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An Elevated Serum Lactate Dehydrogenase-to-albumin Ratio Is a Useful Poor Prognostic Predictor of Nivolumab in Patients With Gastric Cancer

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Abstract. *Background/Aim: This study clarified the predictive impact of serum biomarkers on therapeutic sensitivity to nivolumab in patients with gastric cancer (GC). Patients and Methods: The outcomes of 27 patients who received nivolumab to treat postoperative recurrent or unresectable advanced GC were reviewed. Blood testing was performed immediately before and after two courses of nivolumab. We also focused on the rate of change of each blood variable. Results: The decrease in albumin (Alb) levels (p=0.035) and increase in lactate dehydrogenase (LDH) levels (p=0.012) after two courses of nivolumab were significantly larger in patients with disease progression. Furthermore, therapeutic resistance was significantly associated with an elevated LDH-to-Alb ratio (LAR) after two courses of nivolumab. Conclusion: Decreased Alb or increased LDH levels after two courses of nivolumab predicted nivolumab sensitivity in patients with GC. An increased LAR was a meaningful predictor of nivolumab resistance.*

Gastric cancer (GC) is a common digestive cancer and a leading cause of cancer-related death worldwide (1). The clinical outcome of patients with GC has gradually improved following the development of chemotherapy and immune checkpoint inhibitors. The anti-PD-1 antibody nivolumab improved overall survival (OS) in ATTRACTION-2, the first phase III study of patients with GC who received two or more prior chemotherapy regimens (2). The median OS in this phase III trial was 5.26 months [(95% confidence interval (CI)=4.60-6.37] in the nivolumab group, *versus* 4.14 months (95%CI=3.42-4.86) in the placebo group (hazard ratio=0.63, 95%CI=0.51-0.78; $p<0.0001$). However, to detect the positive therapeutic effects of nivolumab in patients with GC more effectively in the clinic, the establishment of a powerful biomarker predicting therapeutic efficacy is needed.

Blockade of the interaction between programmed cell death receptor 1 (PD-1) and its ligand programmed-death ligand 1 (PD-L1) plays a significant role in regulating immune response through the activation of tumour-specific cytotoxic T lymphocytes (3-5). It was reported that the anti–PD-1 antibody nivolumab produced good therapeutic effects in patients with GC and a high tumour mutation burden (6, 7); Epstein–Barr virus infection positivity; microsatellite instability (8-10); and high PD-1, PD-L1, and CD8 expression (11-22). However, PD-L1 expression alone may be insufficient as a biomarker because of its heterogeneous expression within the tumour and its microenvironment (23, 24). Therefore, the identification of patients with GC who are likely to benefit from nivolumab is critical for clinical treatment. In addition, the detection of serum biomarkers would be extremely useful in clinical practice.

A large retrospective multicentre study revealed the importance of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for predicting therapeutic sensitivity to nivolumab in patients with pre-treated non-small cell lung cancer (NSCLC) (25). In addition, the albumin-to-globulin ratio (AGR) and lactate dehydrogenase (LDH) levels were associated with therapeutic sensitivity to nivolumab in patients with NSCLC (26, 27). However, few studies have examined the relationships of the aforementioned serum biomarkers with therapeutic sensitivity to nivolumab in patients with GC. In addition, the identification of other powerful serum biomarkers is needed.

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Key Words: Gastric cancer, nivolumab, lactate dehydrogenase-to-albumin ratio (LAR).

This study aimed to clarify the predictive impact of serum biomarkers on the sensitivity to nivolumab in patients with GC. In this study, we focused on the periods immediately before and after two courses of nivolumab therapy in patients with GC.

Patients and Methods

Patients. In total, the outcomes of 27 patients who received nivolumab for postoperative recurrent or unresectable advanced GC between 2017 and 2021 at Gunma University Graduate School of Medicine, Department of General Surgical Science in Maebashi, Japan were retrospectively reviewed. The following patient data were collected: age, gender, body mass index (BMI), and Eastern Cooperative Oncology Group Performance Status (ECOG-PS). In addition, the number of previous regimens, presence or absence of postoperative recurrence, number of nivolumab doses, and presence of immune-related adverse events (irAEs) were recorded. The response to nivolumab was determined using the Response Evaluation Criteria in Solid Tumors version 1.1 (28). This study was approved by the institutional review board of Gunma University (approval no. HS2020-085). Written informed consents were obtained from all subjects for the publication of this article and accompanying images.

