Improvement of body weight and nutritional status in gastric cancer patients enhances the efficacy of nivolumab therapy

Tatsuki Ikoma
Kobe City Medical Center General Hospital
Toshihiko Matsumoto (makoharutaro2015@gmail.com)
Kansai Medical University Hospital
Yusuke Kurioka
Japanese Red Cross Society Himeji Hospital
Masahiro Takatani
Japanese Red Cross Society Himeji Hospital
Hiroki Nagai
Kobe City Medical Center General Hospital
Yusuke Matsumoto
Japanese Red Cross Society Himeji Hospital
Hironaga Satake
Kobe City Medical Center General Hospital
Hisateru Yasui
Kobe City Medical Center General Hospital

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Abstract

Background

Nivolumab improves the overall survival (OS) of patients with advanced gastric cancer (AGC) refractory to at least two previous chemotherapy regimens. Here, we investigated whether changes in body weight and nutrition from 1st -line chemotherapy to nivolumab could affect the efficacy of nivolumab.

Methods

We retrospectively examined patients with AGC treated with nivolumab between July 2016 and August 2020. This study examined the correlation between changes in body weight and nutritional status up to the start of nivolumab treatment, and the overall survival (OS) and progression-free survival (PFS) after the initiation of nivolumab treatment. Nutritional status was examined using the C-reactive protein/albumin ratio (CAR).

Results

Ninety-eight patients were enrolled. In our study, a loss in body weight (LBW) from the start of the first treatment of < 4.5% led to OS prolongation. The median OS in the LBW < 4.5% group and in the LBW ≥ 4.5% group was 11.4 months (95% confidence interval [CI] 6.6–14.3) and 3.6 (95%CI 2.2–5.1) months, respectively (hazard ratio [HR] 0.42; 95%CI 0.26–0.66; p < 0.001). Similarly, the change in CAR from first-line chemotherapy (ΔCAR) affected OS, and the ΔCAR < 0.01 group had a better prognosis than ΔCAR ≥ 0.01 group. The median OS in the ΔCAR < 0.01 group and in the ΔCAR ≥ 0.01 group was 9.4 (95%CI, 5.1–13.7) and 4.5 (95%CI 4.0–5.0) months, respectively (HR 0.59; 95%CI 0.37–0.93; p = 0.002). Moreover, the median OS in the group with both LBW < 4.5% and ΔCAR < 0.01 was 12.9 months (95%CI 6.8–19.0). Furthermore, the LBW < 4.5% group showed statistically significantly better PFS (median PFS 2.7 vs. 2.0 months; HR 0.63, 95%CI 0.42–0.94; p = 0.021).

Conclusion

Our study suggested that LBW and deterioration of nutritional status from the start of first-line chemotherapy are poor prognostic factors in AGC patients who received nivolumab as third- or later-line therapy. Early intervention to maintain body weight and nutritional status from the initiation of prior chemotherapy may improve the efficacy of immune checkpoint inhibitors.

Introduction

Advanced gastric cancer (AGC) is one of the most common cancers and is particularly common in Asia [1]. In addition, since AGC is often detected as an unresectable, advanced cancer, the development of

chemotherapy has been an urgent issue. Recently, the development of immune checkpoint inhibitors (ICIs) has significantly improved the survival of patients with various cancers, including those with AGC [2]. In the ATTRACTION-2 trial, nivolumab improved the overall survival (OS) of patients with AGC that had been refractory to at least two previous chemotherapy regimens [2]. The trial obtained a median OS of 5.26 months. Based on this result, in Japan, nivolumab has become the standard chemotherapy for patients with AGC that had been refractory to at least two previous chemotherapy regimens. Moreover, the usefulness of combination chemotherapy and ICIs in first-line chemotherapy has been reported in AGC [3, 4]. The ATTRACTION-4 and CheckMate 649 trials demonstrated the efficacy of chemotherapy combined with nivolumab as a first-line setting, showing a significant improvement in OS as compared with chemotherapy alone [3, 4]. Consequently, chemotherapy plus nivolumab has become one of the standard first-line treatments for AGC patients.

