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The Combination of Inflammation and Nutrition Factors Reinforces the Prognostic Prediction for Stage III Colorectal Cancer Patients After Curative Resection

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Abstract

Purpose

Inflammation and nutritional status are known to be associated with the prognosis of several malignancies. Herein, we attempted to develop inflammation–nutrition scores and predict the prognosis of stage III colorectal cancer (CRC).

Methods

This retrospective study included 262 patients with stage III CRC who underwent curative surgery and were divided into two groups: a training set (TS) of 162 patients and a validation set (VS) of 100 patients. In the TS, clinicopathological factors were tested using a Cox regression model, and the Kansai prognostic score (KPS) was assessed by 1 point each for <3.5 g/dL albumin level, >450 monocyte counts, and $<1.65 \times 10^5$ platelet counts, which were associated with disease-free survival (DFS). Using KPS, DFS and overall survival (OS) were validated in VS.

Results

The C-indices of KPS to predict DFS and OS in TS were 0.707 and 0.772. It was validated in VS that the C-indices of KPS to predict DFS and OS were 0.618 and 0.708, respectively. A high KPS was a significant predictor of DFS and OS.

Conclusion

KPS serves as a new model for the prognosis of patients with stage III CRC.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide and the fourth most common cause of cancer-related deaths[1]. Previous studies have shown that postoperative adjuvant chemotherapy improves overall survival in patients with stage III CRC who have undergone radical resection[2]. Adjuvant chemotherapy with oxaliplatin reduces the risk of recurrence by approximately 20% compared with fluoropyrimidine alone and is the recommended regimen[3 4]. However, oxaliplatin is often associated with adverse events, such as neuropathy and decline in long-term activities of daily living in some patients[5–7]. Therefore, it would be useful to identify a low-risk group for recurrence in which oxaliplatin can be omitted. Nevertheless, there are limitations in predicting the favorable prognosis group among patients with stage III CRC based only on the tumor-node-metastasis (TNM) stage.

Several attempts at nutritional prognostic scores have been made by scientists, including the modified Glasgow prognostic score (mGPS)[8], prognostic nutritional index (PNI)[9], lymphocyte-to-monocyte ratio (LMR)[10], and platelet-to-lymphocyte ratio (PLR)[11]. In addition, we have reported that integrating the TNM stage and the scoring system, which comprises preoperative albumin, total lymphocyte counts (TLC), and C-reactive protein (CRP), enabled accurate prediction of the prognosis of patients with CRC after curative resection[12]. Identifying both the nutritional status and inflammation by these indicators and tumor status by TNM staging is expected to be important and useful in predicting low-risk groups for recurrence and mortality in patients with stage III CRC.

Therefore, we expected that the nutritional and inflammation factors would be useful in predicting the low-risk group, although TNM stage alone has limitations. This study aimed to develop a new nutritional-inflammation score which would be useful in identifying a favorable prognosis group in Stage III CRC patients. In this study, we examined the association of disease-free survival (DFS) and overall survival (OS) with each of multiple clinicopathological factors, and identified the most relevant factors. We developed a new prognostic model, the Kansai prognostic score (KPS), which comprises albumin level, monocyte count (MC), and platelet count (PC), and evaluated the correlation between KPS and clinicopathological factors. Additionally, we demonstrated the association of KPS with DFS and OS. We then tested whether KPS could stratify patients based on DFS and OS and whether it was related to postoperative complications in a separate case set. The combination of several patient status factors may be useful for future clinical studies on the prognosis of patients with stage III CRC.

Methods

Patients and datasets

A total of 740 patients with CRC were selected from patient records for this retrospective study, 478 of whom were excluded due to exerting stage 0, I, II, and IV disease and/or acquiring inadequate data concerning histology and follow-up. All patients had a histologically confirmed diagnosis of CRC and underwent primary resection between 2007 and 2014. The remaining 262 patients were divided into two groups: (i) a training set (TS) of 162 patients who underwent resection of their primary tumors at the Osaka International Cancer Institute (OICI) between 2007 and 2013 and (ii) a validation set (VS) of 100 patients who underwent curative surgery at Osaka University between 2011 and 2014.

Clinicopathological evaluation and follow-up

Data on age, sex, and pathologic findings, such as tumor invasion, lymph node metastasis, lymphovascular invasion, venous invasion, and histologic grade, were obtained from medical records. The extent of tumor spread was assessed using computed tomography (CT), magnetic resonance imaging and/or positron emission tomography (PET). Surgical specimens were fixed in formalin, treated with a stepwise series of ethanol washes, and embedded in paraffin. Sections were stained with hematoxylin and eosin and Elastica van Gieson to determine the histological grade and extent of

lymphatic and venous infiltration respectively. Relevant clinicopathological factors were assessed according to the TNM classification of malignant tumours (8^{th} edition, UICC)[13]. We also acquired data on intraoperative details and postoperative complications and assessed the severity of postoperative complications using the Clavien-Dindo (CD) classification. Postoperative follow-up included evaluation of serum concentrations of the tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9. Further imaging was conducted every 3–6 months using abdominal ultrasonography, CT, chest X-ray, and/or PET, as well as annual colonoscopy according to Japanese guidelines[14]. DFS was defined as the duration of patient survival without signs or symptoms of cancer after the completion of primary CRC surgery.

