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Predictors of Early and Late Mortality after Endoscopic Resection for Esophageal Squamous Cell Carcinoma

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In esophageal squamous cell carcinoma (ESCC) comprising 90% of cases with esophageal cancer, endoscopic resection (ER) is recommended for patients with negligible risk of ESCC-related mortality. In fact, a main cause of death in patients underwent ER is not ESCC. We thus aimed to clarify the predictors for early and late mortality among patients underwent ER of ESCC between 2005 and 2018 at our institution. In this retrospective cohort study, we investigated the prognosis and predictors of early and late mortality with the cut-off value of 3 years. We enrolled 407 patients with a median 69 months follow-up. The 5-year overall survival and disease-specific survival, an indicator of ESCC-related mortality, were 83.4% and 98.4%, respectively. In multivariate Cox analyses, Eastern Cooperative Oncology Group performance status (ECOG-PS), consisting of six grades by a patient's level of activity, ≥ 2 was a predictor for early and late morality [hazard ratio (HR), 7.21 (P = 0.007) and 15.62 (P = 0.021), respectively]. Charlson comorbidity index (CCI), which is an index for predicting mortality by comorbid conditions, ≥ 2 was also a predictor for both mortality [HR, 2.97 (P = 0.017) and 1.90 (P = 0.019), respectively]. However, age was a predictor only for late mortality [HR, 3.08 (P = 0.010) in 80-84 years and 8.38 (P < 0.001) in ≥ 85 years]. Considering the predictive ability for early mortality, we propose that ECOG-PS and/or CCI are better indices compared with age in deciding treatment strategy after ER for ESCC.

Keywords: Charlson comorbidity index; endoscopic resection; esophageal squamous cell carcinoma; performance status; prognosis
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Introduction

Esophageal cancer is ranked ninth for cancer incidence and sixth for cancer death (Global burden of Disease Cancer Collaboration et al. 2015). Squamous cell carcinoma is the most common histopathological type of esophageal cancer and the prevalence is high especially in East Asian counties (Arnold et al. 2015; Malhotra et al. 2017). Especially in Japan, about 90% of cases with esophageal cancer are this histopathological type (Tachimori et al. 2016).

Recent developments in endoscopic technologies enable the detection of esophageal squamous cell carcinomas (ESCCs) in the early stage and curing such tumors with negligible risk of lymph node metastasis (LNM) by endoscopic resection (ER) (Oyama et al. 2005; Fujishiro et al. 2009), and this technique has also been proved to be safe and effective in elderly patients (Song et al. 2017; Qi et al. 2018; Iizuka et al. 2019). According to the current European and Japanese guidelines (Pimentel-Nunes et al. 2015; Kitagawa et al. 2019a, b), additional treatment, such as esophagectomy, chemoradiotherapy (CRT), or radiation therapy, is recommended for patients with ESCCs that do not meet the curability criteria because of the risk of metastasis and recurrence. However, additional treatment is sometimes not selected due to the patient's condition, such

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as old age and comorbidities. Furthermore, in the real-world, the main cause of death in such patients is not ESCC (Mizumoto et al. 2018; Nakajo et al. 2019). To date, many reports have investigated LNM or ESCC-related mortality (Choi et al. 2011; Yamashina et al. 2013). Moreover, regarding cases with ER for gastric cancer, several studies have focused on all-cause mortality as well as gastric cancer-related mortality (Hatta et al. 2020). However, few studies focused on all-cause mortality in patients undergoing ER for ESCC.

Age is a well-known prognostic predictor. Furthermore, inflammation-based prognostic scores, such as prognostic nutritional index (PNI) (Onodera et al. 1984), Glasgow prognostic score (GPS) (Forrest et al. 2003), and C-reactive protein/albumin ratio (CAR) (Fairclough et al. 2009), have been suggested to be useful prognostic tools for a variety of malignant solid tumors (Proctor et al. 2011; Kinoshita et al. 2015). Meanwhile, it is sometimes clinically important to assess early and late mortality separately, because the desired life expectancy for deciding treatment strategy may differ among patients. For example, some very elderly patients may require information for a relatively short life expectancy rather than for a long-life expectancy, to decide the treatment strategy for ESCC. However, it has remained unclear whether prognostic predictors differ between early and late mortality in patients with ER for ESCC. The aim of our study was to clarify predictors of early and late mortality in patients with ER for ESCC.

