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Perioperative Predictive Markers for Recurrence of Esophageal Cancer after Esophagectomy

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Keywords
Esophageal cancer · Prognostic nutritional index · C-reactive protein · Cancer progression · Prognosis

Abstract
Introduction: We studied whether perioperative nutritional, immunological factors or postoperative inflammatory responses predicted esophageal cancer (EC) progression and prognosis in patients who received esophagectomies. ***Methods:*** We evaluated preoperative prognostic nutritional index (PNI), BMI, neutrophil-to-lymphocyte ratio (NLR), intraoperative blood loss, postoperative C-reactive protein (CRP) max, recurrence-free survival (RFS), and overall survival (OS) in 111 patients with pStage I–IV squamous cell EC who received esophagectomies. Optimal cutoff values for each continuous parameter were determined by receiver operating characteristic curves and Youden indices. Univariate and multivariate Cox analyses were used to derive independent prognostic factors. Propensity score matching using inverse probability of treatment weighting was used in groups divided by Youden indices, as appropriate. ***Results:*** Cutoff values of continuous variables were NLR: 2.27, PNI: 44.2, blood loss: 159 mL, and CRPmax: 21.7 mg/dL. In multivariate analyses, PNI, CRPmax, and intraoperative blood loss were independent prognostic factors for OS and RFS. Among patients with stage II–IV disease, low PNI was associated with shorter RFS. Postoperative respiratory complications were associated with both higher CRP and shorter RFS. ***Discussion/Conclusions:*** Low preoperative PNI and high postoperative inflammatory response were associated with postoperative EC progression after esophagectomy. Preoperative nutritional interventions or suppression of postoperative inflammatory response, including respiratory complications, may improve patient prognosis.

Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide [1]. Its 2 most common histologic subtypes are adenocarcinoma and squamous cell carcinoma (SCC). SCC is more common in Asian countries, where most ECs are of the SCC subtype; only 4.5% of ECs in Japan were adenocarcinomas [2]. Surgery is the standard treatment for patients with locoregionally confined EC. Despite the availability of curative surgery, EC has a high

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rate of recurrence [3–5]. Two-thirds of patients with EC have advanced disease at the time of admission; most patients with advanced EC complain of dysphagia, which leads to weight loss and malnutrition [2, 6]. In addition, host-tumor interactions affect the nutritional status and immune system in cancer patients [7], which may exacerbate weight loss and malnutrition in patients with EC. Nutritional and immunological statuses are shown to be significant predictors of cancer progression and survival [8–11]. Preoperative nutritional and/or immunological factors, including BMI, albumin, prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR), were evaluated with respect to progression in many types of cancer, including EC [12–17]. C-reactive protein (CRP) is an acute-phase serum protein and a well-established inflammatory marker; at high concentrations, it is associated with high mortality in solid tumors, including gastrointestinal malignancies [18]. Some studies have investigated postoperative CRP levels and EC progression and prognosis after esophagectomy [19–21], but each study used different methods to measure CRP. Whether preoperative nutritional or immunological factors or postoperative inflammatory reactions predict EC progression after esophagectomy is unclear. In the present study, we retrospectively evaluated nutritional and immunological factors before EC surgery, inflammatory responses after surgery, and the relationships between cancer progression and these parameters, using multivariate analysis.

Materials and Methods

This retrospective study included 111 consecutive patients with biopsy-proven invasive esophageal SCC and no history of previous treatment, who underwent esophagectomies with 2- or 3-field lymphadenectomies, at the Kawasaki Medical School Hospital between January 2010 and June 2019. Tumor staging was based on the UICC classification of malignant tumors (8th edition) [22]. We excluded patients with R1/2 resections and those who received preoperative chemotherapy or chemoradiotherapy. This study was approved by the Kawasaki Medical School Institutional Review Board (Authorization No. 3382). Details of this study are described on the Kawasaki Medical School home page (https://h.kawasaki-m.ac.jp/cgi-image/3644/3644_njbGzmAGzJKXvLIXPmMBEPmYEfwPTbPQOlVqmObuLvggagkgbp.pdf). Data were collected from patients' medical records. All patients were followed up regularly until April 2020 or until death. Informed consent was obtained from all patients.