Assessment of serum biomarkers. The results of laboratory tests, such as the white blood cell count and haemoglobin, platelet, total protein, albumin (Alb), total bilirubin, alanine aminotransferase, LDH, blood urea nitrogen, creatinine, and C-reactive protein levels, were collected immediately before and after two courses of nivolumab therapy in patients with GC. We calculated both NLR and PLR. AGR was calculated as follows: Alb/ (total protein − Alb) (29). Other data were presented as the percent change before and after treatment.

Statistical analysis. Data were analyzed using the Mann–Whitney *U*-test for continuous variables and the chi-squared test for categorical variables. $p<0.05$ indicated statistical significance. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the potential of LAR as a predictor of resistance to nivolumab. All analyses were performed using JMP Pro 12.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. We presented patient characteristics according to the disease response [disease control (DC) or progressive disease PD)] in Table I. In total, 21 patients (77.8%) had PD. The DC and PD groups did not differ in terms of age, gender, and BMI. No patients with DC had ECOG-PS ≥2 ($p=0.041$). In addition, the number of prior regimens before nivolumab therapy did not differ between the DC and PD groups. Conversely, the number of nivolumab doses administered was significantly higher in the DC group than in the PD group ($p<0.0001$). However, the incidence of irAEs did not differ between the groups.

Association between blood variables and therapeutic responses to nivolumab. Table II presents the relationships between blood variables and the response to nivolumab. Blood variables did not differ between the groups before or after treatment. In addition, NLR, PLR, and AGR did not differ between the groups.

Table I. *Examination of patient characteristics according to the treatment response*.

Factors	RECIST		
	DC (n=6)	PD (n=21)	*p*-Value
Age			
years	67	68	0.88
Gender			
Male	5	16	0.70
Female	1	5	
BMI			
kg/m^2	21.4±1.4	20.4±0.7	0.49
PS			
0 or 1	6	14	**0.041**
2 or 3	0	7	
Frequency of previous regimens	2.3±0.3	2.2±0.2	0.70
Postoperative recurrence cases	2	10	0.53
Nivolumab administration times	26.8±4.0	3.8±2.1	**<0.0001**
irAE			
Negative	5	16	0.70
Positive	1	5	

DC: Disease control; PD: progressive disease; BMI: body mass index; PS: performance status; irAE: immune-related adverse event. Bold values indicate statistical significance.

Associations of changes of blood variables with responses to two courses of nivolumab. Because nivolumab was frequently used after third-line chemotherapy in this study, several patients experienced disease progression. Consequently, the results of blood testing greatly differed among the patients. In other words, it was considered insufficient to examine the absolute results of the blood tests. Therefore, we decided to focus on the change (%) of blood test data in each patient.

We presented the relationships between the changes in blood variables with treatment responses before and after two courses of nivolumab. As presented in Table III, the percentage decrease of Alb levels after treatment was significantly larger in patients with PD than in those with DC (107.2%±4.2% *vs*. 96.5%±2.3%, $p=0.035$). Furthermore, the increase of LDH levels was significantly larger in the PD group than in the DC group (116.0%±5.2% *vs*. 86.6%±9.5%, $p=0.012$). Meanwhile, no significant differences were observed for other blood variables between the groups.