In various cancers, including AGC, it has been reported that cancer-induced cachexia, which often occurs in patients with gastrointestinal cancers, who have decreased oral intake, reduces the effects of ICIs [5–7]. Poor oral intake due to cachexia is associated with weight loss [7]. To the best of our knowledge, few studies have investigated the association of weight loss and nutritional status during prior treatment with the effects of ICIs. Therefore, in this retrospective study, we investigated whether loss of body weight (LBW) and worsening nutritional status before the initiation of nivolumab therapy influenced the efficacy of nivolumab in AGC patients.

Methods

Patients characteristics

The clinical data of consecutive patients with AGC treated with nivolumab as the third-line or later treatment were retrospectively collected from the Himeji Red Cross Hospital and Kobe City Medical Center General Hospital. Eligible patients were aged 20 years or older, had advanced, recurrent, or metastatic AGC, and had received at least one cycle of nivolumab between July 2016 and August 2020. Patient data were evaluated from the date of registration to September 2021. The enrolled patients were administered nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks, until tumor progression or until intolerance developed.

This study was conducted in accordance with the Helsinki Declaration of 1964 and its later versions, and with the ethical guidelines for clinical studies. This study was approved by the institutional review boards of all participating institutions: Kobe City Medical Center General Hospital (approval no. zh220109) and Himeji Red Cross Hospital.

Changes in body weight and nutritional factors

We collected data on body weight change at the start of first-line treatment, at the start of pretreatment with nivolumab, and at the start of nivolumab treatment. Additionally, nutritional status was investigated by evaluating the C-reactive protein (CRP)/albumin (Alb) ratio (CAR) [8–10] by blood test at the start of

first-line treatment, at the start of pretreatment with nivolumab, and at the start of nivolumab treatment. We also investigated the change in CAR from prior treatment to nivolumab treatment.

Statistical analysis

OS was defined as the time from the date of the first nivolumab treatment to the date of death. Living patients were censored at the last follow-up visit. Progression-free survival (PFS) was defined as the time from the date of the first nivolumab treatment to the date of exacerbation confirmation on computed tomography (CT) or death for any reason. CT-based disease assessment was usually performed every 8 weeks, based on the Response Evaluation Criteria in Solid Tumors version 1.1. Fisher's exact test was used to compare the patient characteristics. OS and PFS were estimated using the Kaplan–Meier method. The log-rank test was used to compare groups, whereas Cox regression models were used to calculate the hazard ratio (HR) and 95% confidence interval (95%CI). Patient characteristics and nutritional factors were analyzed using Cox regression models. OS prolongation was defined as a survival of at least 5.26 months with reference to the ATTRACTION-2 trial [2]. A receiver operating characteristic (ROC) curve was used to determine the correlation between OS prolongation and changes in body weight or nutritional factors, and was used to determine the cut-off values according to prolonged OS. Predictive performance was evaluated using the area under the ROC curve (AUC).

Statistical analyses were performed using SPSS software, version 28.0 (IBM Corp., Armonk, NY, USA), and a p value < 0.05 was considered to be statistically significant.

Results

ROC curve results for predicting OS by the change in the rate of LBW and CAR value.

ROC curves were to assess the relationship of the rate of LBW from the start of first-line treatment and from the start of nivolumab pre-treatment with OS. The AUC values were 0.712 for LBW from the start of first-line treatment, and 0.590 for the rate of LBW from the start of nivolumab pretreatment.

In addition, ROC curves were used to assess the impact of the change in the CAR value (ΔCAR) from the start of the first treatment and from the start of pretreatment to the start of nivolumab on OS. The AUCs were 0.621 for ΔCAR from the start of the first treatment and 0.578 from the start of pretreatment. These results suggested that changes in LBW and CAR from first-line treatment might impact OS. We determined their optimal cut-off values as 4.5 and 0.01, respectively, and used these values to group patients by change in LBW and in CAR.

Patient characteristics

Between July 2016 and August 2020, 98 consecutive patients with AGC were treated with nivolumab as the third-line or later treatment. The 98 patients were divided into two groups based on the cut-off value of LBW determined by the ROC curve: the LBW $< 4.5\%$ group ($n = 50$) and the LBW $\geq 4.5\%$ group ($n = 47$). The characteristics of the patients in each group are summarized in Table 1. There were significantly

fewer cases of low BMI and many cases of previous surgery in the LBW < 4.5% group. There were no significant differences in other patient background factors or in the efficacy of nivolumab between the two groups.

