Effect of perioperative nutritional status, inflammatory response and postoperative chemotherapy on survival after gastrectomy for advanced gastric cancer

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Abstract. Despite the availability of numerous perioperative prognostic indicators for advanced gastric cancer, their relative predictive accuracy has not been compared. The present study investigated the association of these indicators and postoperative chemotherapy with patient survival in advanced gastric cancer. A total of 142 patients with stage II-IV gastric cancer who underwent gastrectomy with R0/R1 resection were examined. The preoperative modified Glasgow prognostic score (mGPS), controlling nutritional status score, CRP-to-albumin ratio, prognostic nutritional index and neutrophil-to-lymphocyte ratio was calculated. Postoperative serum CRP was evaluated as the CRPmax. Postoperative chemotherapy was administered according to the Japanese Gastric Cancer Treatment Guidelines. Patients were divided into chemotherapy and no chemotherapy groups, followed by propensity score matching to adjust for background factors. The endpoints were relapse-free survival (RFS) and overall survival (OS). Prognostic factors were evaluated using the Cox proportional hazard model. The OS and RFS were found to be improved in the chemotherapy group compared with the no chemotherapy group ($P<0.05$) and in the low mGPS group compared with the high mGPS group ($P<0.05$). Stepwise regression analysis identified the mGPS as the most reliable preoperative marker for both OS and RFS. Cox analysis of the matched groups revealed that postoperative chemotherapy was an independent prognostic factor for RFS and that mGPS was an independent prognostic factor for OS. A preoperative CRP of <0.3 mg/dl and a low mGPS score were found to be independent prognostic factors for RFS in the chemotherapy group. Overall, postoperative chemotherapy was found to reduce recurrence in advanced gastric cancer, while the preoperative mGPS was a strong prognostic marker for OS. Improving the preoperative mGPS may therefore improve both OS and the effectiveness of postoperative chemotherapy, but future large-scale studies are needed.

Introduction

A total of 968,350 cases of newly diagnosed gastric cancer and 659,853 associated mortalities were reported in 2022, making it the fifth leading cause of mortality worldwide. Furthermore, gastric cancer is most prevalent in Northeast Asia (Japan, China and Korea) (1). The most common symptoms of gastric cancer are dyspepsia, anorexia, early satiety, weight loss and abdominal pain. The presence of symptoms at diagnosis corresponds to already advanced and incurable disease (2). Furthermore, poor preoperative nutrition is associated with postoperative complications and poorer outcomes. A previous report suggested that preoperative sarcopenia increases postoperative complications and worsens patient prognosis in TNM stage II-III gastric cancer; however, it does not worsen the prognosis of patients with TNM stage I cancer (3). A number of nutritional markers have been proposed to predict the prognosis of patients with gastric cancer, including the prognostic nutritional index (PNI), controlling nutritional status (CONUT) score, neutrophil-to-lymphocyte ratio (NLR), CRP-to-albumin ratio (CAR) and modified Glasgow prognostic score (mGPS) (4-10). In addition, a high serum CRP concentration has previously been associated with poor prognosis in patients with gastric cancer (11). Postoperative adjuvant chemotherapy (ACT) may improve the prognosis of patients after surgery for stage II-III gastric cancer (12). However, although a number of perioperative inflammatory, immunological and nutritional markers have been proposed, the association between these prognostic markers and postoperative chemotherapy has not been established; hence, the

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most clinically important markers have not yet been determined. The present study therefore first aimed to identify the most important preoperative prognostic nutritional markers for patients with stage II-IV gastric cancer using a multivariate stepwise Cox regression analysis. Subsequently, independent prognostic factors were evaluated, including key preoperative nutritional indicators, postoperative complications/inflammation and postoperative chemotherapy, to propose possible nutritional or medical interventions that may improve survival outcomes. Furthermore, factors associated with enhanced effectiveness of postoperative chemotherapy in these patients were investigated.

Materials and methods

Patient enrolment. A total of 376 patients with gastric cancer who underwent gastrectomy with lymphadenectomy at the Department of Digestive Surgery, Kawasaki Medical School Hospital (Kurashiki, Japan) between January 2011 and December 2021 were enrolled. Inclusion criteria were: i) Patients with gastric adenocarcinoma that received gastrectomy; ii) pathological stage II-IV disease; and iii) R0 or R1 resection. Exclusion criteria were: i) R2 resection; ii) in-hospital death; and iii) pathological stage I disease.

