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ORIGINAL ARTICLE

Inflammatory response and recurrence after minimally invasive esophagectomy

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Abstract

Purpose Esophagectomy for esophageal cancer is a very invasive surgery that induces an intense systemic inflammatory response. Postoperative infectious complications worsen survival after esophagectomy through inflammatory responses, and this study aimed to investigate the impact of the response on disease recurrence.

Methods We assessed 230 patients who underwent curative minimally invasive esophagectomy for esophageal squamous cell carcinoma. The area under the curve of serum C-reactive protein levels from preoperative day through postoperative day 7 was defined as the cumulative magnitude of postoperative inflammatory response.

Results Relapse-free survival was compared among quartiles of the area, and fourth quartile showed the worst relapse-free survival. Patients in the fourth quartile were the high group, and others were low group. Compared with low group ($n = 173$), high group ($n = 57$) showed significantly worse relapse-free survival and overall survival ($P = 0.014$ and 0.028, respectively). Multivariate analyses found that high group ($P = 0.048$) was an independent risk factor for recurrence but not overall survival. Higher body mass index ($P < 0.001$) and postoperative infections ($P < 0.001$) were independent risk factors to become high group. However, the influence of high group on recurrence was not affected by postoperative infections in interaction analysis ($P = 0.889$).

Conclusions Postoperative intense systemic inflammatory response independently increased the risk of recurrence after curative minimally invasive esophagectomy for esophageal squamous cell carcinoma. Factors associating with intensified inflammatory response are higher body mass index and postoperative infections. Therefore, surgeons should make every effort to prevent postoperative infections to improve the long-term outcomes of patients.

Keywords Esophageal squamous cell carcinoma · Systemic inflammatory response · Minimally invasive esophagectomy · Prognosis

Introduction

Esophagectomy for esophageal cancer is one of the most invasive types of surgery, and it can induce an intense systemic inflammatory response (SIR). Minimally invasive esophagectomy (MIE) has been reported to attenuate postoperative SIR compared with open esophagectomy [1]. However, the extent of SIR after MIE still differs among patients, and it remains unclear whether the level of SIR influences long-term outcomes after MIE.

In addition to the surgical invasiveness itself, postoperative infectious complications (PICs) are known to stimulate the release of proinflammatory cytokines [1]. Several recent studies have shown that PICs after esophagectomy had a negative influence on the survival of patients [2–10]. Although the unique mechanism by which PICs worsen survival after esophagectomy has never been elucidated, one possible explanation is that intense SIR initiates cancer cell growth. In addition, it has been suggested that surgery may increase postsurgical risk of cancer recurrence through at least two

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dormancy-related mechanisms that are triggered by neuroendocrine and paracrine stress-inflammatory responses to surgery [11].

Matsuda et al. reported decreased survival of patients after esophagectomy, with intense SIR defined as delayed peak of serum C-reactive protein (CRP) levels and persistent high levels of serum CRP for 6 days or longer [12]. However, it was suggested that postoperative SIR was influenced by each time and each cause [1]. In addition, there was no validated measure to assess the magnitude of postoperative SIR, and there was no distinct definition of intense SIR. In this study, we evaluated the magnitude of postoperative SIR to which patients were cumulatively exposed when calculating the area under the curve (AUC) of postoperative serum CRP levels. We investigated the impact of postoperative intense SIR on disease recurrence following curative surgery for esophageal cancer, as well as risk factors for intense SIR.

Material and methods

Patients

Consecutive patients who underwent curative MIE for esophageal squamous cell carcinoma (ESCC) at The Cancer Institute Hospital of Japanese Foundation for Cancer Research from 2010 to 2015 were assessed. Patients who could be evaluated for CRP levels on postoperative days (PODs) 1, 2, 3, 4, 5, and 7 were eligible. Excluded from this study were patients whose histological type was not SCC and CRP measurements were not completed, those who underwent surgery after chemoradiotherapy, and those with synchronous dual cancers. In the eligible patients, nobody underwent total pharyngolaryngoesophagectomy, transhiatal esophagectomy, two-stage esophagectomy, and reconstruction without using gastric conduit (Fig. 1). The study protocol for this research project was approved by the Institutional Review Board of our institute (approval no. 2018-1194).

Preoperative treatment

Tumor stage was classified in accordance with the Union for International Cancer Control *TNM Classification of Malignant Tumors*, eighth edition [13]. Treatment strategies were provided for each patient in accordance with the Japan Esophageal Society guidelines as follows [14]: surgery alone for cT1N0, neoadjuvant chemotherapy followed by surgery for T1N1-3 or T2-4a any N, definitive chemoradiotherapy for T4b tumor or refusal of surgery irrespective of the stage, and salvage surgery for failure of chemoradiotherapy. The neoadjuvant chemotherapy regimen was two courses of cisplatin and 5-fluorouracil (CF) as used in the randomized trial JCOG 9907 [15].