Statistical analyses

Logistic regression analyses were performed to assess correlations between DFS and each of the factors: albumin level, PC, MC, and TLC. Univariate analyses using a proportional hazards model were performed to identify independent factors for DFS and OS after primary curative resection. Statistical significance was defined as two-sided $p < 0.05$. The three factors used for the prediction model were selected based on the results of the multivariate analysis for DFS using the Cox regression model. Kaplan–Meier survival curves were plotted and compared using the generalized log-rank test. Multiple logistic regression analysis was performed to assess the correlation between postoperative complications and clinicopathological factors. All statistical analyses were performed using the JMP 15.0 statistical software program (SAS Institute, Cary, NC, USA). All C-indices were calculated using R software program, ver. 3.1.3 (CRAN; the R Foundation for Statistical Computing, Vienna, Austria).

Compliance with ethical review

This study was performed in accordance with the principles of the Declaration of Helsinki. It was approved by the Institutional Review Boards of Osaka International Cancer Institute and Osaka University, and informed consent was obtained from all patients according to the guideline.

Results

Independent prognostic factors

The characteristics of the 262 study patients (TS and VS) are shown in Table 1. None of the patients in the TS received preoperative treatment. A total of 137 patients in TS and 70 patients in VS underwent adjuvant chemotherapy after curative resection, whereas 6 patients in VS received neoadjuvant chemotherapy.

Univariate and multivariate analyses of clinicopathological factors for DFS in TS are shown in Table 2. To simplify the analysis, the cutoff values for continuous variables, e.g. albumin, PC, MC, and TLC, were chosen based on the receiver-operating characteristic (ROC) curves for the DFS in the TS and were set as <3.5 g/dL, $<1.65 \times 10^5$, >450, and <1600, respectively (Fig. 1a-d). According to the univariate analysis,

histological grade (poorly differentiated or mucinous adenocarcinoma) (P = 0.028), tumor invasion (T4) (P = 0.040), lymph node metastasis (N2) (P = 0.002), low albumin (P < 0.001), high CRP (P = 0.006), high MC (P = 0.001), and low PC (P = 0.003) were significantly correlated with decreased DFS. Multivariate analyses revealed that lymph node metastasis (N2) (P = 0.002), low albumin (P = 0.017), high MC (P = 0.008), and low PC (P = 0.018) were independent risk factors for DFS.

Univariate and multivariate analyses of clinicopathological factors for OS in TS are shown in Table 3. According to the univariate analysis, tumor invasion (T4) (P = 0.015), lymph node metastasis (N2) (P = 0.003), low albumin (P < 0.001), high CRP (P < 0.001), high MC (P = 0.020), and low PC (P < 0.001) were significantly correlated with decreased OS (Table 3). The multivariate analysis revealed that lymph node metastasis (N2) (P < 0.001), high CRP (P = 0.007), low albumin (P = 0.004), and low PC (P = 0.003) were independent risk factors for OS. These results revealed that the inflammatory and nutritional statuses of patients were as important as the tumor status for the prognosis of DFS and OS.

KPS

The three factors used for the prediction model were selected based on the results of multivariate analysis for DFS using the Cox regression model in TS (Table 2). The KPS incorporated preoperative values for albumin level, MC, and PC. Each factor was used only once and was assigned a single point. The points were summed, and the patients were divided into three groups as follows: low KPS (KPS = 0) defined as the low-risk group, intermediate KPS (KPS = 1) defined as the intermediate-risk group, and high KPS (KPS ≥ 2) defined as the high-risk group (Fig. 1e).

KPS stratifies patients for the prognosis of stage III CRC

The TNM stage III subgroups (stage IIIA, IIIB, and IIIC) were defined by tumor invasion, lymph node metastasis, and KPS were defined by albumin, MC, and PC; therefore, both TNM stage and KPS were independent prognostic factors for DFS and OS in TS (Table 4, 5). A total of 113 patients had a low KPS (KPS = 0), 37 had an intermediate KPS (KPS = 1), and 12 had a high KPS (KPS ≥ 2). Regarding the TNM stage III subgroups, 25, 103, and 34 patients had stage IIIA, IIIB, and IIIC disease, respectively. Kaplan–Meier curves for DFS and OS were drawn according to the TNM stage subgroups and KPS (Fig. 2).

For the purpose of verification, the Kaplan–Meier curves for DFS and OS in VS were drawn in Fig. 3. A total of 51 patients in VS had a low KPS (KPS = 0), 37 had an intermediate KPS (KPS = 1), and 12 had a high KPS (KPS ≥ 2). KPS stratified for patients for the prognosis of stage III CRC in VS. The Kaplan–Meier curves by KPS for DFS and OS in the patients with stage IIIA, IIIB, and IIIC diseases were summarized in Fig. 4 as subgroup analyses.

The C-index of the TNM stage and KPS are shown in Table 6. The C-indices of KPS to predict DFS and OS in TS were 0.707 and 0.772, respectively. It was validated in VS that the C-indices of KPS to predict DFS and OS were 0.618 and 0.708, respectively. We found that KPS was an independent risk factor in all patients with stage III disease, and that KPS was a strong predictor for DFS and OS.