Nutritional, Immunological, and Inflammatory Response Assessment

Peripheral blood samples were collected within 1–4 weeks before surgery. Preoperative PNI was calculated as (10 × albumin [g/dL]) + (0.005 × peripheral lymphocyte counts/mm^3) [23]. Preoperative NLR was defined as absolute neutrophil count divided by absolute lymphocyte count [24]. Preoperative BMI was defined as kg/m^2 [25]. Other preoperative nutritional indices, including serum albumin (mg/dL), were also evaluated. The systemic postoperative inflammatory response was evaluated based on serum CRP level (mg/dL), which was measured on postoperative days 1, 2, 3, 5, and 7 and thereafter as necessary. The highest CRP level (CRPmax) was considered to be a postoperative inflammatory response. We also evaluated the postoperative CRP/albumin ratio, which was defined as the ratio of the postoperative CRP level divided by the serum albumin level, at the highest CRP value on the postoperative day.

Surgery and Associated Factors

Three surgical procedures were performed. Ivor Lewis esophagectomies with 2- or 3-field lymph node dissections were performed in the period through 2013. Esophageal reconstructions were performed using a gastric tube in the retrosternal or posterior mediastinal root. This procedure was changed to a thoracoscopic- and laparoscopic-assisted approach after 2013. Transhiatal esophagectomy with middle, lower mediastinal, and abdominal lymphadenectomy was also performed for patients with relatively early-stage EC. Postoperative complications of Clavien-Dindo classification grade 2 or higher were included in our analysis [26]. Intraoperative blood loss, operation time, and length of hospital stay were also evaluated.

Statistical Analysis

We used the χ^2 or Fisher's exact *t* test for categorical variables and the Mann-Whitney U test for continuous variables. Overall survival (OS) was defined as the time between surgery and death or final available information pertaining to vital status. Recurrence-free survival (RFS) was defined as the time between surgery and cancer recurrence, death, or last available information pertaining to vital status. Optimal cutoff values of variables were used for time-dependent receiver operating characteristic curves for 3-year OS. The Youden index was used to determine optimal threshold values for preoperative PNI, BMI, NLR, and albumin and postoperative CRPmax, CRP/albumin ratio, and intraoperative blood loss. We used median values as the cutoff values for operation time and hospital stay (days). When each group was divided by the Youden index, including those with a small number of patients or confounding variables, we calculated propensity scores, using a multivariable logistic regression model, with age, sex, cancer site, pTNM stage, lymph node metastasis, operative procedure, tumor length, and depth of tumor invasion (pT) as independent variables. We used the propensity scores to match each group, using the inverse probability of treatment weighting (IPTW) method. Using this method, we performed univariate analyses for OS and RFS in 7 parameters including preoperative PNI, BMI, albumin (mg/dL), NLR, and intraoperative blood loss and postoperative CRP/albumin ratio and CRPmax. Cox proportional hazard models for OS and RFS were used to identify independent prognostic factors. Factors in the Cox model were selected with the following criteria: (a) the number of explanatory variables should be approximately 1/10 of the number of event occurrences, (b) we did not enter factors that were dependent on each other, (c) useful independent prognostic factors were selected from previously published data, and (d) we included factors for which $p < 0.2$ in the univariate analysis. Kaplan-Meier curves of