Surgical procedure

In this study, MIE included thoracoscopic or laparoscopic approach. Total MIE was defined as MIE with both approaches, whereas hybrid MIE was defined as MIE with either approach. Thoracoscopic and laparoscopic approach was introduced in esophagectomy in 2010 and 2013, respectively. During the study period, the indication of MIE did not change, and open approach tended to be chosen for patients with tumors possibly invading surrounding organs, bulky primary tumors, and bulky lymph node metastases. Patients underwent radical esophagectomy with mediastinal lymph node dissection using a cervicothoracoabdominal approach. Thoracic procedures were performed using a thoracoscopic approach in the prone position or an open transthoracic approach in the left lateral decubitus position. For abdominal procedures, gastric mobilization was performed, and the abdominal lymph nodes were dissected using a laparoscopic approach or an open abdominal approach. We used a gastric conduit through the retrosternal route or the posterior mediastinal route with cervical or intrathoracic anastomosis. A hand-sewn end-to-end cervical anastomosis was mainly performed, using single- or double-layered running or interrupted absorbable sutures, until August 2013. From September 2013, we primarily performed mechanical anastomosis with a triangulating stapling technique using linear staplers [16, 17].

Perioperative management

The management of perioperative care and drugs that could attenuate postoperative SIR remained the same during the study period. Methylprednisolone was routinely administered at a dose of 250 mg just before commencing the operation. All patients were admitted to the intensive care unit after extubation of the endotracheal tube if their general condition was stable after surgery. Preoperative oral nutritional support was performed for 5 days, enteral feeding started from POD 1, and oral food intake was resumed after POD 7. Prophylactic antibiotics were administered intraoperatively and postoperatively until POD 1. If PICs developed, culture specimens were collected and empiric therapy using broad-spectrum antibiotics was initiated. Antimicrobial susceptibility testing was performed if a pathogenic microorganism was identified in the cultures, and antibiotic de-escalation was performed based on the results.

We introduced a multidisciplinary perioperative care team in October 2013. In the team management, perioperative oral cleaning and breathing exercises using a training device were routinely performed. A bedside breathing exercise and gait training were started from POD 1, and an advanced physical training program using an exercise bike was performed after POD 4.

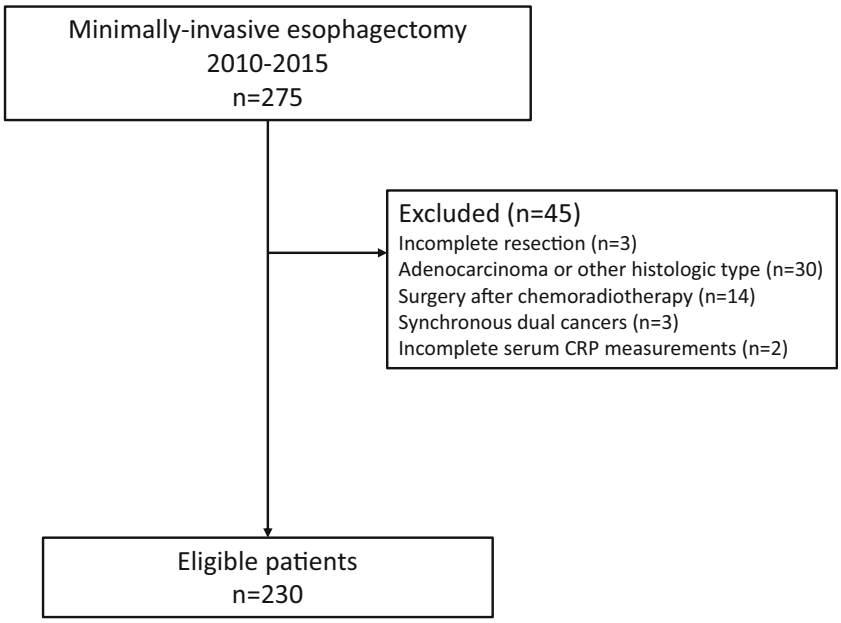

Fig. 1 Flow diagram

Serum CRP measurements and evaluation for the magnitude of postoperative SIR

Serum CRP levels were measured in the morning preoperatively and on POD 1, 2, 3, 4, 5, and 7. To evaluate the magnitude of postoperative SIR, AUC of serum CRP levels was calculated preoperatively through POD 7 as the integral (intCRP).

Postoperative complications

Based on the results of physical and blood examination, additional examination was performed as needed. All postoperative complications were diagnosed clinically or radiologically and classified according to the Clavien-Dindo (CD) grading system [18]. PICs that commonly induced SIR, including pneumonia (≥ CD grade 2), anastomotic leak (AL) (≥ CD grade 1), surgical site infection (SSI) without AL (≥ CD grade 1), and other infectious complications (≥ CD grade 2) were investigated.