In total, 142 patients with stage II-IV gastric cancer who underwent gastrectomy with R0 or R1 resection were ultimately examined (Fig. 1). All included patients exhibited evidence of gastric adenocarcinoma in biopsy specimens. Preoperative tumour staging was based on the findings of upper gastrointestinal series, endoscopy and enhanced CT scans according to the eighth edition of the UICC classification of malignant tumours (13). Notable postoperative complications were classified as those with a Clavien-Dindo grade of ≥2 (14,15). The Institutional Review Board of Kawasaki Medical School (Kurashiki, Japan) approved the present study (approval no. 6680-01). Data were collected from the medical records and the details of the present retrospective study were provided on the website of the hospital. All patients were followed up regularly until April 2024 or mortality.

Preoperative nutritional factors. Routine laboratory measurements of the albumin, cholesterol and CRP concentrations were performed 1-4 weeks before surgery. The preoperative NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count (16). The CAR was evaluated simultaneously (10). The mGPS was determined by serum CRP and albumin concentrations (17,18). A mGPS of 2 was defined by the presence of both increased CRP (>0.3 mg/dl) and hypoalbuminemia (<3.5 g/dl). The presence of only one of these abnormalities was allocated a mGPS of 1, whereas the absence of both abnormalities was allocated a mGPS of 0. The CONUT score was calculated as previously described (17). Patients were categorised based on their CONUT score as having a normal nutritional status (CONUT score: 0-1), mild risk of malnutrition (CONUT score: 2-4), moderate risk of malnutrition (CONUT score: 5-8) or severe risk of malnutrition (CONUT score: 9-12). The preoperative PNI was calculated as: PNI=10x serum albumin concentration (g/dl) + 0.005 x peripheral lymphocyte count/mm^3. The cut-off value of the PNI was set at 45 according to previously published data (18).

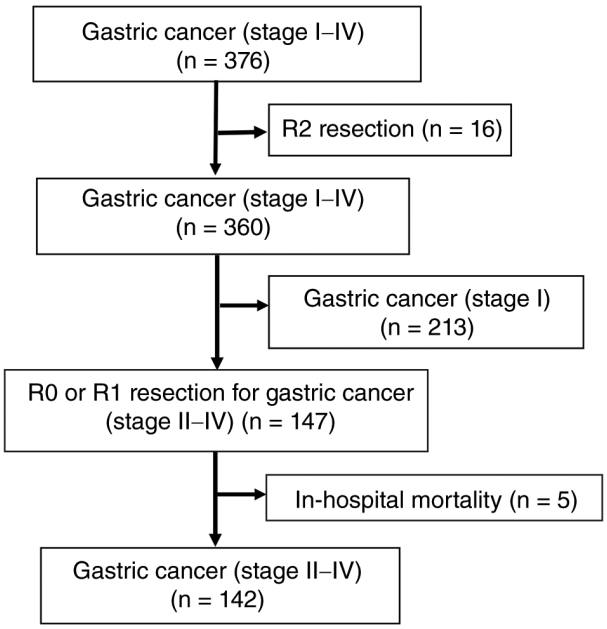

Figure 1. Flow diagram of patient inclusion and exclusion.

Postoperative inflammatory response. Systemic inflammatory response after gastrectomy was evaluated based on serum CRP measured on postoperative days 1, 3, 5 and 7, with additional measurements performed depending on the condition of each patient. The highest serum CRP concentration from surgery until hospital discharge was defined as the CRPmax, while the cut-off value was set as the median (11).

Postoperative chemotherapy. Postoperative chemotherapy or ACT was administered following the Japanese Gastric Cancer Treatment Guidelines (12). Before 2017, S-1 monotherapy was selected for all patients. Since 2018, S-1/docetaxel, S-1/cisplatin, capecitabine/cisplatin or oxaliplatin have been selected as postoperative chemotherapy or ACT for pathological stage III-IV gastric cancer. The final decision regarding the postoperative chemotherapy or ACT was made by outpatient doctors (19-23).

Statistical analysis. A time-dependent receiver operating characteristic curve was generated to evaluate the sensitivity and specificity of the NLR, CAR and CRPmax in predicting relapse-free survival (RFS). Subsequently, the Youden's index was used to determine the optimal cut-off values for these continuous variables. Overall survival (OS) was defined as the time between surgery and mortality or the final date on which the vital status information was available. RFS was defined as the time from surgery to the date of disease relapse or mortality from any cause. Patients without recurrence or mortality were censored at the last follow-up. For patients with R1 resection, recurrence was determined by the attending physician based on clinical findings, including imaging studies and tumour marker concentrations. Survival was estimated using the Kaplan-Meier method and the groups were compared using the two-sided log-rank test. Multiple comparisons of survival rates were performed using the Holm method. Univariate and multivariate analyses for OS

Table I. Characteristics of patients who underwent gastrectomy with or without postoperative chemotherapy.