High KPS is an independent risk factor for postoperative complications

We examined the relationship between KPS and postoperative complications in VS. Intraoperative details and the breakdown of the postoperative complications (CD grade ≥II) within 30 days after surgery are listed in Supplementary Tables S1 and S2. The cutoff values for operative time and blood loss were selected from the ROC curves for postoperative complications (CD grade ≥II) and were set as 280 min and 140 mL, respectively (Supplementary Fig. S1). Univariate analyses showed that postoperative complications were significantly associated with rectal cancer ($P = 0.010$), open surgery ($P = 0.027$), operative time exceeding 280 min ($p = 0.001$), blood loss >140 mL ($P = 0.006$), and KPS ≥2 ($P < 0.001$) (Supplementary Table S3). Multivariate analyses showed that KPS ≥2 ($P = 0.020$) was an independent prognostic factor for postoperative complications of CD grade II or higher (Supplementary Table S4). These results demonstrated that inflammation and malnutrition had a negative impact on short-term postoperative outcomes.

Discussion

In this study, we found a correlation between KPS, which is a new simple scoring system, and DFS and OS in patients with stage III CRC. KPS stratified patients based on DFS and OS, indicating that it may be useful prognostic indicator for patients with stage III CRC. KPS is very simple; however, the weights of continuous variables and their risks may not be reflected.

Serum albumin level was used to reflect the patients' inflammatory and nutritional status. Reportedly, 31–87% of patients with a malignancy have a low nutritional status, which affects response to treatment and survival[15]. Inflammatory cytokines associated with malignancy have been reported to promote cancer growth and metastasis[16]. Albumin is a simple and low-cost indicator that reflects the nutritional status and inflammation. MC was used to reflect the patients' inflammatory and immune status[17]. The finding that increased MC is associated with poor prognosis is consistent with previous reports that LMR is an independent prognostic factor in CRC[18]. However, the utility of MC in predicting prognosis has only been assessed recently, and only preliminary hypotheses have been proposed. Serum monocytes differentiate into macrophages within the tumor after infiltration. Tumor-associated macrophages (TAMs) exert their activity primarily as progenitor cells, which promote metastasis, immunosuppression, and tumor angiogenesis[17]. Thus, elevated levels of monocytes in the serum may reflect elevated TAM levels and poor prognosis[18]. Platelets are indicators that reflect coagulation response. Malignant tumors increase coagulability and are associated with the development of thrombosis, thrombocytopenia, and disseminated intravascular coagulation (DIC)[19]. Activation of coagulation is not uncommon in solid tumors; for instance, DIC was diagnosed in approximately 6.8% of patients with solid tumors, while advanced cancer and tumor necrosis are independent risk factors[20]. In solid tumors, adenocarcinoma cells and activated monocytes release tissue factor, which activates coagulation factors in a chain reaction, resulting in consumptive thrombocytopenia[19 21]. In this study, low platelet levels were associated with poor prognosis. This result can possibly be explained by the already mentioned role of

the coagulation response in advanced stage III CRC[19 21], which represents the condition of the patients selected in this study. Further studies are needed to investigate the relationship between the status of inflammation, nutrition, and coagulation and the malignancy status.

We revealed that tumor status, as determined using TNM stage, and the patients' general condition, which is defined by KPS, are strong predictors of DFS and OS. TNM stage is a good predictor because it reflects the grade of the cancer well. KPS was a good prognostic indicator not only in the OS but also in the DFS, because tumor progression may have a more significant impact on the general condition of the patients with stage III CRC than those with other early stages. In the subgroup analyses, KPS was useful for identifying low-risk stage IIIB and IIIC patients. In stage IIIA, KPS did not stratify DFS and OS, owing to the small number of patients included and/or the fact that the malignancies rarely worsen the nutritional status of these patients. As expected, a high KPS was an independent risk factor for postoperative complications of CD grade II or higher. Preoperative malnutrition and inflammation are known to be the risk factors for additional postoperative complications, prolonged hospital stays, and adverse oncological outcomes[22–26], and the KPS includes indicators of malnutrition and inflammation.

This study had several limitations. Firstly, this was a retrospective study, which evaluated only a small number of patients and institutes and was affected by several selection and information biases. Secondly, a predictive model was created using data from patients attending a single facility. More patients and multicenter studies are needed to fully evaluate the model. Well-designed follow-up studies and/or use of selected interventions to recover the inflammatory and nutritional status of patients at high risk for stage III CRC may improve their prognosis. The predictive models that we have developed will help us identify patients at low risk for stage III CRC. The possibility of omitting postoperative adjuvant chemotherapy, such as oxaliplatin, for low-risk patients was not investigated in this study and needs to be carefully examined in the future.

In conclusion, we report a novel prognostic scoring system, the KPS, for patients with stage III CRC. KPS stratified patients for the prognosis of OS and DFS, and was useful for identifying low-risk groups.

Abbreviations

CRC: Colorectal cancer, OS: Overall survival, DFS: Disease-free survival, TNM stage: Tumor-node-metastasis stage, mGPS: modified Glasgow prognostic score, PNI: Prognostic nutritional index, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, TLC: Total lymphocyte counts, CRP: C-reactive protein, MC: monocyte counts, PC: Platelet counts, KPS: Kansai Prognostic Score, TS: Training set, VS: Validation set, CT: Computed tomography, PET: Positron emission tomography, CD: Clavien-Dindo, ROC: Receiver-operating characteristic, AUC: Area under the curve, TAM: Tumor-associated macrophages, DIC: Disseminated intravascular coagulation

Declarations

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Author contributions

S.K., N.M., S.K., Y.D., and H.E. contributed to the study conception and design. Material preparation and data collection were performed by S.K., C.M., M.Y., M.O., Y.S., T.O., T.H., H.T., H.Y., and M.U. Data analysis were performed by SK, N.M, S.F., and S.M. The first draft of the manuscript was written by SK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Data Availability

The dataset used and analyzed in the present study is available from the corresponding author on reasonable request.