Patient follow-up

Patients were followed every 4 months for 1 year postoperatively and every 6 months thereafter. Each follow-up visit consisted of a physical examination, assessment of serum levels of SCC antigen, and computed tomography. In addition, esophagogastroduodenoscopy was performed annually. The postoperative follow-up duration was at least 5 years.

Statistical analysis

All data were presented as median (range) or number (%). In survival analysis, relapse-free and overall survival (RFS and OS) were evaluated. Survival differences were analyzed using the Kaplan–Meier method and log-rank test. Cox proportional hazards model was used to elucidate the impact of variables on survival, with results presented as hazard ratio (HR) and 95% confidence interval (CI). To assess risk factors for intense SIR, logistic regression model was used to calculate odds ratio (OR) and 95% CI. Multivariate analyzes were performed by backward elimination. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0; IBM-SPSS, Inc., Armonk, NY, USA).

Results

Patient characteristics and surgical outcomes

In this study, 230 patients met the eligibility. Patient characteristics and surgical outcomes are summarized in Table 1. Of all patients, 188 (81.7%) were male, and median age was 65 years. One hundred fourteen patients (49.6%) were treated with neoadjuvant chemotherapy before surgery, and 111 patients (48.3%) underwent total MIE. Postoperatively, 87 patients (38.3%) had PICs. Of these patients, pneumonia, AL, and SSI was observed in 55 (23.9%), 28 (12.2%), and 22 (9.6%), respectively.

Table 1 Patient characteristics and surgical outcomes

Variable	Value
Sex	
Male/female	188 (81.7)/42 (18.3)
Age (years)	65 (40–82)
BMI (kg/m^2)	21.7 (15.1–30.8)
Preoperative treatment	
None/NAC	116 (50.4)/114 (49.6)
(y)pStage category	
(y)pStage I–II/III–IV	149 (64.8)/81 (35.2)
Surgical approach	
Total MIE/hybrid MIE	111 (48.3)/119 (51.7)
Thoracoscopic/open	204 (88.7)/26 (11.3)
Laparoscopic/open	137 (59.6)/93 (40.4)
Field of dissection	
Two-field/Three-field	87 (37.8)/143 (83.6)
Operative duration (min)	604 (396–957)
Operative blood loss (mL)	200 (20–1250)
PICs	87 (38.3)
Pneumonia	55 (23.9)
AL	28 (12.2)
SSI without AL	22 (9.6)

Data are presented as median (range) or *n* (%)

BMI body mass index, *NAC* neoadjuvant chemotherapy, *MIE* minimally invasive esophagectomy, *PIC* postoperative infectious complication, *AL* anastomotic leak, *SSI* surgical site infection

Postoperative changes in serum CRP levels and distribution of intCRP

Postoperative changes in serum CRP levels were evaluated. Serum CRP levels peaked on POD 2 and gradually decreased after the peak (Supplementary Fig. 1). The median intCRP was 577.5 mg/L (138.5–1636.5).

Patient survival and intCRP

According to the percentiles of intCRP, patients were classified as first quartile (Q1; 138.5–412.0), second quartile (Q2; 419.0–577.0), third quartile (Q3; 578.0–743.0), and fourth quartile (Q4; 747.0–1636.5). Kaplan–Meier curves for RFS were calculated for each group as shown in Supplementary Fig. 2. In a univariate Cox proportional hazards model, HR for RFS was highest in group Q4 (Supplementary Table 1). From this finding, dichotomous intCRP defined groups Q1–3 as low-intCRP group and group Q4 as high-intCRP group. In Kaplan–Meier analysis (Fig. 2), RFS and OS of high-intCRP group were significantly worse than those of low-intCRP group (P = 0.014 and 0.028).

Clinical significance of intCRP on patient survival

As shown in Table 2, univariate Cox proportional hazard analysis found that neoadjuvant chemotherapy ($P < 0.001$), (y)pStage III–IV ($P < 0.001$), three-field lymph node dissection ($P = 0.021$), blood loss ($P = 0.003$), and high-intCRP ($P = 0.016$) were significant variables for poorer RFS. Further multivariate Cox analyses found neoadjuvant chemotherapy ($P = 0.024$), (y)pStage III–IV ($P = 0.002$), blood loss ($P = 0.014$), and high-intCRP ($P = 0.048$) to be independent poor prognosticators for RFS. In the analysis for OS, high-intCRP was a significant factor for poorer survival in univariate analysis ($P = 0.035$), but it was not an independent factor in multivariate analysis (Table 3). Supplementally, HRs of each serum CRP level on RFS were calculated in a univariate Cox proportional hazards model (Supplementary Table 2). Then, the HR of POD 7 was highest, followed by POD 5.