Covariate	Chemotherapy (+), n=80	Chemotherapy (-), n=62	P-value
Mean age, years	67.33±8.95	77.40±7.33	0.001[a]
Sex			
Male	63	45	0.432
Female	17	17	
Tumor location			
Upper	22	9	0.154
Middle	31	31	
Lower	27	22	
Lauren classification			
Intestinal	34	33	0.237
Diffuse	46	29	
pStage[b]			0.020[a]
II	29	35	
III	43	19	
IV	8	8	
Depth of tumor invasion			
pT1	3	2	0.226
pT2	12	8	
pT3	24	29	
pT4a, T4b	41	23	
Lymph node metastasis			
N0	14	28	0.001[a]
N1	14	8	
N2	21	16	
N3	31	10	
Extent of resection			
R0	73	54	0.583
R1	7	8	
Procedures			
TG	37	18	0.075
PG	1	1	
DG	42	43	
Postoperative complications (≥Clavien-Dindo grade II)			0.115
Yes	15	19	
No	65	43	

[a]Statistically significant. [b]TNM classification 8th edition. TG, total gastrectomy; DG, distal gastrectomy; PG, proximal gastrectomy.

were performed using the Cox proportional hazard regression model and survival was determined by the 95% CIs. P<0.05 was considered to indicate a statistically significant difference. Preoperative variables were entered into a multivariable Cox proportional hazards model and subjected to backward step-wise variable selection based on P-values. At each step, the variable with the highest non-significant P-value was removed and the procedure was repeated until only variables meeting the predefined significance criterion remained in the final model. Only variables retained in the final model are reported in the multivariable analysis tables. The propensity score (PS) was calculated using a multivariable logistic regression model in which the independent variables were age, sex, cancer site, operative procedures, Lauren classification, pathological TNM stage, lymph node metastasis and depth of tumour invasion. The inverse probability of treatment weighting (IPTW) was calculated using the formula (1/PS) for the postoperative chemotherapy group and [1/(1-PS)] for the no chemotherapy group. The PS was used to match the postoperative chemotherapy and no chemotherapy groups using the IPTW method. Next, the Cox proportional hazards model was used to analyse the PS-matched groups.

Statistical analyses were performed using commercial software including JMP (version 17; JMP Statistical

Table II. Univariate analyses of the prognostic factors for RFS and OS.

A, RFS

	Univariate analysis		
Covariate	HR	95% CI	P-value
Age, >75 years	1.423	0.881-2.298	0.149
Sex			
Male:female	1.482	0.810-2.713	0.202
Stage			
II:III:IV	1.987	1.379	0.001[a]
Lauren classification			
Intestinal:diffuse	1.433	0.887-2.315	0.145
Tumor location			
Upper:middle:lower	0.855	0.624-1.172	0.331
Procedures			
TG:DG and PG	0.966	0.603-1.548	0.885
Postoperative complications			
≥Clavien-Dindo grade II	1.757	1.056-2.923	0.030[a]
mGPS			
0:1:2	1.433	1.083-1.896	0.012[a]
CONUT score			
Mild:moderate:severe	1.050	0.871-1.518	0.326
PNI			
>45	0.681	0.423-1.097	0.114
NLR			
High:low	1.747	1.086-2.808	0.021[a]
CAR			
High:low	1.790	1.116-2.870	0.016[a]
Postoperative CRPmax			
High:low	1.144	0.715-1.829	0.576
Postoperative chemotherapy			
Yes:no	0.600	0.373-0.966	0.036[a]
Hospital stay, median	1.696	0.963-2.987	0.067

B, OS

	Univariate analysis		
Covariate	HR	95% CI	P-value
Age, >75 years	1.867	1.132-3.079	0.014[a]
Sex			
Male:female	1.548	0.825-2.906	0.174
Stage			
II:III:IV	1.583	1.098-2.283	0.014[a]
Lauren classification			
Intestinal:diffuse	1.405	0.849-2.324	0.186
Tumor location			
Upper:middle:lower	0.783	0.563-1.087	0.143

Table II. Continued.

