanced malignant melanoma, the opposite trend is seen in non-responders (23). The balance between the values of neutrophils and lymphocytes may be an important parameter in predicting disease conditions. In our study, an increase in NLR value is associated with an increased risk of disease progression (Fig. 2).

Fig. 3 shows the risk of disease progression by stratification of baseline NLR. Compared to previous reports (15,17,24,25), the NLR interquartile range (1.74-3.19) in our study was in a reasonable range. Previous reports (14-17) have shown that patients with a high baseline NLR have poor PFS and OS, while some patients who respond well to nivolumab therapy and have decreased NLR may have long-term disease control. There were 16 cases with NLR >3, and 8 had a decrease in NLR after initial nivolumab treatment in this study. One of them maintained PR until the end of the observation period (752 days). It is important to observe NLR trends while considering the baseline NLR to predict the risk of disease progression.

As shown in Table IV, NLR and CEA are significantly associated with developing PD. NLR and tumor markers, including CEA and CA19-9, are biomarkers that can be measured by blood tests. Tumor markers are measured monthly, whereas neutrophils and lymphocytes are measured at each treatment, which is more convenient. Elevated tumor markers correlate with increased tumor burden and have been reported to be useful for detecting recurrence or distant metastasis after radical resection (11). CEA is significantly associated with differentiated tumors and is an independent predictor of liver metastases (26). CA19-9 has been associated with lymph node metastasis (27). Conversely, unresectable or recurrent GC often has nonmeasurable lesions, including peritoneal dissemination. Peritoneal metastasis is often observed in diffuse-type adenocarcinoma, and tumor marker elevation is often not observed (13). In some cases, despite the clinical benefits of chemotherapy, tumor markers may show transient elevations after the initiation of chemotherapy (11). It should be noted that tumor markers may not accurately reflect tumor activity. Therefore, not only tumor markers but also NLR should be considered in order to understand tumor activity.

In clinical practice, the dynamics of the NLR can be used to consider the treatment strategy. If the NLR remains above 3 during treatment, regardless of the baseline NLR, the tumor is poorly controlled. Therefore, an early evaluation of treatment efficacy, including CT imaging, is necessary, and a change in treatment strategy should be considered. Conversely, if the NLR remains below 3, a curve estimated by the Baseline NLR can be generated, and treatment can be continued while keeping track of the relative risk of PD.

Our study has several limitations. First, this was a retrospective single-center study with a small sample size. Second, infections, including pneumonia, may be a confounding factor. Cases with infections were included. Neutrophils are elevated in infection, and NLR is accordingly elevated. Patients who underwent third- or later-line chemotherapy are generally frailer than those in first-line chemotherapy, and infectious disease occurs more frequently than the patients in first-line therapy. More accurate results could be obtained if data with infectious conditions could be excluded and still have larger sample sizes. Third, nivolumab is currently used as a first-line therapy, and it is unclear whether the results of a third-line or later therapy can be adapted for first-line therapy. Therefore, further analysis is needed to evaluate the correlation between NLR and tumor progression in patients who underwent first-line chemotherapy in the future.

In conclusion, NLR during treatment could predict the risk of developing PD and could be another new biomarker to evaluate tumor activity other than tumor markers or imaging examination in patients with unresectable or recurrent GC treated with nivolumab monotherapy.

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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

HH, IY, YS, SF, WC and NM conceptualized the study. HH, ME, TH, RY, KMa, MK, YS, MF, RA, JYT, AM, SK, YT, KMu and TI designed the methodology and analyzed the data. HH wrote the original draft preparation. IY reviewed and edited the manuscript. HH and NM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective observational study was approved by the Institutional Review Board of Gifu University Hospital (approval no. 2021-B185) and was conducted in compliance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. Informed consent was obtained from all participants.

Patient consent for publication

Written informed consent was obtained from the patient for publication.

Competing interests

The authors declare that they have no competing interests.

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