Interactions between high-intCRP and other variables on RFS

We evaluated whether the influence of high-intCRP on RFS was affected by any other clinicopathological variables. Results showed that the impact of high-intCRP was not significantly affected by age, body mass index (BMI), neoadjuvant chemotherapy, pathological stage, surgical approach, field of lymph node dissection, and PICs (Fig. 3). The interaction between sex and high-intCRP was difficult to assess because the number of female patients was small.

Risk factors for high-intCRP

Finally, risk factors for high-intCRP were evaluated (Table 4). In univariate analysis, male ($P = 0.017$), BMI ($P < 0.001$), and PICs ($P < 0.001$) were significantly associated with high-intCRP. Meanwhile, laparoscopic approach tended to be associated with low-intCRP ($P = 0.088$). In multivariate analysis, BMI ($P < 0.001$) and PICs ($P < 0.001$) were independent risk factors for high-intCRP.

Discussion

In this study, we analyzed the relationship between postoperative SIR and long-term outcomes following curative esophagectomy for ESCC in 230 patients. In the results, we observed that RFS and OS were significantly worse in patients who experienced intense SIR compared with those who did not, and postoperative intense SIR independently increased the risk of recurrence after curative surgery for ESCC. In addition, factors associated with intense SIR were higher BMI and PICs. Therefore, surgeons should make every effort to prevent PICs to improve the long-term outcomes of patients.

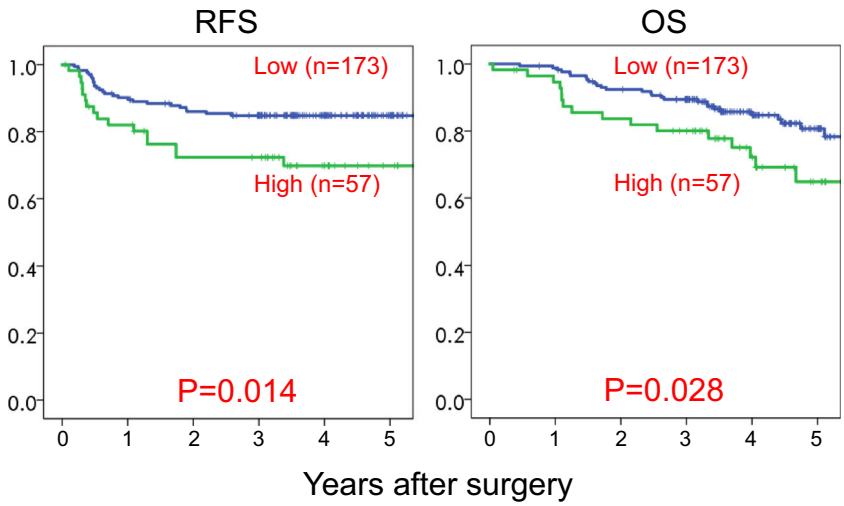

Fig. 2 Kaplan–Meier analysis for relapse-free survival (RFS) and overall survival (OS) of low-intCRP group and high-intCRP group

Several studies have shown that PICs after esophagectomy had a negative influence on patient survival [2–10]. Although the specific mechanism remains unclear, one possible explanation is that inflammatory cytokines, which are produced when PICs occur, promote cancer cell growth. Interleukin (IL)-6 is known to play a potential role in the progression and treatment response of ESCC [19–21]. In addition, it has been reported that increased expression of both IL-8 and its receptor CXCR-2 correlated with cancer progression and poor prognosis after esophagectomy for ESCC [22, 23]. These results suggest that SIR may enhance cancer progression through the overproduction of inflammatory cytokines. Additionally, PICs themselves may have a negative influence on patient survival. It is already known that infection of certain microorganisms is associated with the development or progression of cancer [24–26]. Moreover, some experimental studies reported that molecules expressed on bacterial cell surface or lipopolysaccharides could have the potential for a proliferative effect on gastric and colorectal cancer cells through their ligand receptors [25, 26].

Although PICs are major causes of intense SIR after esophagectomy, Matsuda et al. showed that 23% of patients with intense SIR were not diagnosed with PICs [12]. The current study showed that the impact of intense SIR on RFS was not affected by PICs in interaction analysis. The significant risk factor for intense SIR after MIE was higher BMI, as well as PICs. It has been suggested that there are various causes of intense SIR other than PICs after esophagectomy [1].