B, OS

Covariate	Univariate analysis		
	HR	95% CI	P-value
Procedures			
TG:DG and PG	1.045	0.634-1.721	0.864
Postoperative complications			
≥Clavien-Dindo grade II	1.524	0.883-2.632	0.131
mGPS			
0:1:2	1.497	1.120-2.000	0.006
CONUT score			
Mild:moderate:severe	1.160	0.865-1.555	0.321
PNI			
>45	0.755	0.459-1.24	0.266
NLR			
High:low	1.472	0.899-2.410	0.124
CAR			
High:low	1.801	1.099-2.951	0.020[a]
Postoperative CRPmax			
High:low	0.968	0.592-1.581	0.896
Postoperative chemotherapy			
Yes:no	0.538	0.327-0.886	0.015[a]
Hospital stay, median	1.716	0.977-3.014	0.060

[a]Statistically significant. TG, total gastrectomy; DG, distal gastrectomy; PG, proximal gastrectomy; mGPS, modified Glasgow prognostic score; CONUT, controlling the nutritional status; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; CAR, CRP-to-albumin ratio; CRPmax, maximum CRP concentration from surgery until hospital discharge; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival.

Discovery LLC) and Stata (version 14; StataCorp LLC), as well as open-source software including R (version 3.1.1; Posit Software, PBC).

Results

Table I outlines the characteristics of the groups with and without postoperative chemotherapy. A total of 80 patients received postoperative chemotherapy, while 62 received no chemotherapy. The median period of postoperative chemotherapy administration was 312 days (25th-75th percentile: 111.4-365.0 days). Postoperative chemotherapy was more commonly administered to younger patients compared with older patients (P=0.00001). The resection extent was R0 in 127 patients and R1 in 15 patients. A total of 12 patients with R1 resection exhibited positive peritoneal lavage cytology and 8 of the 15 patients with R1 resection received postoperative S-1-based chemotherapy. A total of 72 patients with stage II or III gastric cancer received ACT. Furthermore, 62 patients refused ACT or chemotherapy because of concerns regarding age, toxic effects or comorbidities. Fig. 2 demonstrates the RFS and OS in the chemotherapy and no chemotherapy groups. The 3- and 5-year RFS was 67.8 and 58.8% in the postoperative chemotherapy group, respectively and 52.1 and 42.1% in the no chemotherapy group, respectively. The postoperative chemotherapy group exhibited significantly improved RFS compared with the no chemotherapy group (P=0.0338; Fig. 2A). The 3- and 5-year OS was 79.3 and 66.4% in the postoperative chemotherapy group, respectively and 61.9 and 49.5% in the no chemotherapy group, respectively. The postoperative chemotherapy group exhibited significantly improved OS compared with the no chemotherapy group (P=0.0133; Fig. 2B). Fig. 3 shows the RFS and OS according to the mGPS. The RFS was significantly improved in the mGPS 0 group compared with the mGPS 2 group (P=0.0389; Fig. 3A). Similarly, the OS was significantly improved in the mGPS 0 group compared with the mGPS 2 group (P=0.0214; Fig. 3B).

The cut-off values were 2.534 for the NLR [area under the curve (AUC): 0.559; sensitivity: 0.586; specificity: 0.634) and 0.079 for the CAR (AUC: 0.599; sensitivity: 0.476; specificity: 0.714), which were evaluated by comparing low vs. high values. Table IIA and B presents the univariate analyses of prognostic factors for OS and RFS. The prognostic factors for RFS were the pathological stage, postoperative complications, mGPS,