Table 1. Clinical characteristics in this study

		PNI (cutoff = 44.2, *n* = 104)		*p* value	CRP (cutoff = 21.7)		*p* value
		PNI >44.2	PNI <44.2		CRP <21.7	CRP >21.7	
Patients, *n*	111	83	21	0.111	85	26	0.84
Age, years	66.3±7.77	65.64±7.91	68.67±7.64		66.5±6.37	66.24±8.18	
Gender							
Male	93	73	14	0.041	70	23	0.557
Female	18	10	7		15	3	
Location							
Upper	23	15	6	0.146	13	10	0.019
Middle	62	51	8		53	9	
Lower	26	17	7		19	7	
TNM classification							
T factors							
T1b	55	43	7	0.44	44	11	0.646
T2	13	9	3		9	4	
T3	34	24	9		26	8	
T4	9	7	2		6	3	
N factors							
N0	45	34	6	0.831	34	11	0.543
N1	29	22	6		20	9	
N2	22	17	5		19	3	
N3	15	10	4		12	3	
M factors							
M0	104	77	20	1.00	78	26	0.196
M1	7	6	1		7	0	
pStage*							
I	39	30	5	0.288	32	7	0.087
II	16	13	1		8	8	
III	36	26	10		29	7	
IV	20	14	5		16	4	
Procedures							
Thoracoscopic	83	11	7	0.124	15	4	0.735
Ivor Lewis	17	61	12		58	20	
THE	11	11	2		12	2	

PNI, prognostic nutritional index; CRP, C-reactive protein; THE, transhiatal esophagectomy. * UICC TNM 8th edition.

estimated RFS were generated and compared between the groups, using log-rank tests. $p < 0.05$ was considered significant. Statistical analyses were performed using JMP (version 14; SAS, Tokyo, Japan), Stata (Version14; LightStone, Tokyo, Japan), and R version 3.1.1 (R Project for Statistical Computing; Vienna, Austria).

Results

Patient Characteristics

We evaluated 111 patients with squamous cell EC in this study (Table 1). Their 3-year OS and RFS were 58.8 and 57.5%, respectively. There were 44 events (death) between observation periods. Mean follow-up time was 1,233 days (range: 111–3,256 days). Cutoff values were PNI: 44.2 (false positive: 0.891, true positive: 0.333, and area under the curve: 0.585) and CRPmax: 21.7 mg/dL (false positive: 0.809, true positive: 0.326, and area under the curve: 0.589). Clinical factors related to postoperative CRPmax or preoperative PNI divided by the cutoff values are shown in Table 1. The PNI groups had 104 patients because 7 patients did not have preoperative lymphocyte counts. Table 2 shows univariate analysis of prognostic factors for OS and RFS, with cutoff continuous variables, including PNI and CRPmax. Preoperative PNI, albumin and intraoperative blood loss, pTNM, and tumor location were prognostic factors for OS and RFS. Postoperative CRPmax was an independent prognostic

Table 2. Univariate analysis for OS and RFS in the present study

Covariants	Cutoff value (FP, TP)	HR	RFS		HR	OS	
			95% CI	*p* value		95% CI	*p* value
Age		1.068	0.819–1.394	0.627	1.117	0.855–1.461	0.417
Gender		0.969	0.432–2.176	0.94	0.859	0.362–2.036	0.729
pT		1.622	1.247–2.109	0.001*	1.521	1.159–1.995	0.003*
pN		1.658	1.270–2.165	0.001*	1.674	1.265–2.214	0.001*
pM		1.477	0.528–4.133	0.457	1.333	0.475–3.741	0.585
pTNM		1.829	1.378–2.428	0.001*	1.726	1.296–2.300	0.001*
Tumor location		0.467	0.292–0.747	0.002*	0.394	0.243–0.637	0.001*
Operative procedures		0.685	0.392–1.197	0.184	0.837	0.491–1.429	0.515
Preoperative PNI	44.2 (0.891, 0.333)	0.292	0.155–0.552	0.001*	0.315	0.164–0.606	0.001*
Preoperative albumin, g/dL	3.5 (0.897, 0.279)	0.459	0.251–0.839	0.011*	0.471	0.254–0.876	0.017*
NLR	2.272 (0.484, 0.600)	0.84	0.459–1.536	0.571	0.716	0.382–1.342	0.297
BMI, kg/m^2	21.4 (0.441, 0.698)	0.669	0.354–1.263	0.216	0.686	0.364–1.295	0.246
Blood loss, g	159 (0.515, 0.767)	2.549	1.313–4.946	0.006*	2.467	1.242–4.897	0.01*
CRPmax	21.7 (0.809, 0.326)	1.944	1.047–3.608	0.0321*	1.735	0.9023–3.337	0.0942
CRP/albumin ratio	8.512 (0.735, 0.395)	1.702	0.939–3.084	0.076	1.726	0.933–3.193	0.081
Operation time	360 min (median)	1.369	0.735–2.550	0.322	1.26	0.690–2.304	4.522
Hospital stay	42 days (median)	1.161	0.629–2.144	0.663	1.32	0.724–2.409	0.365
Postoperative complications		1.129	0.625–2.041	0.625	1.056	0.583–1.941	0.855