Based on the current results, it is essential to prevent PICs and to attenuate SIR to improve long-term outcomes after

Table 2 Cox proportional hazard regression analysis for factors influencing RFS

Variable (reference)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male (female)	3.19 (0.99–10.3)	0.053	–	–
Age	0.99 (0.96–1.03)	0.683	–	–
BMI	1.00 (0.89–1.12)	0.946	–	–
NAC (none)	5.70 (2.53–12.8)	< 0.001*	2.86 (1.15–7.08)	0.024*
(y)pStage III–IV (I–II)	5.64 (2.88–11.0)	< 0.001*	3.32 (1.57–7.01)	0.002*
Thoracoscopic (open)	0.90 (0.35–2.29)	0.827	–	–
Laparoscopic (open)	0.81 (0.44–1.49)	0.498	–	–
Three-field dissection (two-field dissection)	2.38 (1.14–4.98)	0.021*	–	–
Operative duration	1.00 (1.00–1.01)	0.321	–	–
Operative blood loss	1.02 (1.01–1.03)	0.003*	1.01 (1.00–1.02)	0.014*
PICs	1.54 (0.84–2.83)	0.161	–	–
High-IntCRP	2.15 (1.15–4.01)	0.016*	1.88 (1.01–3.50)	0.048*

RFS relapse-free survival, *HR* hazard ratio, *BMI* body mass index, *NAC* neoadjuvant chemotherapy, *MIE* minimally invasive esophagectomy, *PIC* postoperative infectious complication

*$P < 0.05$

Table 3 Cox proportional hazard regression analysis for factors influencing OS

Variable (reference)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male (female)	5.03 (1.22–20.8)	0.026*	4.46 (1.08–18.5)	0.039*
Age	1.01 (0.97–1.05)	0.598	–	–
BMI	0.98 (0.88–1.10)	0.721	–	–
NAC (none)	2.08 (1.12–3.85)	0.021*	–	–
(y)pStage III–IV (I–II)	3.21 (1.76–5.87)	< 0.001*	3.05 (1.64–5.66)	< 0.001*
Thoracoscopic (open)	0.58 (0.26–1.30)	0.183	0.34 (0.13–0.89)	0.028*
Laparoscopic (open)	0.55 (0.29–1.03)	0.064	0.41 (0.20–0.88)	0.021*
Three-field dissection (two-field dissection)	1.11 (0.60–2.05)	0.745	–	–
Operative duration	1.00 (1.00–1.02)	0.604	–	–
Operative blood loss	1.02 (1.00–1.03)	0.010*	–	–
PICs	1.26 (0.69–2.28)	0.454	–	–
High-IntCRP	1.94 (1.05–3.58)	0.035*	–	–

OS overall survival, *HR* hazard ratio, *BMI* body mass index, *NAC* neoadjuvant chemotherapy, *MIE* minimally invasive esophagectomy, *PIC* postoperative infectious complication

*$P < 0.05$

MIE. Previously, we reported that the introduction of multidisciplinary perioperative care team significantly decreased the incidence of postoperative complications, especially pneumonia [27]. Systematic perioperative care bundle could reduce PICs after esophagectomy. Regarding the anastomotic technique, although previous meta-analyses reported that there was no significant difference between hand-sewn and stapled anastomoses in the prevalence of AL after esophagectomy, several studies have also reported that use of a triangulating stapling technique could reduce the prevalence of AL [16, 17]. Therefore, we introduced this method as the first choice of anastomotic technique.

In addition, urgent intervention or diagnosis for PICs could contribute to prevent intense SIR. Miki et al. suggested that serum CRP level on POD 4 ≥ 111 mg/L was an independent predictive factor for PICs in patients who underwent MIE [28], although the time shift of postoperative inflammatory response varies among types of complications [29]. Regarding AL, Asti et al. reported that serum CRP level on POD 5 < 83 mg/L may be useful to exclude AL [30], and Park

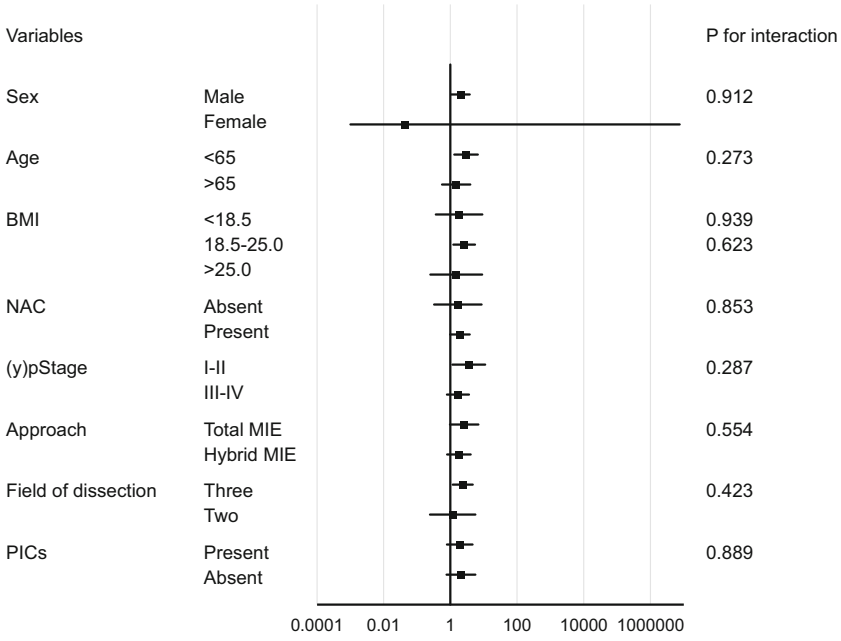

Fig. 3 Interactions between high-intCRP group and other variables on recurrence-free survival (RFS). BMI, body mass index; NAC, neoadjuvant chemotherapy; PIC, postoperative infectious complication