Ethics declarations

Not applicable

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Tables

Table 1 Patients' characteristics

Factors	Training set (n = 162)	Validation set (n = 100)
Age, years (range)	65 (32–88)	65 (20–90)
Sex (female/male)	69 / 93	47 / 53
Tumor location (rectum/colon)	86 / 76	31 / 69
Surgical approach (open/lap)	154 / 8	8 / 92
Histological grade (tub1/tub2/por, muc)	41 / 110 / 21	26 / 67 / 7
Lymphatic invasion (absent/present)	28 / 134	4 / 96
Vascular invasion (absent/present)	52 / 110	53 / 47
Tumor invasion (T1/T2/T3/T4)	11 / 16 / 90 / 45	8 / 16 / 65 / 11
Lymph node metastasis (N1/N2)	111 / 51	76 / 24
Stage (IIIA/IIIB/IIIC)	25 / 103 / 34	23 / 62 / 15

open = open surgery, lap = laparoscopic surgery, tub1 = well-differentiated adenocarcinoma, tub2: moderately differentiated adenocarcinoma, por = poorly differentiated adenocarcinoma, muc = mucinous adenocarcinoma

Table 2 Results of univariate and multivariate analyses of the disease-free survival in the training set

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years) (≥66/<66)	1.081	0.602-1.939	0.795			
Sex (female/male)	1.043	0.579-1.878	0.889			
Tumor location (rectum/colon)	1.456	0.378-1.254	0.222			
Surgical approach (open /lap)	1.160	0.209-3.561	0.838			
Histological grade (por, muc/tub1, tub2)	2.630	1.111-6.225	0.028*	1.295	0.482-3.478	0.608
Lymphatic invasion (present/absent)	1.132	0.394-1.978	0.761			
Vascular invasion (present/absent)	1.808	0.895-3.652	0.099			
Tumor invasion (T4/T1–3)	1.873	1.030-3.406	0.040*	1.342	0.681-2.644	0.396
Lymph node metastasis (N2/N1)	2.539	1.414-4.558	0.002*	2.765	1.447-5.284	0.002*
CRP, mg/dL (< 1.0/≥ 1.0)	3.110	1.387-6.976	0.006*	1.278	0.428-3.812	0.661
Alb, g/dL (< 3.5/≥ 3.5)	5.456	2.792-10.663	<0.001*	2.627	1.192-5.788	0.017*
Total lymphocyte counts (<1600/≥1600)	1.430	0.792-2.584	0.236			
Monocyte counts (≥450/<450)	2.887	1.532-5.438	0.001*	2.878	1.316-6.290	0.008*
Platelet counts ($\times 10^3$) (<165/≥165)	3.3793	1.666-6.853	0.003*	1.614	1.182-5.778	0.018*

HR = hazard ratio, CI = confidence interval, lap = laparoscopic surgery, open = open surgery, por = poorly differentiated adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, CRP = C-reacted protein

Asterisk values indicate *P*-values < 0.05

Table 3 Results of univariate and multivariate analyses of the overall survival in the training set

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years) (≥66/<66)	1.542	0.699-3.402	0.283			
Sex (female/male)	1.210	0.552-2.653	0.634			
Tumor location (rectum/colon)	1.560	0.704-3.455	0.273			
Surgical approach (open /lap)	1.157	0.156-8.587	0.886			
Histological grade (por, muc/tub1–tub2)	1.949	0.571-6.644	0.286			
Lymphatic invasion (present/absent)	0.888	0.303-2.603	0.828			
Vascular invasion (present/absent)	2.116	0.793-5.648	0.135			
Tumor invasion (T4/T1–3)	2.662	1.209-5.862	0.015*	1.812	0.749-4.385	0.181
Lymph node metastasis (N2/N1)	3.419	1.533-7.627	0.003*	4.959	2.009-12.291	<0.001*
CRP, mg/dL (< 1.0/≥ 1.0)	7.009	2.863-17.158	<0.001*	4.775	1.539-14.815	0.007*
Alb, g/dL (< 3.5/≥ 3.5)	12.540	5.197-30.264	<0.001*	4.489	1.620-12.439	0.004*
Total lymphocyte counts (<1600/≥1600)	1.900	0.839-4.305	0.123			
Monocyte counts (≥450/<450)	2.738	1.170-6.409	0.020*	2.564	0.868-7.577	0.089
Platelet counts ($\times 10^3$)(<165/≥165)	6.384	2.696-15.120	<0.001*	5.419	1.746-16.817	0.003*

HR = hazard ratio, CI = confidence interval, lap = laparoscopic surgery, open = open surgery, por = poorly differentiated adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, CRP = C-reacted protein

Asterisk values indicate *P*-values < 0.05

Table 4 Results of univariate and multivariate analyses of the disease-free survival in the training set based on the KPS and TNM stage