OS, overall survival; RFS, recurrence-free survival; FP, false positive TP, true positive; PNI, prognostic nutritional index; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant.

Table 3. Univariate analysis for RFS and OS of advanced EC patients after IPTW

Covariants	HR	OS after IPTW 95% CI	*p* value	HR	RFS after IPTW 95% CI	*p* value
PNI	0.391	0.177–0.863	0.02*	0.36	0.178–0.729	0.005*
CRPmax	1.507	0.760–2.988	0.24	1.841	1.014–3.342	0.045*
NLR	0.878	0.460–1.674	0.694	0.913	0.496–1.679	0.771
Blood loss	1.528	0.757–3.085	0.236	1.479	0.769–2.842	0.24
BMI	0.767	0.393–1.496	0.437	0.698	0.361–1.347	0.284
Albumin (preoperative)	0.502	0.253–0.995	0.048*	0.496	0.263–0.935	0.03*
CRP/albumin ratio	1.35	0.713–2.558	0.356	1.326	0.713–2.465	0.372

OS, overall survival; RFS, recurrence-free survival; EC, esophageal cancer; IPTW, inverse probability of treatment weighting; PNI, prognostic nutritional index; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant.

factor for RFS, but not for OS. Postoperative complications were not associated with cancer recurrence and prognosis. Univariate analyses of prognostic factors after IPTW propensity scoring are shown in Table 3. Preoperative PNI was an independent prognostic factor for both OS and RFS. CRPmax was an independent prognostic factor for PFS, but not OS. Intraoperative blood loss was not a prognostic factor for either OS or RFS. When patients were divided by the cutoff value into high and low PNI groups, their 3-year RFS rates after IPTW significantly differed (64.5 vs. 36.18%; $p < 0.05$; shown in Fig. 1). The 3-year RFS rates of the low and high CRP groups after IPTW were also significantly different (62.49 vs. 36.18%; $p < 0.05$; shown in Fig. 2). Among patients with pStage II–IV EC, the high PNI group had better OS and RFS than did the low PNI group ($p < 0.01$);

Table 4. Univariate analysis for OS and RFS between low and high PNI groups after IPTW in different stages

Covariants	For OS			For RFS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
pStage I						
High versus low PNI	0.41	0.326–51.66	0.274	2.939	0.281–30.74	0.368
pStage II–IV						
High versus low PNI	0.233	0.125–0.432	0.001*	0.24	0.130–0.440	0.001*

OS, overall survival; RFS, recurrence-free survival; IPTW, inverse probability of treatment weighting; PNI, prognostic nutritional index. * Statistically significant.