Table 1
Patient characteristics

Characteristic	LBW < 4.5% n = 50	LBW ≥ 4.5% n = 47	p-value
Age (years) Median [range]	68 [37–85]	70 [31–86]	0.42
Sex Male/Female	39/11 (78/22)	38/9 (81/19)	0.81
ECOG PS < 2/≥ 2	38/12 (76/24)	31/16 (66/34)	0.37
BMI (kg/m^2) < 18.5/≥ 18.5	8/42 (16/84)	20/27 (43/57)	**0.01**
Location U/M/L/other	8/21/19/2 (16/42/38/4)	12/23/10/2 (26/49/21/4)	0.30
Histology Diffuse/Intestinal	27/23 (54/46)	20/27 (57/43)	0.31
HER2 Positive/Negative	7/43 (14/86)	11/35 (24/76)	0.30
Previous surgery Yes/No	29/21 (58/42)	17/30 (36/64)	**0.04**
Lung metastasis Yes/No	10/40 (20/80)	6/41 (13/87)	0.42
Liver metastasis Yes/No	18/32 (36/64)	16/31 (34/66)	1.00
Peritoneal metastasis Yes/No	30/20 (60/40)	28/19 (60/40)	1.00
Asictes Yes/No	27/23 (54/46)	31/16 (66/34)	0.30

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; U, upper; M, middle; L, lower; HER2, human epidermal growth factor receptor; No., number

No. of previous regimens	40/10	31/16	0.17
2/≥ 3	(80/20)	(66/34)	

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; U, upper; M, middle; L, lower; HER2, human epidermal growth factor receptor; No., number

Correlation of OS with LBW and CAR

With a median observation period of 5.0 (range, 1.8–44.2) months for censored cases, the median OS in the LBW < 4.5% group (11.4 [95%CI 6.6–14.3] months) was significantly greater than that in the LBW ≥ 4.5% group (3.6 [95%CI 2.2–5.1] months) (HR 0.42; 95%CI 0.26–0.66; p < 0.001) (Fig. 1A). Additionally, the median OS in the ΔCAR < 0.01 group (9.4 [95%CI 5.1–13.7] months) was significantly longer than that in the ΔCAR ≥ 0.01 group (4.5 [95%CI 4.0–5.0] months) (HR 0.59; 95%CI 0.37–0.93; p = 0.002) (Fig. 1B). These results suggest that minimizing weight loss and maintaining patients' nutritional status before the initiation of nivolumab therapy might prolong OS. We defined the well-nutrition (WN) group as patients who maintained their body weight and remained well-nourished (ΔCAR < 0.01) from the start of first-line treatment and before the start of nivolumab therapy. The OS was significantly prolonged in the WN group as compared to the not well-nutrition (NWN) group (median OS, 12.9 vs. 4.5 months; HR 0.43; 95%CI 0.26–0.73; p = 0.001) (Fig. 1C).

Univariate and multivariate analyses of various factors with OS

Table 2 shows the univariate and multivariate analyses of prognostic OS factors. Eastern Cooperative Oncology Group Performance Status < 2, LBW < 4.5%, ΔCAR < 0.01, and the absence of peritoneal metastasis may be factors predicting a better prognosis, while no other factors were prognostic in this study. Among these prognostic factors, LBW < 4.5% correlated most strongly with OS.

Table 2
Cox regression analysis for overall survival.

Variable		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	(< 65 vs. ≥ 65 years)	0.91 (0.52–1.60)	0.75		
ECOG PS	**(< 2 vs. ≥ 2)**	**0.42 (0.25–0.72)**	**0.002**	**0.47 (0.28–0.78)**	**0.004**
Histology	(Intestinal vs. Diffuse)	0.78 (0.40–1.52)	0.47		
Previous surgery	(yes vs. no)	0.63 (0.33–1.01)	0.15		
Liver metastasis	(no vs. yes)	0.58 (0.33–1.01)	0.05		
Peritoneal metastasis	**(no vs. yes)**	**0.46 (0.25–0.82)**	**0.01**	**0.43 (0.26–0.71)**	**0.001**
Ascites	(no vs. yes)	0.68 (0.39–1.12)	0.16		
LBW	**(< 4.5% vs. ≥ 4.5%)**	**0.38 (0.23–0.64)**	**< .001**	**0.37 (0.23–0.60)**	**< .001**
ΔCAR	**(< 0.01 vs. ≥ 0.01)**	**0.38 (0.23–0.64)**	**0.04**	**0.67 (0.35–0.91)**	**0.02**