Table 4 Logistic regression analysis for risk factors of high-intCRP

Variable (reference)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male (female)	3.73 (1.27–11.0)	0.017*	–	–
Age	1.01 (0.98–1.05)	0.439	–	–
BMI	1.26 (1.12–1.42)	< 0.001*	1.28 (1.13–1.46)	< 0.001*
NAC (none)	1.64 (0.89–3.01)	0.110	–	–
(y)pStage III–IV (I–II)	1.22 (0.65–2.26)	0.538	–	–
Thoracoscopic (open)	0.73 (0.30–1.78)	0.490	–	–
Laparoscopic (open)	0.59 (0.33–1.08)	0.088	–	–
Three-field dissection (two-field dissection)	1.44 (0.76–2.72)	0.263	–	–
Operative duration	1.03 (1.00–1.06)	0.088	–	–
Operative blood loss	1.01 (1.00–1.03)	0.058	–	–
PICs	4.78 (2.52–9.08)	< 0.001*	4.70 (2.42–9.13)	< 0.001*

BMI body mass index, *NAC* neoadjuvant chemotherapy, *MIE* minimally invasive esophagectomy, *PIC* postoperative infectious complication
*$P < 0.05$

et al. reported that serum CRP level on POD 3 had a significant cutoff value for early detection of AL after esophagectomy [31]. Supplementary Fig. 3 shows the receiver operating characteristic curves which evaluated the predictive value of serum CRP levels of different PODs on the occurrence of PICs. The AUCs on POD 1, POD 2, POD 3, POD 4, POD 5, and POD 7 were 0.507, 0.584, 0.646, 0.689, 0.743, and 0.787, respectively, and the AUC increased as POD passed. However, from predictive perspective, the timing is important as well as the accuracy. In this study, we would like to show the significant relationship between postoperative inflammatory response and prognosis after MIE for ESCC. Therefore, we could not refer the clinical utility of postoperative CRP levels as the predictive marker for a certain postoperative complication precisely.

Meanwhile, a less invasive approach may improve survival, although it did not reach statistical significance in the analysis for RFS. Previously, we also showed that MIE attenuated postoperative SIR and improved survival compared with open esophagectomy (OE) in a propensity score-matched study [32]. Furthermore, in the French MIRO trial, Mariette et al. reported that non-significant survival prolongation with significant lower incidence of major complications (specifically pulmonary complications) in laparoscopic abdominal approach when comparing with open abdominal approach in open transthoracic esophagectomy [33]. To evaluate whether a less invasive approach may influence patient survival, a randomized phase III study (JCOG1409) is ongoing in Japan, comparing MIE versus OE for OS in cStage I–III esophageal cancer [34].

Serum CRP is a classic acute-phase reactant produced by the liver, and production is regulated by IL-6 in hepatocytes [35]. The circulating concentration of serum CRP rises rapidly and extensively during a cytokine-mediated response to tissue injury, infection, or inflammation [36]. Serum CRP levels after elective surgery are consistently associated with the magnitude of surgical invasiveness [37]. In addition, it is easily obtained in daily practice. Therefore, serum CRP is useful to assess postoperative SIR after elective surgery.

Our study has several limitations that should be addressed. First, this relatively small, retrospective observational study is conducted in a single institution. In addition, the parameter used to assess SIR is CRP alone. Therefore, other inflammatory markers such as serum cytokine levels should be evaluated in further investigation. Second, we calculate the AUC of serum CRP levels to determine the extent of postoperative cumulative exposure to SIR because postoperative SIR may be influenced by each time and each cause [1]. However, because there is no validated measure to assess the magnitude of postoperative SIR, the methodology should be validated.

In summary, RFS and OS in patients who are exposed to intense SIR are significantly worse than those who are not, and intense SIR is independently associated with disease recurrence following curative MIE for ESCC. Factors associating with intense SIR are higher BMI and PICs. Thus, further evaluation is needed to determine whether control of intense SIR leads to improvement of survival.