Table 5. Multivariate Cox analysis for RFS and OS in EC patients

	For RFS		*p* value	For OS		*p* value
	HR	95% CI		HR	95% CI	
Age	0.9123	0.498–1.670	0.766	0.924	0.489–1.743	0.807
pTNM	1.745	1.305–2.334	0.001*	1.757	1.281–2.410	0.001*
PNI	0.258	0.133–0.498	0.001*	0.292	0.145–0.588	0.001*
CRPmax	2.432	1.226–4.823	0.01*	2.079	1.010–4.282	0.047*
Blood loss	1.92	1.001–3.683	0.049*	2.264	1.116–4.589	0.023*

OS, overall survival; RFS, recurrence-free survival; EC, esophageal cancer; PNI, prognostic nutritional index; CRP, C-reactive protein. * Statistically significant.

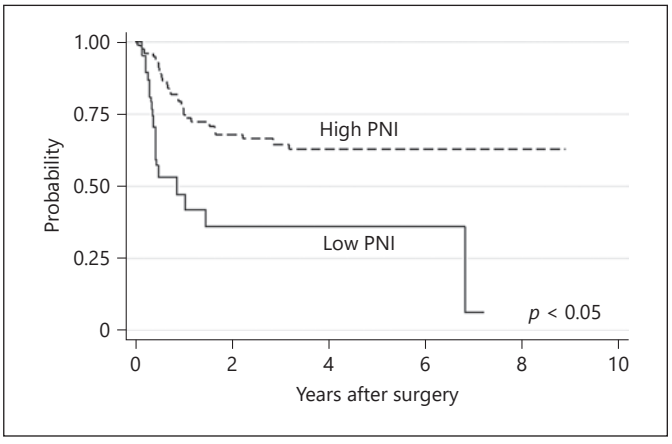

Fig. 1. Kaplan-Meier curves for RFS significantly differed between the high and low PNI groups ($p < 0.05$). RFS, recurrence-free survival; PNI, prognostic nutritional index.

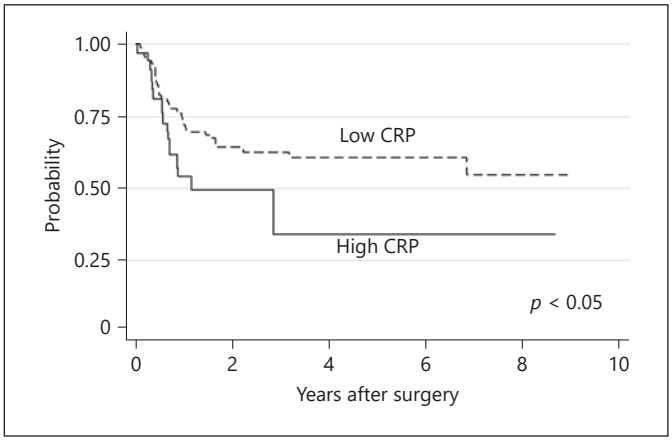

Fig. 2. Kaplan-Meier curves for RFS significantly differed between the high and low CRP groups ($p < 0.05$). RFS, recurrence-free survival; CRP, C-reactive protein.

however, among pStage I patients, OS and RFS did not significantly differ between the high and low PNI groups after IPTW (Table 4). PNI, postoperative CRPmax, intraoperative blood loss, and pTNM stage were independent prognostic factors for RFS and OS (Table 5). Postoperative complications (Clavien-Dindo ≥2) are shown in Table 6. Fifty patients suffered postoperative complications, including 25 (22.5%, 25/111) who suffered re-

Table 6. Postoperative complications in this study, Clavien-Dindo ≥2

Complications	Incidence, *n/N* (%)
Anastomotic leakages	9/111 (8.1)
Recurrent nerve palsy	11/111 (9.9)
Pneumonia	17/111 (19.9)
Pleural effusion	8/111 (7.2)
SSI	12/111 (10.71)
Others	5/111 (4.5)

Others: chylothorax, ileus, peritonitis (2 patients), and abdominal abscess. Duplicate cases were included. SSI, surgical site infection.