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; LBW, loss of body weight; CAR, C-reactive protein/albumin ratio; HR, hazard ratio; CI, confidence interval

Correlation of PFS with LBW and nutritional status in univariate and multivariate analyses

Similarly, we analyzed PFS in the three groups (Fig. 2). In the LBW < 4.5% group, PFS was statistically significantly better than that in the LBW ≥ 4.5% (median PFS, 2.7 vs. 2.0 months; HR, 0.63; 95%CI, 0.42–

0.94; p = 0.021) (Fig. 2A). There was also a trend towards better PFS in the WN group, although the difference was not statistically significant (HR, 0.63; 95%CI, 0.39–1.01; p = 0.050) (Fig. 2C). The univariate and multivariate results suggested that LBW < 4.5% might contribute to prolonged PFS (Table 3).

Table 3
Cox regression analysis for progression-free survival

Variable		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p–value	HR (95% CI)	p–value
Age	(< 65 vs. ≥ 65 years)	0.93 (0.56–1.53)	0.76		
ECOG PS	**(< 2 vs. ≥ 2)**	**0.55 (0.34–0.88)**	**0.01**	**0.53 (0.33–0.85)**	**0.008**
Histology	(Intestinal vs. Diffuse)	0.79 (0.46–1.36)	0.39		
Previous surgery	(yes vs. no)	0.78 (0.45–1.33)	0.35		
Liver metastasis	**(no vs. yes)**	**0.58 (0.35–0.96)**	**0.03**	**0.62 (0.40–0.98)**	**0.039**
Peritoneal metastasis	**(no vs. yes)**	**0.66 (0.39–1.12)**	**0.02**	**0.59 (0.38–0.91)**	**0.018**
Ascites	(no vs. yes)	0.74 (0.45–1.22)	0.24		
LBW	**(< 4.5% vs. ≥ 4.5%)**	**0.57 (0.37–0.90)**	**0.02**	**0.55 (0.36–0.85)**	**0.006**
ΔCAR	(< 0.01 vs. ≥ 0.01)	0.82 (0.53–1.27)	0.37		

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; LBW, loss of body weight; CAR, C-reactive protein/albumin ratio; HR, hazard ratio; CI, confidence interval

Discussion

We retrospectively examined the relationship of changes in body weight and nutritional status with the efficacy of nivolumab for AGC. To our knowledge, no previous study has shown that weight loss and worsening nutritional status from first-line chemotherapy to the start of nivolumab treatment might affect the efficacy of body weight maintenance. Moreover, we showed that good nutritional status improved OS after initiation of nivolumab. Our study suggested that if LBW can be stopped early and nutritional status can be maintained, it could greatly benefit OS after the initiation of treatment in AGC.

LBW has been reported to affect prognosis during other chemotherapy regimens for AGC [11]. However, in our study, we focused on the use of nivolumab and investigated the importance of LBW during treatment prior to nivolumab. Our results showed that LBW < 4.5% after the initiation of first-line therapy was associated with improvement in OS and PFS in AGC patients later receiving nivolumab treatment. We then investigated the effect of nutritional status before the initiation of nivolumab treatment. We evaluated the CAR, which is a simple nutritional index, and has previously been reported to correlate with prognosis in cancer patients. We found that minimal changes in the CAR from first-line chemotherapy to start of nivolumab (ΔCAR < 0.01) correlated with a better prognosis, and that improvement or maintenance of nutritional status before starting nivolumab had a positive impact on prognosis. Thus, this study suggested that maintaining nutritional status during treatment prior to nivolumab had a positive effect on patients during subsequent nivolumab treatment.

We found that the CAR is a promising indicator of nutritional status. Cancer induces inflammatory cytokines, such as IL-6 and TNF-α, and causes LBW [6, 12]. Therefore, nutritional indicators reflecting these cytokines may more sensitively indicate cancer cachexia. The CAR has been established as a prognostic indicator in patients with acute disease [13], and is a useful prognostic factor in various cancers, including AGC [9]. IL-6 induces CRP production and affects cancer cell proliferation, invasion, metastasis, angiogenesis, and resistance to treatment, via the JAK/STAT3 pathway [12]. In addition, Alb is not only a nutritional indicator, but also an indicator of inflammation in the presence of inflammatory cytokines, such as IL-8. Therefore, the CAR might be an effective marker for investigating both nutrition and inflammation. It has been reported to be a better prognostic indicator for ICI treatment than other inflammatory factors, because it reflects IL-6 [14].