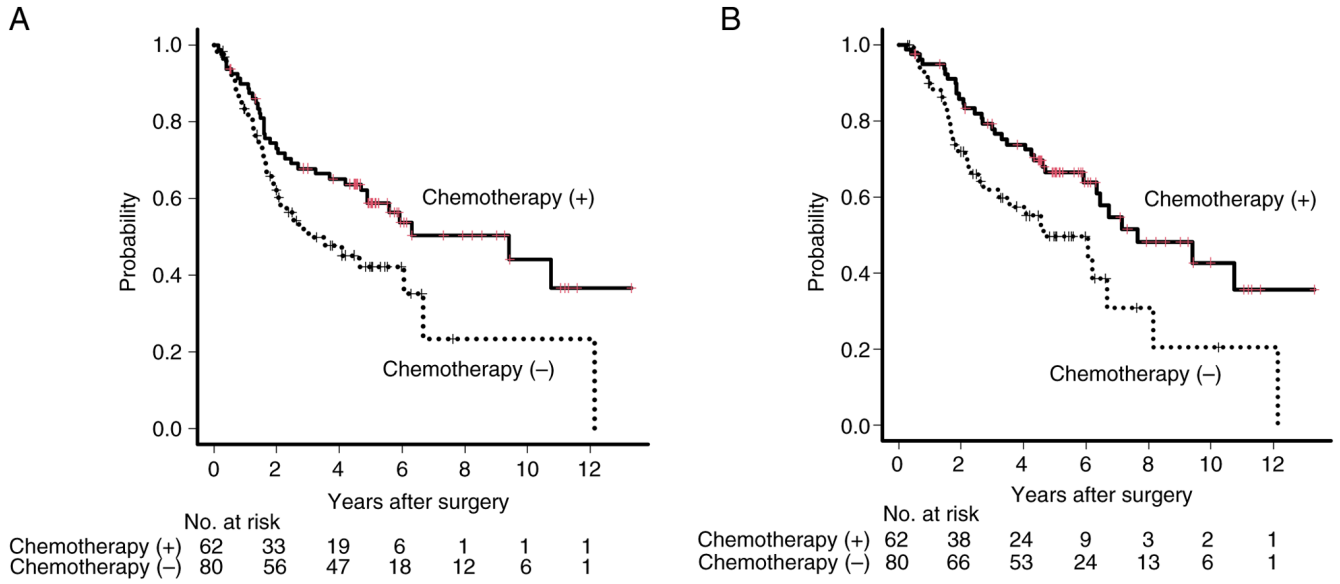

Figure 2. (A) RFS of patients who underwent gastrectomy for advanced gastric cancer with vs. without postoperative chemotherapy. The RFS was significantly improved in the postoperative chemotherapy group compared with the no chemotherapy group (P=0.0338). (B) OS of patients who underwent gastrectomy for advanced gastric cancer with vs. without postoperative chemotherapy. The OS was significantly improved in the postoperative chemotherapy group compared with the no chemotherapy group (P=0.0133). RFS, relapse-free survival; OS, overall survival.

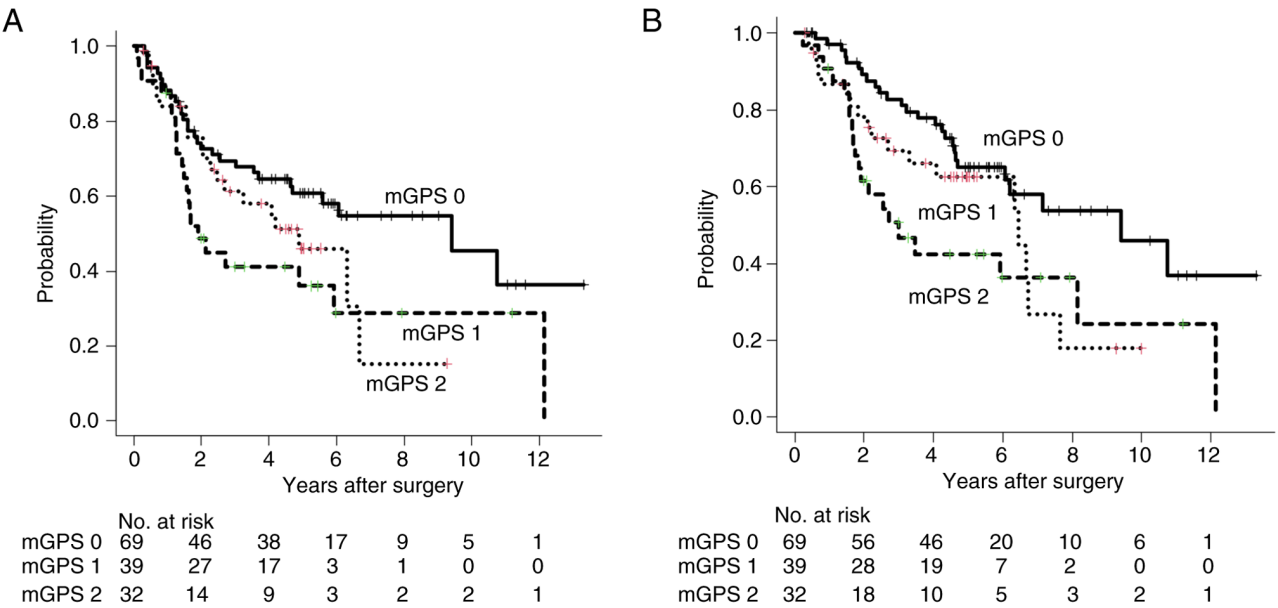

Figure 3. (A) RFS according to the mGPS of patients who underwent gastrectomy for advanced gastric cancer. The RFS was significantly improved in the mGPS 0 group compared with the mGPS 2 group (P=0.0389). (B) OS according to the mGPS of patients who underwent gastrectomy for advanced gastric cancer. The OS was significantly improved in the mGPS 0 group compared with the mGPS 2 group (P=0.0214). RFS, relapse-free survival; OS, overall survival; mGPS, modified Glasgow prognostic score.