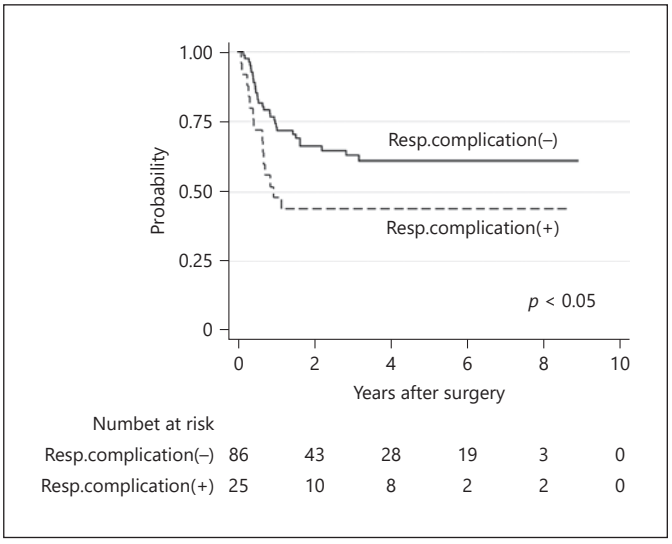

Fig. 3. Kaplan-Meier curves for RFS were significantly worse in patients with postoperative respiratory complications than in patients without postoperative respiratory complications ($p < 0.05$). RFS, recurrence-free survival.

spiratory complications (pneumonia, pleural effusion, and chylothorax). The postoperative complication group had a higher median CRP level (18.41 mg/dL) than did the no-complication group (16.10 mg/dL) but not significantly so ($p = 0.062$). However, the median value of CRP in the respiratory complication group (20.92 mg/dL) was significantly greater than that of the no-complication group (16.79 mg/dL; $p < 0.05$). Figure 3 shows RFS among patients with and without postoperative respiratory complications. Three-year RFS was 63.5% without respiratory complications and 44% with complications ($p < 0.05$).

Discussion

The present study retrospectively evaluated perioperative nutritional and immunological parameters and inflammatory response after esophagectomy and their effects, if any, on cancer progression and prognosis in patients with squamous cell EC. In multivariate analysis, PNI, CRPmax, and intraoperative blood loss were independent prognostic factors for OS and RFS. PNI was first introduced by Onodera et al. [23] in 1984, as an indicator of postoperative complications. A recent meta-analysis showed that lower PNI was correlated with unfavorable prognosis in patients with EC [16, 17, 27]. However, this meta-analysis included patients who had received neoadjuvant treatment and/or chemoradiotherapy. We excluded such patients in the present study to avoid biasing prognostic factors by inserting these factors in multivariate analysis. We found 7 articles on preoperative PNI and prognosis after EC surgery in patients who did not receive neoadjuvant treatment [28–34]. The findings of these studies are controversial; only 2 of 7 studies showed a favorable survival in the high preoperative PNI group, while the other studies arrived at conflicting results. One reason for this difference might be that patients with all stages of cancer were included, and subgroup analyses were not performed in these studies. Therefore, we analyzed the association between PNI and prognosis in EC patients in various stages of cancer (pStage I vs. II–IV) using the IPTW method of propensity scoring. Survival by patients with pStage I EC was similar in the low and high PNI groups, probably because most stage I patients are asymptomatic and few have malnutrition, which generally develops as the cancer progresses [6]. Poor prognosis in the low PNI group was seen in patients with more advanced EC. Therefore, preoperative nutritional intervention may improve the prognosis of advanced EC patients. However, there are some problems with preoperative nutritional intervention in advanced cancer. McMillan et al. [35] reported that systemic inflammatory response plays a major role in the progressive nutritional and functional decline of patients with cancer. Based on this finding, Crumley et al. [36] reported that low albumin concentrations were associated with low survival in patients with gastric cancer, and it was dependent on the presence of a systemic inflammatory response from tumor. Furthermore, Ligthart-Melis et al. [37] reported that the benefits of preoperative nutritional support in patients with EC were found mainly in neoadjuvant settings. Thus, preoperative nutritional support in patients with EC is presumed to be effective only for limited pop-

ulations, and it is a possibility that improved preoperative nutritional status may improve the survival in these patients. We hope that further examinations or clinical study including nutritional intervention in advanced EC might be planned in the future.