Authors' contributions Study conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: Okamura, Watanabe, Yamashita, Mine. Drafting manuscript: Okamura, Watanabe, Yamashita, Mine. Critical revision of manuscript: all authors.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national

research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Okamura A, Takeuchi H, Matsuda S, Ogura M, Miyasho T, Nakamura R, Takahashi T, Wada N, Kawakubo H, Saikawa Y, Kitagawa Y (2015) Factors affecting cytokine change after esophagectomy for esophageal cancer. Ann Surg Oncol 22:3130–3135
2. Takeuchi H, Saikawa Y, Oyama T, Ozawa S, Suda K, Wada N, Takahashi T, Nakamura R, Shigematsu N, Ando N, Kitajima M, Kitagawa Y (2010) Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. World J Surg 34:277–284
3. Booka E, Takeuchi H, Nishi T, Matsuda S, Kaburagi T, Fukuda K, Nakamura R, Takahashi T, Wada N, Kawakubo H, Omori T, Kitagawa Y (2015) The impact of postoperative complications on survivals after esophagectomy for esophageal cancer. Medicine 94: e1369
4. Markar S, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, Lefevre JH, Brigand C, Vaillant JC, Adham M, Msika S, Demartines N, Nakadi IE, Meunier B, Collet D, Mariette C (2015) The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg 262:972–980
5. Baba Y, Yoshida N, Shigaki H, Iwatsuki M, Miyamoto Y, Sakamoto Y, Watanabe M, Baba H (2016) Prognostic impact of postoperative complications in 502 patients with surgically resected esophageal squamous cell carcinoma: a retrospective single-institution study. Ann Surg 264:305–311
6. Yamashita K, Makino T, Miyata H, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M, Nakajima K, Takiguchi S, Mori M, Doki Y (2016) Postoperative infectious complications are associated with adverse oncologic outcomes in esophageal cancer patients undergoing preoperative chemotherapy. Ann Surg Oncol 23:2106–2114
7. Kataoka K, Takeuchi H, Mizusawa J, Igaki H, Ozawa S, Abe T, Nakamura K, Kato K, Ando N, Kitagawa Y (2017) Prognostic impact of postoperative morbidity after esophagectomy for esophageal cancer: exploratory analysis of JCOG9907. Ann Surg 265: 1152–1157
8. Saeki H, Tsutsumi S, Tajiri H, Yukaya T, Tsutsumi R, Nishimura S, Nakaji Y, Kudou K, Akiyama S, Kasagi Y, Nakanishi R, Nakashima Y, Sugiyama M, Ohgaki K, Sonoda H, Oki E, Maehara Y (2017) Prognostic significance of postoperative complications after curative resection for patients with esophageal squamous cell carcinoma. Ann Surg 265:527–533
9. Hayami M, Watanabe M, Ishizuka N, Mine S, Imamura Y, Okamura A, Kurogochi T, Yamashita K (2018) Prognostic impact of postoperative pulmonary complications following salvage esophagectomy after definitive chemoradiotherapy. J Surg Oncol 117:1251–1259
10. Shimada H, Fukagawa T, Haga Y, Oba K (2017) Does postoperative morbidity worsen the oncological outcome after radical surgery for gastrointestinal cancers? A systematic review of the literature. Ann Gastroenterol Surg 1:11–23
11. Haldar R, Ben-Eliyahu S (2018) Reducing the risk of post-surgical cancer recurrence: a perioperative anti-inflammatory anti-stress approach. Future Oncol 14:1017–1021
12. Matsuda S, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Kitagawa Y (2015) Correlation between intense postoperative inflammatory response and survival of esophageal cancer patients who underwent transthoracic esophagectomy. Ann Surg Oncol 22:4453–4460
13. Brierley JD, Gospodarowicz MK, Wittekind C (eds) (2017) TNM classification of malignant tumors. International Union Against Cancer, 8th edn. Wiley, Oxford
14. Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, Shimada H, Takiuchi H, Toh Y, Doki Y, Naomoto Y, Matsubara H, Miyazaki T, Muto M, Yanagisawa A (2015) Guidelines for diagnosis and treatment of carcinoma of the esophagus April 2012 edited by the Japan Esophageal Society. Esophagus 12:1–30
15. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K, Fukuda H (2012) A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 19:68–74
16. Toh Y, Sakaguchi Y, Ikeda O, Adachi E, Ohgaki K, Yamashita Y, Oki E, Minami K, Okamura T (2009) The triangulating stapling technique for cervical esophagogastric anastomosis after esophagectomy. Surg Today 39:201–206
17. Yoshida N, Baba Y, Watanabe M, Hiyoshi Y, Ishimoto T, Iwagami S, Kurashige J, Sakamoto Y, Miyamoto Y, Baba H (2015) Triangulating stapling technique covered with the pedicled omental flap for esophagogastric anastomosis: a safe anastomosis with fewer complications. J Am Coll Surg 220:e13–e16
18. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
19. Oka M, Yamamoto K, Takahashi M et al (1996) Relationship between serum levels of interleukin 6, various disease parameters and malnutrition in patients with esophageal squamous cell carcinoma. Cancer Res 56:2776–2780
20. Wang LS, Chow KC, Wu CW (1999) Expression and up-regulation of interleukin-6 in esophageal carcinoma cells by n-sodium butyrate. Br J Cancer 80:1617–1622
21. Yoneda M, Fujiwara H, Furutani A et al (2013) Prognostic impact of tumor IL-6 expression after preoperative chemoradiotherapy in patients with advanced esophageal squamous cell carcinoma. Anticancer Res 33:2699–2705
22. Ogura M, Takeuchi H, Kawakubo H, Nishi T, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Omori T, Miyasho T, Yamada S, Kitagawa Y (2013) Clinical significance of CXCL-8/CXCR-2 network in esophageal squamous cell carcinoma. Surgery 154:512–520
23. Nishi T, Takeuchi H, Matsuda S, Ogura M, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Omori T, Kitagawa Y (2015) CXCR2 expression and postoperative complications affect long-term survival in patients with esophageal cancer. World J Surg Oncol 13:232
24. Blaser MJ (2008) Understanding microbe-induced cancers. Cancer Prev Res (Phila) 1:15–20
25. Chochi K, Ichikura T, Kinoshita M, Majima T, Shinomiya N, Tsujimoto H, Kawabata T, Sugasawa H, Ono S, Seki S, Mochizuki H (2008) Helicobacter pylori augments growth of gastric cancers via the lipopolysaccharide-toll-like receptor 4 pathway whereas its lipopolysaccharide attenuates antitumor activities of human mononuclear cells. Clin Cancer Res 14:2909–2917
26. Bonnet M, Buc E, Sauvanet P, Darcha C, Dubois D, Pereira B, Dechelotte P, Bonnet R, Pezet D, Darfeuille-Michaud A (2014)