NLR, CAR and postoperative chemotherapy. The prognostic factors for OS comprised age, pathological stage, mGPS, CAR and postoperative chemotherapy.

The preoperative nutritional/inflammatory indicators of the candidate entered in the final Cox model were extracted from univariate and multivariate analyses using the stepwise method. The mGPS was found to be the most reliable preoperative marker for both OS and RFS (Table IIIA and B). Table IVA and B describes the final Cox regression analysis. The pathological stage was an independent prognostic factor for OS and a low mGPS tended to be associated with improved OS (P=0.0957). Postoperative chemotherapy and pathological stage were independent prognostic factors for RFS. After IPTW, postoperative chemotherapy and postoperative complications were independent prognostic factors for RFS and the mGPS was an independent prognostic factor for OS (Tables V and VI).

The associations between the timing of postoperative chemotherapy administration, relative performance (RP) value (administered/planned doses x 100%) and perioperative

Table III. Univariate and multivariate analysis of preoperative nutritional/inflammatory factors for RFS and OS using the stepwise method.

A, RFS

	Univariate analysis			Multivariate analysis after stepwise		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
CAR						
High:low	1.231	0.461-3.286	0.678			
CONUT score						
Mild:moderate:severe	0.722	0.449-1.161	0.179			
NLR						
High:low	1.573	0.950-2.606	0.078			
PNI						
>45	0.710	0.346-1.455	0.349			
mGPS						
0:1:2	1.364	0.656-2.829	0.405	1.433	1.083-1.896	0.012[a]

B, OS

	Univariate analysis			Multivariate analysis after stepwise		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
CAR						
High:low	0.814	0.282-2.351	0.722			
CONUT score						
Mild:moderate:severe	0.749	0.449-1.250	0.088			
NLR						
High:low	1.315	0.779-2.218	0.533			
PNI						
>45	0.962	0.438-2.112	0.504			
mGPS						
0:1:2	1.939	0.867-4.339	0.086	1.497	1.120-2.000	0.006

[a]Statistically significant. CAR, CRP-to-albumin ratio; CONUT, controlling the nutritional status; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; HR, hazard ratio; RFS, relapse-free survival; OS, overall survival.

inflammatory response with RFS and OS were also investigated. The preoperative mGPS and serum CRP of <0.3 mg/dl were independent prognostic factors for RFS (Table VII).

Discussion

Associations between perioperative nutritional and inflammatory immunological markers and postoperative chemotherapy with the prognosis of patients who underwent gastrectomy for advanced gastric cancer were evaluated in the present study. The present study was unique as the priorities of perioperative prognostic biomarkers were analyzed using the stepwise method and incorporated into the final Cox model. Postoperative chemotherapy, including ACT, was found to be an independent prognostic factor for both OS and RFS in the overall cohort. However, after PS matching, postoperative chemotherapy was independently associated only with RFS, whereas mGPS remained an independent prognostic factor for OS.

The mGPS, which is based on serum CRP and albumin concentrations, was found to be an independent prognostic factor for OS after gastrectomy for advanced gastric cancer. Previously, a negative association between serum albumin and CRP concentrations was reported (24). Furthermore, the present authors previously reported that nutritional intervention in patients scheduled for gastrointestinal cancer surgery was only effective for those with CRP of ≤0.82 mg/dl before the intervention (25). A number of reports have evaluated the association between gastric cancer progression and the mGPS (26-29). A previous meta-analysis also showed that a high Glasgow prognostic score or mGPS is associated with poor survival in patients with gastric cancer (30). Thus, the

Table IV. Multivariate Cox analyses of the prognostic factors for RFS and OS.