Based on our results, it is important to maintain weight loss below 4.5% and change in the CAR value below 0.01. However, it is particularly difficult to improve the nutritional status of patients with gastrointestinal cancer who have poor oral intake, and consequently cachexia [15]. Moreover, in a previous report, the existence of cancer cachexia was associated with a poor clinical outcome after nivolumab treatment in AGC [5]. Anamorelin has been developed as a selective and novel oral ghrelin-like agonist [16]. Ghrelin is an endogenous peptide, secreted primarily from the stomach, which binds to its receptors and stimulates multiple pathways that regulate body weight, muscle mass, appetite, and metabolism. Anamorelin increases body weight, muscle mass, and appetite in AGC patients with cancer cachexia. While general enteral nutritional supplements and professional nutritional guidance by a dietitian are important, anamorelin may also become an important factor in future. It should be noted,

however, that although use of anamorelin has shown improvement in nutritional status, there are few data on the contribution of anamorelin itself to survival; therefore, further studies are required.

In the univariate and multivariate analyses, the LBW < 4.5% and ΔCAR < 0.01 groups had a better prognosis after nivolumab treatment (median OS, 12.9 months). In addition, the LBW < 4.5% group demonstrated better nivolumab efficacy. Our results suggested that OS and PFS in the good nutritional status group tended to be superior to those reported in the ATTRACTION-2 trial. Therefore, our study suggests that maintaining nutritional status may influence the effects of ICIs.

Our study had some limitations. First, only a few patients were included in our retrospective study. Second, the timing of the CT scans varied from case to case.

In conclusion, our study suggested that maintaining nutritional status during previous treatment may improve the effectiveness of subsequent ICI treatment. Nevertheless, further research is required in this regard.

Declarations

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Data Statement: The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Competing interests: TM received research funding from Ono Pharmaceutical Co., Ltd., Sanofi; honoraria from Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan Co., Ltd., Merck Bio Pharma Co., Ltd., MSD Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd., and Yakult Honsha Co., Ltd. However, these funding sources were not relevant to this study, and these authors declare that they have no competing interests. The rest of the authors declare no conflicts of interest.

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Ethics approval: This study was conducted in accordance with the Helsinki Declaration of 1964 and later versions and with the Ethical Guidelines for Clinical Studies. This study was approved by the institutional review boards of three participating institutions: Kobe City Medical Center General Hospital (approval no. zn210501) and Himeji Red Cross Hospital.

Author Contributions: TI: conceptualization, methodology, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and visualization. TM: conceptualization, methodology, formal analysis, investigation, data curation, writing–original draft, writing–review and editing,

visualization, supervision, project administration. Other authors: investigation, writing–review and editing, visualization.

Consent to Participate/Publish: The requirement for informed consent was waived because of the retrospective nature of the study.