Changes in LAR after nivolumab treatment according to the therapeutic response. Next, we focused on the change in

Table II. *Association of patients' blood test data with the therapeutic response to nivolumab.*

Factors	Before administration of nivolumab			After two courses of nivolumab		
	RECIST			RECIST		
	DC (n=6)	PD (n=21)	*p*-Value	DC (n=6)	PD (n=21)	*p*-Value
WBC						
mm^3	6,400±913	5,810±489	0.57	6,267±955	6,270±523	1.00
Neutrophil-to-Lymphocyte ratio						
(NLR)	3.56±1.14	3.36±0.61	0.88	3.14±0.90	3.42±0.51	0.79
Hb						
g/dl	11.0±0.7	11.2±0.4	0.75	11.6±0.7	11.3±0.4	0.75
Plt						
$10^3/\mu l$	250.8±40.9	221.0±21.9	0.53	248.7±51.0	220.6±27.9	0.63
Platelet-to-Lymphocyte ratio						
(PLR)	204.3±60.9	186.9±32.5	0.80	174.5±40.1	167.0±22.5	0.87
Total protein						
g/dl	6.5±0.2	6.4±0.1	0.48	7.0±0.2	6.5±0.1	0.13
Alb						
g/dl	3.5±0.2	3.4±0.1	0.76	3.7±0.2	3.4±0.1	0.13
Albumin/Globulin ratio						
(A/G ratio)	1.20±0.15	1.22±0.08	0.91	1.22±0.32	1.12±0.31	0.51
T-bil						
mg/dl	0.52±0.07	0.54±0.04	0.80	0.60±0.10	0.59±0.05	0.93
ALT						
U/l	20.5±3.9	17.3±2.1	0.48	19.5±9.7	25.2±5.3	0.61
LDH						
U/l	256±39	204±21	0.25	175±24	231±13	0.05
BUN						
mg/dl	16.3±2.6	15.5±1.4	0.77	16.8±3.5	18.0±1.9	0.77
Cr						
mg/dl	0.87±0.10	0.75±0.05	0.28	0.86±0.18	0.95±0.10	0.66
CRP						
mg/dl	1.02±0.63	0.87±0.35	0.84	0.25±0.40	0.79±0.22	0.24

DC: Disease control; PD: progressive disease; WBC: white blood cell; Hb: hemoglobin; Plt: platelet; Alb: albumin; T-bil: total bilirubin; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; Cr: creatinine; CRP: C-reactive protein.

LAR after two courses of nivolumab therapy. As presented in Table IV, the percentage increase of LAR after two courses of nivolumab relative to before treatment was significantly greater in the PD group than in the DC group (122.5%±6.8% *vs*. 81.6%±12.4%, p=0.0078). LAR elevation was observed in 16 of 27 patients (59.3%), including one patient (16.7%) in the DC group and 15 patients (75.0%) in the PD group (p=0.0094). Increased LAR had 75.0% sensitivity and 83.3% specificity for predicting PD.

Relationship of changes of LAR with sensitivity to nivolumab. The association between the changes in LAR and sensitivity to nivolumab was examined using ROC curve analysis. As presented in Figure 1, the optimal LAR cut-off for predicting PD was 105% (area under the curve, 0.892; sensitivity, 75.0%; specificity, 100%). Using this cut-off, we assessed patient characteristics according to the response, as presented in Table V. In the LAR <105% group, all patients had ECOG-PS 0 or 1 (p=0.0049). Furthermore, all patients in the LAR ≥105% group had PD (p=0.0003). In addition, significantly fewer patients in the LAR=105% group were able to continue chemotherapy after nivolumab administration (p=0.018).

Discussion

In this study, we analyzed the utility of serum biomarkers for predicting sensitivity to nivolumab in patients with GC. In particular, we focused on the periods immediately before and after two courses of nivolumab in this study. Interestingly, the decrease in Alb levels and the increase in LDH levels after two courses of nivolumab were significantly larger in the PD group than in the DC group. Furthermore, there was a significant association between therapeutic resistance and LAR elevation after two courses of nivolumab relative to the

Table III. *Changes in blood test data according to treatment response before and after two courses of nivolumab.*