We found CRP to be an independent prognostic factor for RFS and OS. CRP is an indicator of postoperative inflammatory responses; it is produced by the liver when IL-6 is elevated [38, 39] and is easily measurable in clinical practice. Hirai et al. [40] reported that excessive surgical stress aggravates liver metastasis in rat laparotomy and/or thoracotomy models. Postoperative surgery wound fluid obtained from breast cancer patients promoted breast cancer cell proliferation; this fluid contains a large number of inflammatory cytokines [41]. Thus, experimental studies demonstrated that inflammatory cytokines or excessive surgical stress contributes to cancer progression. Postoperative inflammatory cytokines may have caused cancer progression in this study. High preoperative CRP level was associated with cancer progression and poor survival in patients with EC [42–44]. Several studies have demonstrated that postoperative CRP level is associated with EC prognosis, despite the differences in their methods and timing of CRP evaluation [19–21]. We measured postoperative serum CRP levels as CRPmax, based on a report by Saito et al. [45]; however, we do not know whether this method is optimal and are looking forward to further investigations. In this study, we evaluated the associations among postoperative complications after esophagectomy, CRP levels, and cancer progression. Patients with postoperative complications tended to have higher CRPmax levels, but this was not associated with the cancer prognosis (shown in Table 2). CRPmax was significantly higher in patients with respiratory complications. Although we found no relationship between general postoperative complications and prognosis, the RFS of patients whose complications were specifically respiratory was significantly worse than for patients with no complications. Reportedly, IL-6 levels are significantly elevated by acute lung injury or pneumonia after esophagectomy [46, 47]. Based on these reports, we believe that postoperative respiratory complications might lead to marked CRP elevations, and postoperative inflammatory cytokines might activate cancer cells at the microscopic level to cause cancer recurrence and metastasis. Therefore, reducing postoperative respiratory complications might be necessary to improve prognosis in patients with EC.

Blood loss during surgery is reportedly associated with cancer recurrence in patients with gastric cancer who undergo radical surgery [48, 49]. Komatsu et al. [50] reported that intraoperative blood loss during EC surgery was a prognostic factor in multivariate analysis; however, the cutoff value of intraoperative blood loss was 510 mL, which is larger than the value in our study. Because blood loss was not an independent prognostic factor for RFS and OS after IPTW in this study, further study might be necessary. Nevertheless, efforts to reduce intraoperative blood loss may help improve the prognosis of patients with EC. Surgeons should always keep in mind the development of surgical procedures that reduce intraoperative bleeding and prevent postoperative complications.

Conclusions

PNI is an independent prognostic indicator for patients with advanced EC who undergo esophagectomy. This is the first study to evaluate postoperative CRP, especially its maximum values; we found that high CRP level is associated with EC progression. Interventions by nutritional support teams to improve preoperative nutritional status and suppression of postoperative inflammatory response might improve the prognosis of EC patients after esophagectomy.

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Statement of Ethics

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. All study participants provided informed consent, and the study design was approved by an ethics review board (Authorization No. 3382, Kawasaki Medical School).

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Y.F. was involved in data analysis, formation of manuscript concept, and drafting the manuscript; S.E. revised the manuscript of important issue and statistical suggestions; M.H. and H.K. were involved in data collection and auxiliary analysis. S.M. and Y.O. assisted with table and figure formation. T.U. agrees to be accountable for all aspects of this work and permission for submission.

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