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Figures

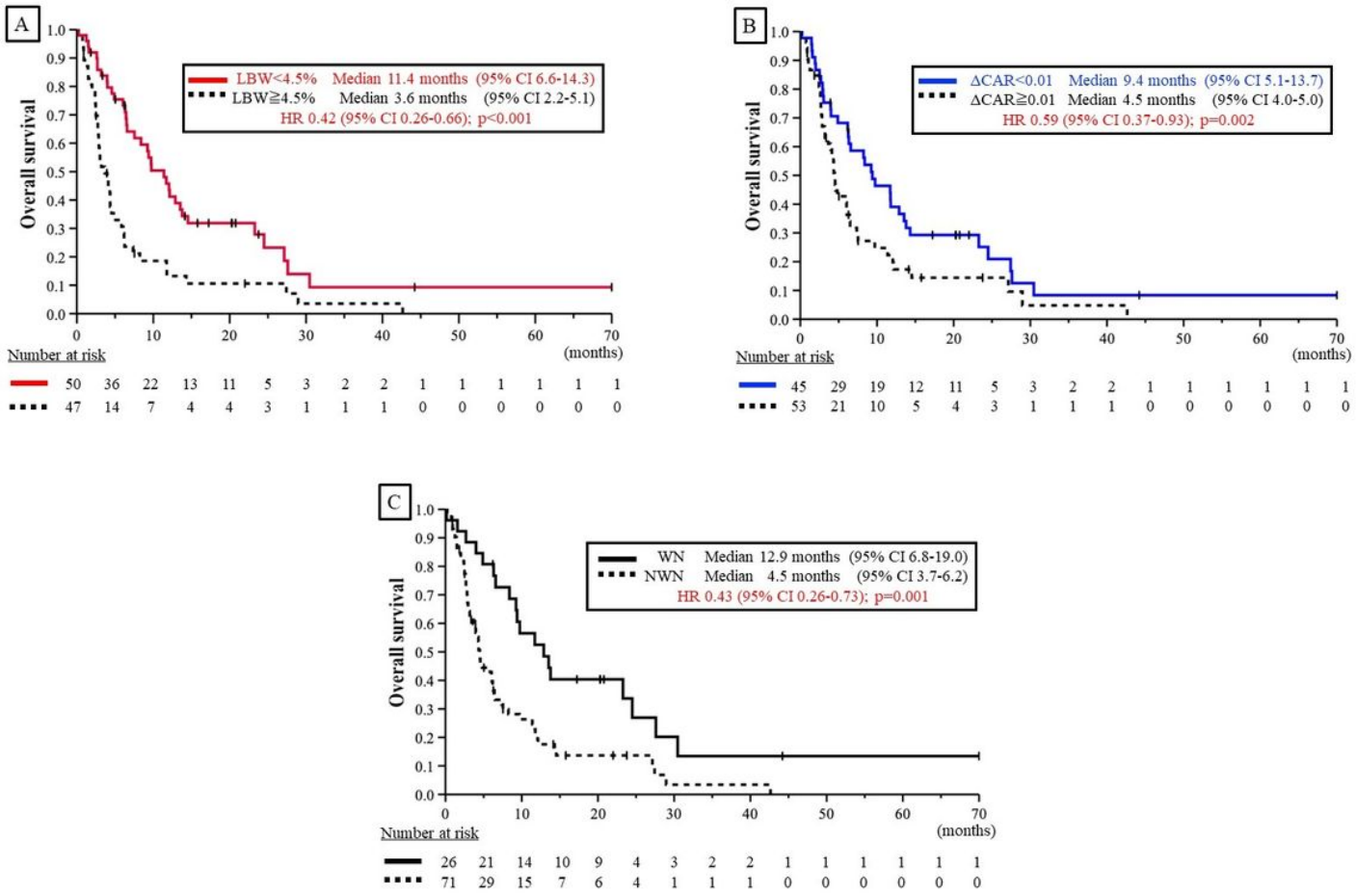

Figure 1

A. Overall survival curve in nivolumab-treated advanced gastric cancer patients classified by the rate of loss in body weight (LBW) from the start of first-line treatment to the start of nivolumab treatment (LBW < 4.5%)

Red line: LBW < 4.5% group; black dashed line: LBW ≥ 4.5% group.

B. Overall survival curve in nivolumab classified by the change in the value of C-reactive protein/albumin ratio (CAR) from the start of first-line treatment to the start of nivolumab treatment (ΔCAR < 0.01)

Blue line: CAR < 0.01 group; black dashed line: CAR ≥ 0.01 group

C. Overall survival curve in nivolumab-treated advanced gastric cancer patients classified by well-nutrition (WN) status. The WN group was defined as patients who maintained their body weight and nutrision from the start of first-line treatment to the start of nivolumab treatment (WN vs. non-WN [NWN]).