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years) (≥66/<66)	1.081	0.602-1.939	0.795			
Sex (female/male)	1.043	0.579-1.878	0.889			
Tumor location (rectum/colon)	1.456	0.378-1.254	0.222			
Surgical approach (open /lap)	1.160	0.209-3.561	0.838			
Histological grade (por, muc/tub1, tub2)	2.630	1.111-6.225	0.028	1.663	0.670-4.128	0.273
Lymphatic invasion (present/absent)	1.132	0.394-1.978	0.761			
Vascular invasion (present/absent)	1.808	0.895-3.652	0.099			
CRP, mg/dL (< 1.0/≥ 1.0)	3.110	1.387-6.976	0.006	1.276	0.501-3.247	0.609
Total lymphocyte counts (<1600/≥1600)	1.430	0.792-2.584	0.236			
Adjuvant chemotherapy (absent/present)	1.679	0.892-3.158	0.108			
Stage						
(IIIB/IIIA)	3.262	0.766-13.887	0.110	2.108	0.624-7.117	0.230
(IIIC/IIIA)	6.456	1.454-28.661	0.014*	3.709	1.043-13.194	0.043*
(IIIC/IIIB)	2.081	1.048-4.134	0.036*	1.76	0.912-3.397	0.092
KPS						
(1/0)	4.523	0.116-0.423	<0.001*	4.017	2.068-7.804	<0.001*
(≥2/0)	8.177	3.505-19.077	<0.001*	5.957	2.245-15.805	<0.001*
(≥2/1)	1.903	0.831-	0.128	1.483	0.589-	0.403

	4.360	3.732

HR = hazard ratio, CI = confidence interval, lap = laparoscopic surgery, open = open surgery, por = poorly differentiated adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, CRP = C-reacted protein, KPS = Kansai Prognostic Score

Asterisk values indicate *P*-values < 0.05

Table 5 Results of univariate and multivariate analyses of the overall survival in the training set based on the KPS and TNM stage

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years) (≥66/<66)	1.542	0.699-3.402	0.283			
Sex (female/male)	1.210	0.552-2.653	0.634			
Tumor location (rectum/colon)	1.560	0.704-3.455	0.273			
Surgical method (open /lap)	1.157	0.156-8.587	0.886			
Histological grade (por, muc/tub1, tub2)	1.949	0.571-6.644	0.286			
Lymphatic invasion (present/absent)	0.888	0.303-2.603	0.828			
Vascular invasion (present/absent)	2.116	0.793-5.648	0.135			
CRP, mg/dL (< 1.0/≥ 1.0)	7.009	2.863-17.158	<0.001*	2.588	0.902-7.420	0.077
Total lymphocyte counts (<1600/≥1600)	1.900	0.839-4.305	0.123			
Adjuvant chemotherapy (absent/present)	2.295	1.010-5.216	0.047*	1.900	0.677-5.330	0.223
Stage						
(IIIB/IIIA)	1.968	0.242-16.003	0.527	2.398	0.306-18.800	0.405
(IIIC/IIIA)	8.919	1.126-70.667	0.038*	6.015	0.748-48.347	0.092
(IIIC/IIIB)	3.821	1.472-9.915	0.006*	2.508	1.103-5.703	0.028*
KPS						
(1/0)	5.575	2.105-14.767	<0.001*	4.588	1.674-12.574	0.003*
(≥2/0)	21.564	7.036-	<0.001*	14.252	3.987-	<0.001*

		66.094			50.944	
(≥2/1)	4.053	1.511-10.872	0.005*	3.106	1.037-9.305	0.043*

HR = hazard ratio, CI = confidence interval, lap = laparoscopic surgery, open = open surgery, por = poorly differentiated adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well-differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, CRP = C-reacted protein, KPS = Kansai Prognostic Score

Asterisk values indicate *P*-values < 0.05

Table 6 C-indices of the TNM stage and the Kansai Prognostic score for the disease-free survival and overall survival

			Prognostic score system	
			TNM stage	KPS (Alb, PC, MC)
C-index	Disease-free survival	TS	0.613*	0.707*
		VS	0.586	0.618*
	Overall survival	TS	0.660*	0.772*
		VS	0.621*	0.708*

TNM stage = tumor-node-metastasis stage, KPS = Kansai Prognostic Score, Alb = albumin, PC = platelet counts, MC = monocyte counts, TS = training set, VS = validation set

Asterisk values indicate c-indices more than 0.600 (high)