A, RFS

Covariate	HR	95% CI	P-value
Age, >75 years	0.957	0.523-1.751	0.886
Sex			
Male:female	1.297	0.696-2.418	0.412
Stage			
II:III:IV	2.218	1.518-3.241	0.001[a]
Procedures			
TG:others (PG and DG)	0.952	0.568-1.596	0.851
mGPS			
0:1:2	1.247	0.926-1.681	0.146
Postoperative chemotherapy			
Yes:no	0.547	0.305-0.983	0.043[a]
Postoperative complications			
≥Clavien-Dindo grade II	1.568	0.907-2.711	0.108

B, OS

Covariate	HR	95% CI	P-value
Age, >75 years	1.392	0.750-2.582	0.294
Sex			
Male:female	1.805	0.930-3.500	0.081
Stage			
II/III:IV	1.682	1.154-2.449	0.007[a]
Procedure			
TG:others (PG and DG)	0.939	0.547-1.626	0.821
mGPS			
0:1:2	1.301	0.956-1.773	0.097
Postoperative chemotherapy			
Yes:no	0.615	0.338-1.121	0.112
Postoperative complications			
≥Clavien-Dindo grade II	1.182	0.675-2.070	0.558

[a]Statistically significant. TG, total gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; mGPS, modified Glasgow prognostic core; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio.

Table V. Multivariate Cox analyses of the prognostic factors for relapse-free survival after inverse probability of treatment weighting.

Covariate	HR	95% CI	P-value
Age, >75 years	0.912	0.473-1.757	0.784
Sex			
Male:female	1.153	0.569-2.337	0.692
Stage			
II:III:IV	2.022	1.239-3.299	0.050
Procedures			
TG:others (PG and DG)	0.771	0.411-1.444	0.417
mGPS			
0:1:2)	1.337	0.954-1.872	0.091
Postoperative chemotherapy			
Yes:no	0.488	0.256-0.930	0.029[a]
Postoperative complications			
≥Clavien-Dindo grade II	2.108	1.061-4.189	0.033[a]

[a]Statistically significant. TG, total gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; mGPS, modified Glasgow prognostic core; HR, hazard ratio.

Table VI. Multivariate Cox analyses of the prognostic factors for overall survival after inverse probability of treatment weighting.

Covariate	HR	95% CI	P-value
Age, >75 years	1.366	0.763-2.446	0.293
Sex			
Male:female	1.792	0.847-3.793	0.127
Stage			
II:III:IV	1.575	0.973-2.551	0.064
Procedure			
TG:others (PG and DG)	0.819	0.431-1.554	0.542
mGPS			
0:1:2	1.675	1.198-2.340	0.003[a]
Postoperative chemotherapy			
Yes:no	0.549	0.295-1.021	0.058
Postoperative complications			
≥Grade II	1.268	0.695-2.315	0.438

[a]Statistically significant. TG, total gastrectomy; PG, proximal gastrectomy; DG, distal gastrectomy; mGPS, modified Glasgow prognostic score; HR, hazard ratio.

survival of patients with advanced gastric cancer can be improved by increasing the mGPS through the suppression of the preoperative inflammatory response and increasing serum albumin concentration. However, a limitation of the present study was the lack of a direct comparison between mGPS, CAR and NLR. Such a comparison was not feasible because of the marked overlap between CAR and mGPS and the limited number of events. Further studies with larger sample sizes are warranted to compare their prognostic performance.

There are two methods that may be used to decrease the amount of CRP released from tumours and increase serum albumin concentration. Firstly, one method is to improve the preoperative nutritional status by administering supplements. According to the European Society for Clinical Nutrition

Table VII. Univariate analysis of the prognostic factors in patients who received chemotherapy after gastrectomy for advanced gastric cancer.

	Relapse-free survival			Overall survival		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Relative performance						
≥70 vs. <70%	1.025	0.513-2.047	0.945	0.992	0.474-2.074	0.983
Administration period						
Before 2017 vs. after 2018	0.756	0.338-1.687	0.494	0.782	0.329-1.859	0.578
Preoperative CRP concentration						
≥0.3 mg/dl vs. <0.3 mg/dl	1.984	1.018-3.866	0.044[a]	1.740	0.861-3.515	0.123
Postoperative CRPmax						
≥12.27 mg/dl vs. <12.27 mg/dl	1.255	0.651-2.420	0.497	1.060	0.532-2.112	0.869
Postoperative complications						
Yes vs. no	1.904	0.889-4.078	0.097	1.634	0.729-3.662	0.233
mGPS						
0/1/2	1.565	1.043-2.350	0.031[a]	1.423	0.924-2.191	0.109