Black line: WN group; black dashed line: NWN group

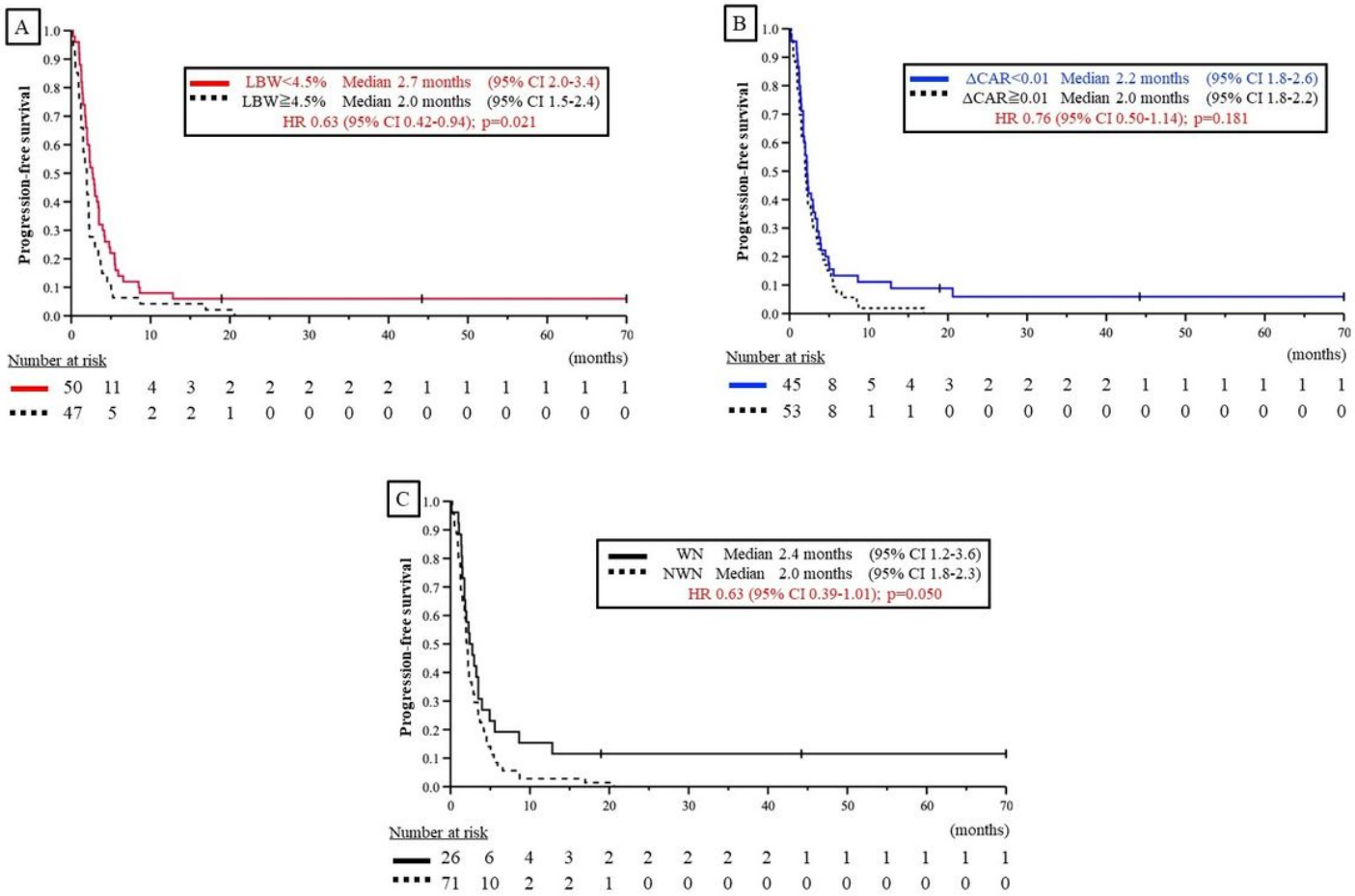

Figure 2

A. Progression-free survival curve in nivolumab-treated advanced gastric cancer patients classified by the rate of loss in body weight (LBW) from the start of first-line treatment to the start of nivolumab treatment (LBW < 4.5%)

Red line: LBW < 4.5% group; black dashed line: LBW ≥ 4.5% group.

B. Progression-free survival curve in nivolumab-treated advanced gastric cancer patients classified by the change in the value of C-reactive protein/albumin ratio (CAR) from the start of first-line treatment to the start of nivolumab treatment (ΔCAR < 0.01)

Blue line: CAR < 0.01 group; black dashed line: CAR ≥ 0.01 group

C. Progression-free survival curve in nivolumab classified by well-nutrition (WN) status. WN group was defined as patients who maintained their body weight and nutrision from the start of first-line treatment to the start of nivolumab (WN vs. non-WN [NWN]).

Black line: WN group; black dashed line: NWN group