Figures

Figure 1

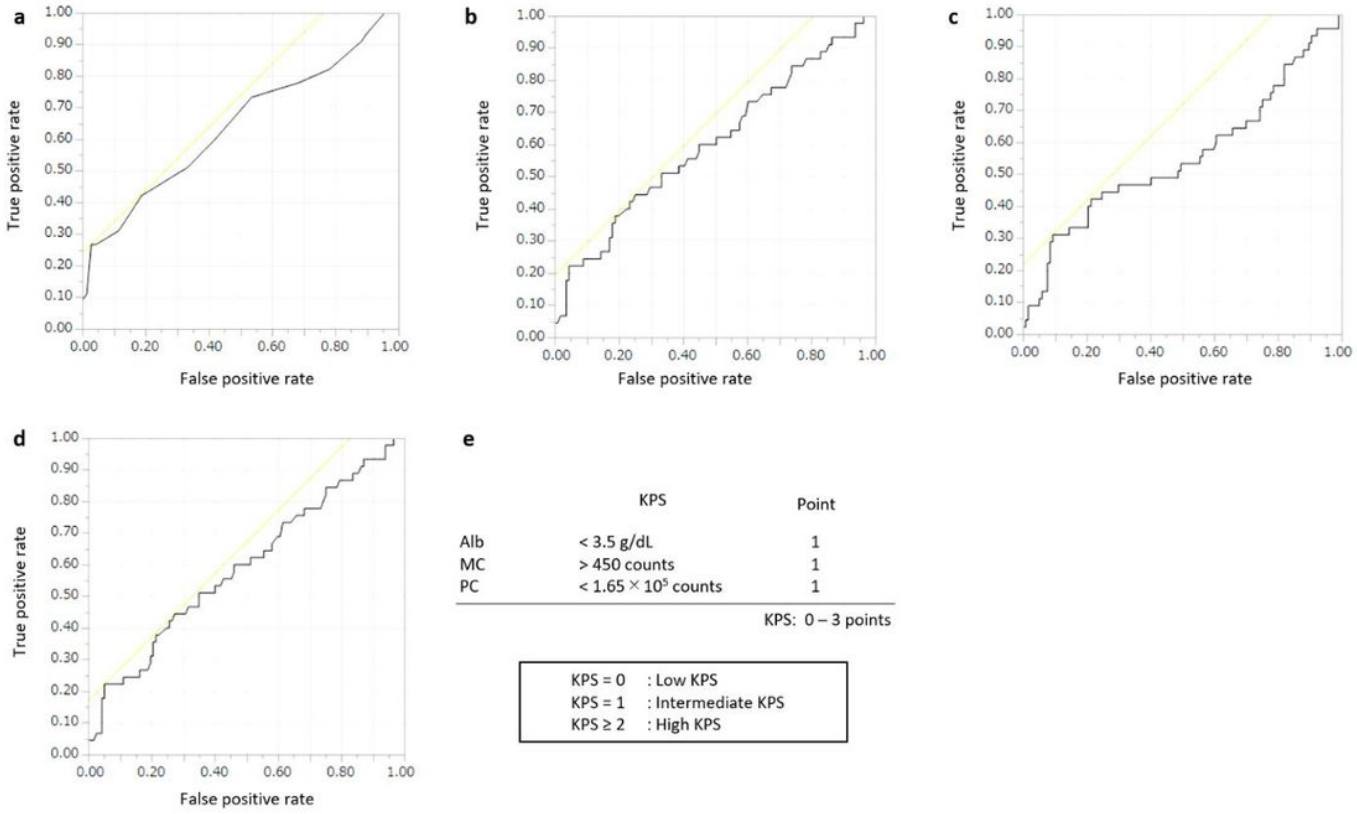

Figure 1

(a-d) Receiver-operating characteristic (ROC) curves analysis for the cut-off value of the albumin, the platelet counts (PC), the monocyte counts (MC), and the total lymphocyte counts (TLC). (a) The area under the curve (AUC) of the albumin was 0.640. The optimal cut-off value in the ROC curve was 3.5 g/dL which was set as the cut-off value. (b) AUC of PC was 0.604. The optimal cut-off value in the ROC curve was 1.62×10^5 cells/μL; 1.65×10^5 cells/μL was set as the cut-off value. (c) AUC of MC was 0.552. The optimal cut-off value in the ROC curve was 461 cells/μL; 450 cells/μL was set as the cut-off value. (d) AUC of TLC was 0.544. The optimal cut-off value in the ROC curve was 1608 cells/μL; 1600 cells/μL was set as the cut-off value. (e) The KPS was constructed by three variables: albumin, MC, and PC.