Factors	After two courses of nivolumab RECIST		
	DC (n=6)	PD (n=21)	*p*-Value
WBC			
%	111.0±16.5	108.1±8.8	0.88
NLR			
%	96.7±27.8	129.8±15.6	0.31
Hb			
%	105.9±8.9	95.7±4.8	0.32
Plt			
%	96.4±11.4	97.2±6.1	0.95
PLR			
%	87.1±17.2	111.0±9.7	0.24
Total protein			
%	106.0±8.6	96.9±4.6	0.36
Alb			
%	107.2±4.2	96.5±2.3	**0.035**
A/G ratio			
%	102.3±8.9	85.9±4.8	0.12
T-bil			
%	118.1±14.7	105.0±7.8	0.44
ALT			
%	122.2±17.2	90.0±9.4	0.11
LDH			
%	86.6±9.5	116.0±5.2	**0.012**
BUN			
%	107.9±26.5	115.7±14.2	0.8
Cr			
%	98.6±27.4	120.8±14.5	0.48
CRP			
%	71.4±176.1	286.5±96.4	0.29

DC: Disease control; PD: progressive disease; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; Plt: platelet; Alb: albumin; A/G ratio: albumin-to-globulin ratio; T-bil: total bilirubin; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; Cr: creatinine; CRP: C-reactive protein. Bold values indicate statistical significance.

Table IV. *Changes in LAR before and after two courses of nivolumab according to treatment response.*

Factors	After two courses of nivolumab RECIST		
	DC (n=6)	PD (n=20)	*p*-Value
LAR			
%	81.6±12.4	122.5±6.8	**0.0078**
LAR			
Decrease	5	5	**0.0094**
Increase	1	15	

DC: Disease control; PD: progressive disease; LAR: lactate dehydrogenase-to-albumin ratio. Bold values indicate statistical significance.

Table V. *Patient characteristics according to the cut-off of LAR.*

Factors	LAR		
	≥105% (n=15)	<105% (n=11)	*p*-Value
Age			
Years	67	69	0.70
Gender			
Male	11	9	0.61
Female	4	2	
BMI			
kg/m^2	20.0±0.9	21.1±1.0	0.42
PS			
0 or 1	9	11	**0.0049**
2 or 3	6	0	
Frequency of previous regimens	2.1±0.2	2.3±0.2	0.44
Postoperative recurrence cases	6	5	0.78
RECIST			
DC	0	6	**0.0003**
PD	15	5	
Nivolumab administration times	4.1±3.3	16.1±3.9	0.027
irAE			
Negative	13	8	0.38
Positive	2	3	
Post-treatment of nivolumab			
Negative	11	3	**0.018**
Positive or ongoing	4	8	

LAR: Lactate dehydrogenase-to-albumin ratio; BMI: body mass index; PS: performance status; DC: disease control; PD: progressive disease; irAE: immune-related adverse event. Bold values indicate statistical significance.

findings before treatment. The optimal cut-off for LAR was identified as 105% using ROC curve analysis. This study is novel in that it examined the relationships of nivolumab sensitivity with LAR and immunonutrition indices including NLR, PLR, and AGR in patients with GC. The potential to predict nivolumab resistance by focusing on the change in LAR appears clinically meaningful.

In this study, we focused on the periods immediately before and after two courses of nivolumab therapy. ATTRACTION 2 revealed a significant difference in the objective response rate between the nivolumab and placebo arms (11.2% *vs.* 0.0%) (2). Given the low therapeutic sensitivity, it is critical to identify a blood biomarker that can predict sensitivity to nivolumab quickly and accurately at an early point after administration. Furthermore, because blood tests are commonly performed after each dose of nivolumab, it would be significant if therapeutic sensitivity could be predicted from the results of blood tests.

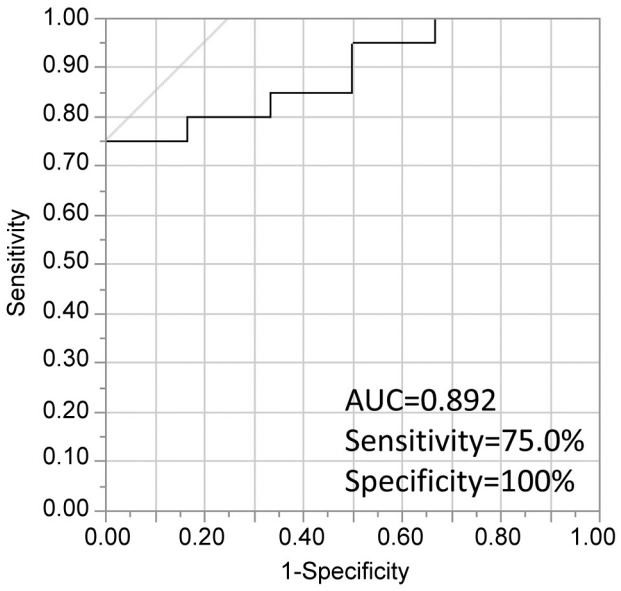

Figure 1. *Receiver operating characteristic curve analysis of the change in the lactate dehydrogenase-to-albumin ratio for discriminating between disease control and progressive disease.*