[a]Statistically significant. HR, hazard ratio; CRPmax, maximum CRP concentration from surgery until hospital discharge; mGPS, modified Glasgow prognostic score.

and Metabolism recommendation, oral nutritional supplements alone are insufficient as nutritional therapy for cancer accompanied by inflammation (26). However, the nutritional status can be improved by administering fish oil containing omega-3 fatty acids and immunonutrition (31). The alternative method used to reduce CRP concentration and increase albumin concentration is neoadjuvant therapy. According to the Japanese Gastric Cancer Treatment guidelines, there is no consensus on the usefulness of neoadjuvant therapy for gastric cancer (12), while the National Comprehensive Cancer Network guidelines recommend preoperative chemotherapy or chemoradiotherapy for grade T2 or higher gastric cancer (32). Hence, suppressing cytokine release from tumours while improving the nutritional status by neoadjuvant therapy administered before surgery may be important to improve the prognosis of patients with advanced gastric cancer. However, this hypothesis requires further verification in clinical studies on neoadjuvant therapy for gastric cancer in Japan.

The present study also demonstrated that postoperative chemotherapy, including ACT, decreased recurrence after gastrectomy, which is compatible with the Japanese Gastric Cancer Treatment guidelines (12). Univariate analysis of the postoperative chemotherapy group showed that preoperative CRP of <0.3 mg/dl and a low mGPS score were prognostic factors for RFS, but not for OS. Thus, the inflammatory and nutritional status of the host may influence the effectiveness of postoperative chemotherapy. A possible explanation is that an elevated mGPS, reflecting increased CRP levels and hypoalbuminemia, is associated with an immunosuppressive tumour microenvironment (TME). Previous studies have suggested that systemic inflammation may promote the expansion of myeloid-derived suppressor cells, induce M2 macrophage polarisation and impair cytotoxic T-cell activity, thereby facilitating tumour recurrence and reducing sensitivity to chemotherapy (33-35). Improving the preoperative TME may increase the intensity of postoperative chemotherapy and contribute to improving the prognosis of patients with advanced gastric cancer. Namely, perioperative immunonutrition enriched with omega-3 fatty acids may reduce systemic inflammation and improve nutritional status (31).

Furthermore, neoadjuvant chemotherapy may reduce systemic inflammation by decreasing tumour burden (36), potentially improving the mGPS score before surgery. Therefore, neoadjuvant treatment and/or perioperative immunonutrition rich in omega-3 fatty acids may be beneficial for improving preoperative mGPS. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trials showed that S-1 is an effective adjuvant treatment for East Asian patients who have undergone D2 dissection for locally advanced gastric cancer (stage II-III) (36). Subsequently, the Japan Clinical Cancer Research Organization Gastric Cancer-07 trial showed that adding docetaxel to S-1 is effective and has few safety concerns in patients with stage III gastric cancer (22). Therefore, the effect of postoperative chemotherapy was analysed in patients treated before 2017 compared with those treated after 2018. However, survival did not differ between the two periods. A previous analysis of the RP values showed that continuing S-1 ACT for a full year exhibited a greater effect on survival compared with the ACT dosage (37). Furthermore, 1-year continued S-1 ACT and RP values of >70% were associated with improved survival in the ACTS-GC trial (38). However, the association between RP levels and prognosis in patients who receive ACT after gastric cancer surgery remains debatable. Whether these discrepancies between the studies were due to differences between facilities or differences between clinical trials and actual clinical practice remains unclear.

In conclusion, the present study showed that postoperative chemotherapy for advanced gastric cancer suppressed

postoperative recurrence but did not extend OS. In addition, improving the preoperative mGPS may contribute to improved OS and potentially enhance the effectiveness of postoperative chemotherapy. It is further hypothesised that neoadjuvant setting and/or immunonutrition rich in omega-3 fatty acids should be recommended to improve the prognosis of patients with advanced gastric cancer. However, as the present study was retrospective and had a small sample size, further investigations are needed to validate the present results.

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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

YF, YE and MK designed the present study. YF, SE, MHo and MHi analysed the data. YF, AF and RM interpreted the data. KY and TU critically reviewed the study findings, provided important intellectual input on the interpretation of the results and the revision of the manuscript, and approved the final manuscript. YF and SE confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Kawasaki Medical School (approval no. 6680-01) and the details of the present retrospective study were provided on the website of the hospital. The patients were given the opportunity to decline participation (opt-out). Patients who would decline participation would be excluded from the study. No patients were excluded.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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