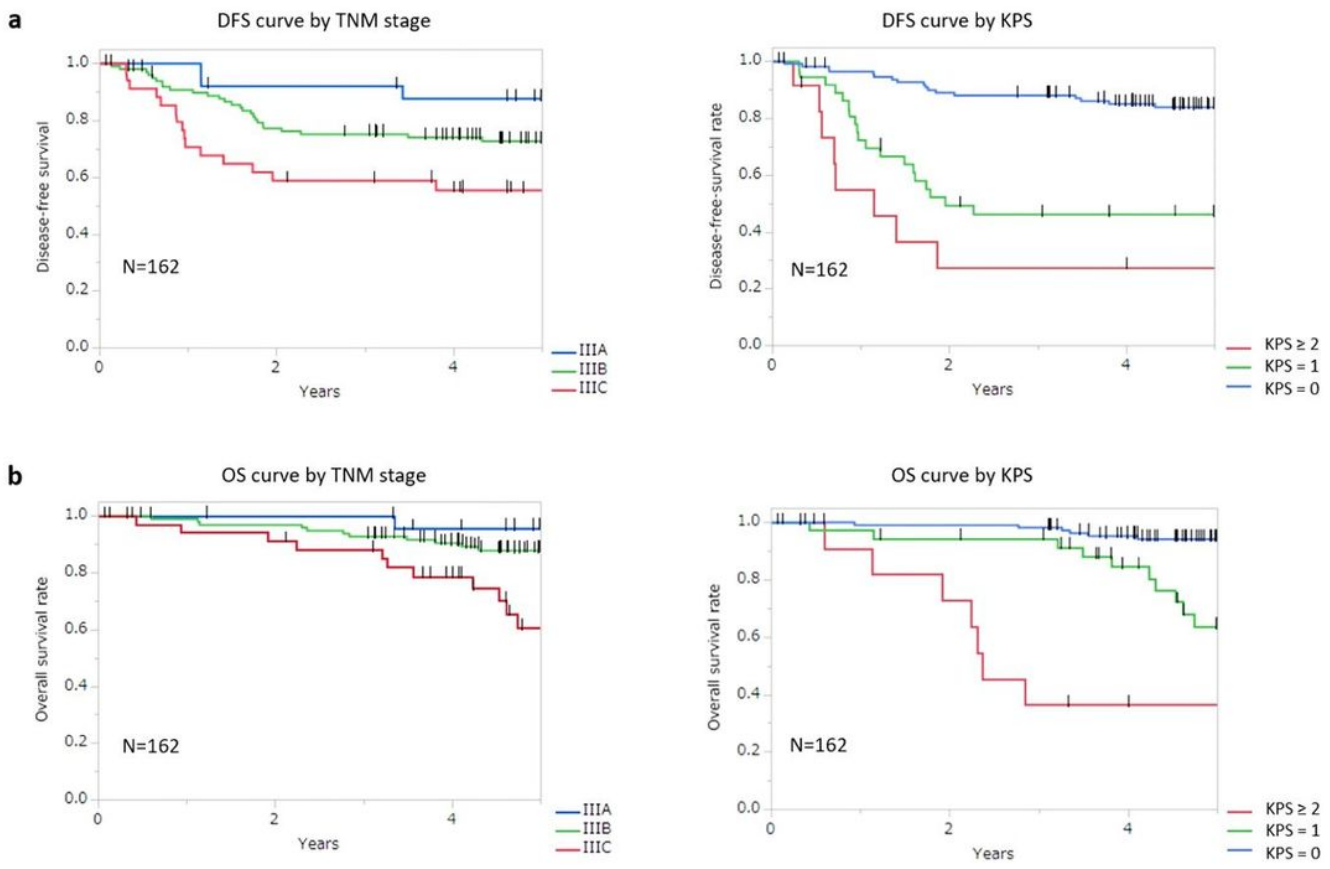

Figure 2

Survival curves of training set (TS) for the disease-free survival (DFS) and overall survival (OS) by the TNM stage and Kansai Prognostic Score (KPS). (a) DFS curves by TNM stage (left) and KPS score (right). The 5-year DFS rate was 88% (n = 25) in patients with Stage IIIA disease, 73% (n = 103) in those with Stage IIIB, and 55% (n =34) in those with Stage IIIC. The 5-year DFS rate was 84% (n = 113) in those with a low KPS (KPS = 0), 46% (n = 37) in those with an intermediate KPS (KPS = 1), 28% (n = 12) in those with a high KPS (KPS ≥ 2). (b) OS curves by TNM stage (left) and KPS score (right). The 5-year OS rate was 96% (n = 25) in patients with Stage IIIA disease, 88% (n = 103) in those with Stage IIIB, and 60% (n = 34) in those with Stage IIIC. The 5-year OS rate was 94% (n = 113) in those with a low KPS (KPS = 0), 64% (n = 37) in those with an intermediate KPS (KPS = 1), 36% (n = 12) in those with a high KPS (KPS ≥ 2)

Figure 3

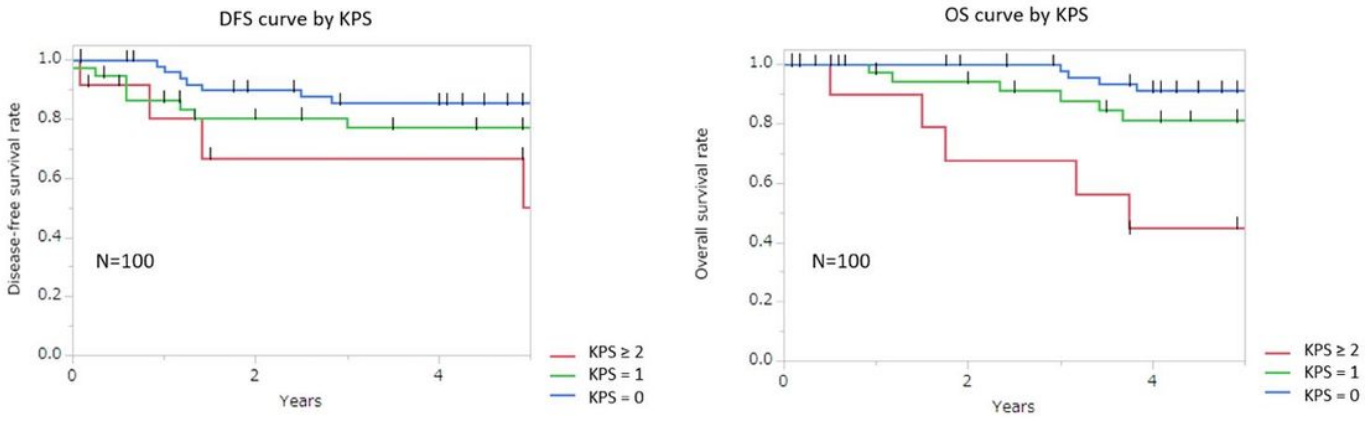

Figure 3

Survival curves of validation set (VS) for the disease-free survival (DFS: left) and overall survival (OS: right) by the Kansai Prognostic Score (KPS). The DFS rate of high KPS (KPS ≥ 2) was significantly worser than that of low KPS (KPS = 0) in the log-rank test ($P = 0.020$). The OS rate of high KPS (KPS ≥ 2) was significantly worser than that of low KPS (KPS = 0) ($P < 0.001$) and intermediate KPS (KPS = 1) ($P = 0.008$) in the log-rank test.