Several studies have found that a decrease in Alb levels reflect the development of cancer and predict poor prognosis in patients with several malignancies (30-35). Tumours are known to induce chronic inflammation; inhibit Alb production by producing cytokines such as interleukin (IL)-1b, IL-6, and tumour necrosis factor; and enhance capillary permeability (36). Furthermore, we focused on AGR in this study. AGR is a predictive biomarker of the therapeutic efficacy of anti–PD-1 antibodies in patients with NSCLC (28). To our knowledge, this is the first study to examine the relationship between AGR and nivolumab sensitivity in patients with GC, but no significant correlation was found.

LDH is an important enzyme in glycolysis, and is required for the metabolism of pyruvate to lactic acid. LDH levels have been shown to reflect tumour growth and invasive potential, and LDH is a significant prognostic marker in several gastrointestinal tract cancers (37, 38). Concerning immune checkpoint inhibitors, several reports have found that LDH levels are predictive of poor prognosis in patients with NSCLC treated with nivolumab (27, 39) and patients with melanoma (40). This is the first finding of an association between LDH levels and therapeutic responses to nivolumab in patients with GC. Focusing on the changes of LDH levels before and after two courses of nivolumab, the potential of LDH levels to predict therapeutic sensitivity was highlighted.

Because Alb levels decreased and LDH levels increased after two courses of nivolumab in many patients in this study, we focused on LAR to identify a more sensitive biomarker. Although high LAR has been reported to be correlated with poor prognosis in colorectal cancer (41) and oesophageal cancer (42), the association between LAR and immune checkpoint inhibitor sensitivity in patients with GC was unknown. We clarified that the increase in LAR after two courses of nivolumab relative to that before treatment was significantly larger in the PD group. This suggested that LAR is an extremely good biomarker for predicting therapeutic sensitivity in patients with GC who received nivolumab.

Interestingly, all patients with LAR ≥105% had PD, and significantly fewer patients (26.7%) received continuous chemotherapy after nivolumab in this group than in the LAR <105% group. By focusing on the change in LAR after two courses of nivolumab, it was suggested that it may be useful to change to later line chemotherapy earlier. Furthermore, all patients in LAR <105% had ECOG-PS 0 or 1. It may be useful to switch to nivolumab before ECOG-PS deteriorates.

Our study had several limitations, including its small sample size, which may have biased the results. Further large-scale clinical trials are needed to clarify the potential of LAR as a new predictive biomarker for nivolumab sensitivity.

In conclusion, decreased Alb levels or increased LDH levels after two courses of nivolumab relative those before treatment may be predictive of nivolumab sensitivity in patients with GC. In particular, the change in LAR was a useful prognostic predictor. Because blood testing is performed during follow-up in almost all patients with GC who receive nivolumab, the study findings could result in improved clinical outcomes. The novelty of this study was that therapeutic resistance could be predicted by evaluating blood test data early after the start of nivolumab, before computed tomography evaluations.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and design: N. Nakazawa, M. Sohda, A. Sano, K. Shirabe, and H. Saeki; Acquisition of data: N. Nakazawa; Analysis and interpretation: N. Nakazawa, M. Sohda, A. Yamaguchi, T. Watanabe, H. Saito, Y. Ubukata, K. Kuriyama, A. Sano, M. Sakai, T. Yokobori, H. Ogawa, K. Shirabe, and H. Saeki; Writing, review, and/or revision of the manuscript: N. Nakazawa, M. Sohda, K. Shirabe, and H. Saeki; Study supervision: K. Shirabe, and H. Saeki. All Authors have read and approved the final manuscript.

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