Colonization of the human gut by *E. coli* and colorectal cancer risk. Clin Cancer Res 20:859–867
27. Watanabe M, Mine S, Nishida K, Yamada K, Shigaki H, Oya S, Matsumoto A, Kurogochi T, Okamura A, Imamura Y, Sano T (2016) Improvement in short-term outcomes after esophagectomy with a multidisciplinary perioperative care team. Esophagus 13: 337–342
28. Miki Y, Toyokawa T, Kubo N, Tamura T, Sakurai K, Tanaka H, Muguruma K, Yashiro M, Hirakawa K, Ohira M (2017) C-reactive protein indicates early stage of postoperative infectious complications in patients following minimally invasive esophagectomy. World J Surg 41:796–803
29. Okamura A, Watanabe M, Fukudome I, Yamashita K, Yuda M, Hayami M, Imamura Y, Mine S (2018) Relationship between visceral obesity and postoperative inflammatory response following minimally invasive esophagectomy. World J Surg 42:3651–3657
30. Asti E, Bonitta G, Melloni M, Tornese S, Milito P, Sironi A, Costa E, Bonavina L (2018) Utility of C-reactive protein as predictive biomarker of anastomotic leak after minimally invasive esophagectomy. Langenbeck's Arch Surg 403:235–244
31. Park JK, Kim JJ, Moon SW (2017) C-reactive protein for the early prediction of anastomotic leak after esophagectomy in both neoadjuvant and non-neoadjuvant therapy case: a propensity score matching analysis. J Thorac Dis 9:3963–3702
32. Yamashita K, Watanabe M, Mine S, Toihata T, Fukudome I, Okamura A, Yuda M, Hayami M, Ishizuka N, Imamura Y (2018) Minimally invasive esophagectomy attenuates the postoperative inflammatory response and improves survival compared with open esophagectomy in patients with esophageal cancer: a propensity score matched analysis. Surg Endosc 32:4443–4450
33. Mariette C, Markar SR, Dabakuyo-Yonli TS et al (2019) Hybrid minimally invasive esophagectomy for esophageal cancer. N Engl J Med 380:152–162
34. Kataoka K, Takeuchi H, Mizusawa J, Ando M, Tsubosa Y, Koyanagi K, Daiko H, Matsuda S, Nakamura K, Kato K, Kitagawa Y (2016) A randomized phase III trial of thoracoscopic versus open esophagectomy for thoracic esophageal cancer: Japan clinical oncology group study JCOG1409. Jpn J Clin Oncol 46: 174–177
35. Rahman SH, Evans J, Toogood GJ, Lodge PA, Prasad KR (2008) Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. Arch Surg 143:247–253 discussion 53
36. Thompson D, Pepys MB, Wood SP (1999) The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 7:169–177
37. Watt DG, Horgan PG, McMillan DC (2015) Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery 157:362–380