Figure 4

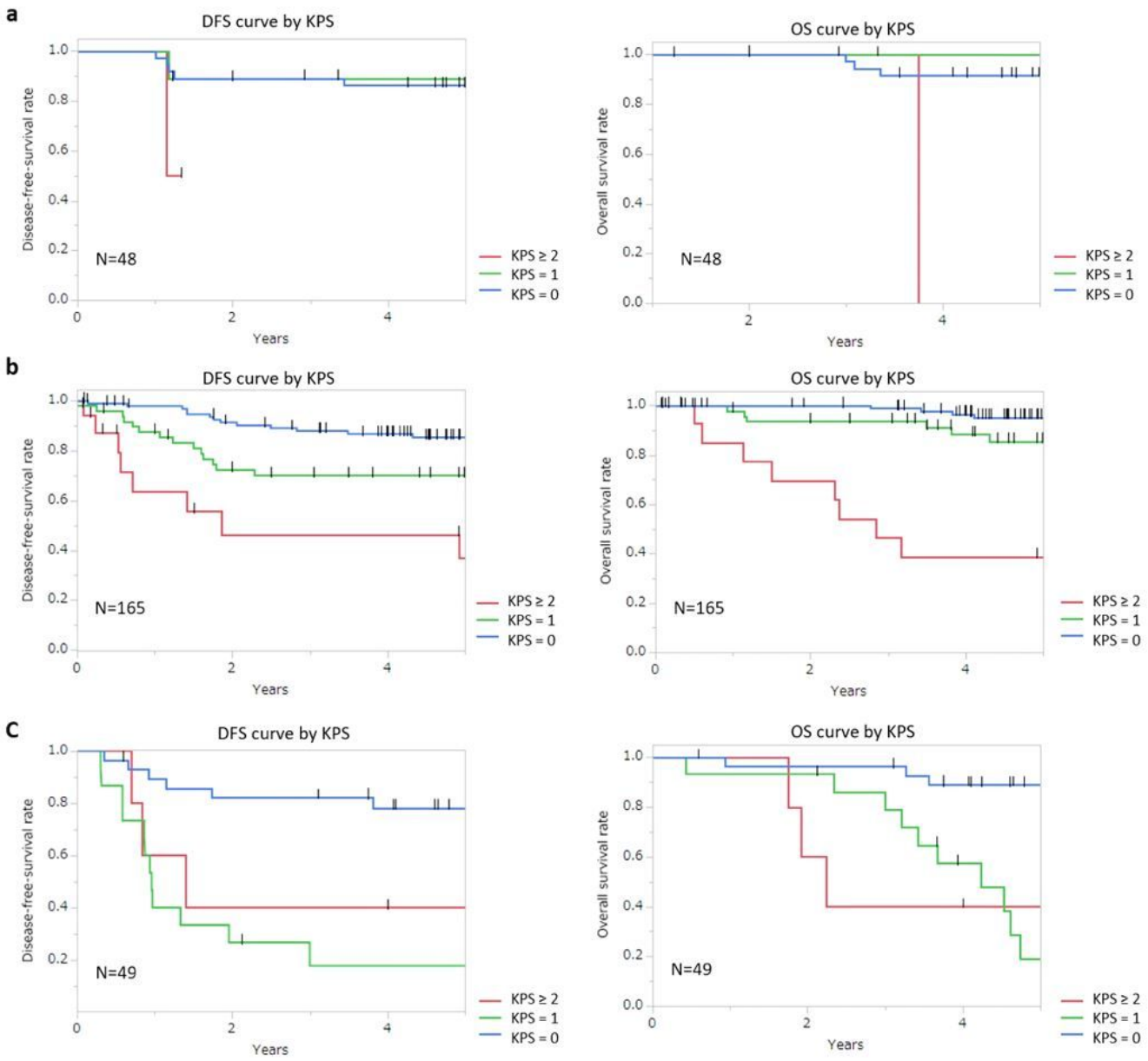

Figure 4

Survival curves of patients with Stage IIIA, IIIB and IIIC. (a) DFS curves (left) and OS curves (right) of patients with Stage IIIA (n = 48) by the Kansai Prognostic Score (KPS). There was no significant difference in the prognosis of patients with stage IIIA based on each KPS. (b) DFS curves (left) and OS curves (right) of patients with Stage IIIB (n = 165) by KPS. The DFS rate of patients with low KPS (KPS = 0) was significantly better than that of patients with intermediate (KPS = 1, $P = 0.023$) and high KPS (KPS ≥ 2, $P < 0.001$) in the log-rank test. The OS rate of patients with low KPS (KPS = 0) was significantly better than that of patients with high KPS (KPS ≥2) in the log-rank test ($P < 0.001$) (c) DFS curves (left) and OS curves (right) of patients with Stage IIIB (n = 49) by KPS. The DFS rate of patients with low KPS (KPS = 0) was significantly better than that of patients with intermediate (KPS = 1, $P < 0.001$) and high

(KPS ≥ 2, P = 0.049) KPS in the log-rank test. The OS rate of patients with low KPS (KPS = 0) was significantly better than that of patients with intermediate (KPS = 1, P < 0.001) and high (KPS ≥ 2, P = 0.003) KPS in the log-rank test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20211224Supplementaryv2.docx