Materials and Methods

Study population and Ethics statement

This study was a single-center, retrospective cohort study. Patients who underwent ER for ESCC at our institution between January 2005 and February 2018 were assessed for eligibility to enroll in this study. Patients were excluded if they had a history of esophagectomy, CRT, or radiation therapy for an esophageal tumor. The study protocol was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology statement and was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2019-1-983). Written informed consent for ER was obtained from all patients before the procedure. However, the need for informed consent in this study was waived via the opt-out method on the website at our institution.

Therapeutic approach and follow-up after ER

According to the Japanese guidelines (Kitagawa et al. 2019a, b), curability criteria in ER for ESCC were classified into three categories as follows.

Category A (negligible LNM risk): pT1a-EP/LPM (confined to epithelium or lamina propria mucosae) with no lymphovascular invasion (LVI) and negative vertical margin (VM)

Category B (certain LNM risk): pT1a-MM (invading into muscularis mucosae) with no LVI and negative VM

Category C (high LNM risk): pT1a (confined to mucosae) with LVI/positive VM or pT1b (invading into submucosa)

In the guidelines, no additional treatment after ER is recommended for patients with category A, whereas additional esophagectomy, CRT, or radiation therapy is recommended for those with category C. In those with category B, the recommended treatment strategy is inconclusive. In this study, additional treatment was recommended for those with categories B or C, but whether to undergo additional therapy depended on the risk of LNM, patient's condition, age, and patients' preference.

In cases with category A, esophagogastroduodenoscopy (EGD) was performed every 6-12 months. Cases with categories B or C were generally followed up with computed tomography every 6-12 months for at least 5 years, in addition to EGD, regardless of additional treatment.

Date collection and the definition

The data were collected from medical records, and missing information was obtained by interviews of the patients over the telephone. Regarding the stratification of mortality into early and late mortality, no definite criteria have been determined. According to a previous report that investigated the long-term outcome after esophagectomy for stage I ESCC (Igaki et al. 2001), about 50% of the mortality occurred within 3 years. In addition, 3-year survival is often used as a criterion for the prognosis in the field of ER for early-stage gastrointestinal cancer (Hatta et al. 2017; Minashi et al. 2019). Thus, the cut-off value of early and late mortality was determined as 3 years after ER in the present study.

Outcome measures

First, we investigated overall survival (OS) and disease-specific survival (DSS), which is an indicator of ESCC-related mortality. Second, the details of patients with ESCC-related or treatment-related mortality were investigated. Finally, we investigated predictors of early and late mortality, separately.

In the third outcome measures, we evaluated 9 candidate indices, the detail of which is shown in Table 1. The values of them were divided into high and low; Eastern Cooperative Oncology Group performance status (ECOG-PS) (< 2, ≥ 2), American Society of Anesthesiologists physical status (ASA-PS) (< 3, ≥ 3), Charlson comorbidity index (CCI) (< 2, ≥ 2), PNI (< 45, ≥ 45), modified GPS (mGPS) (< 1, ≥ 1), CAR, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and psoas muscle mass index (PMI, cm^2/m^2) for evaluating sarcopenia. The cut-offs of the former 5 indices were based on previous reports (Onodera et al. 1984; Toiyama et al. 2011; Zhang et al. 2015; Dolan et al. 2019; Nakajo et al. 2019; Tanoue et al. 2019). Since CAR, NLR, and PLR have no definite cut-offs for predicting OS, the cut-offs of

Table 1. The details of 9 candidate indices, the values of which were divided into high and low in this study.

Indices	High/low	Explanation
Physical activity and comorbidity		
ECOG-PS	≥ 2/< 2	0: Fully active, able to carry on all pre-disease performance without restriction
		1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
		2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
		3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
		4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
		5: Dead
ASA-PS	≥ 3/< 3	1: A normal healthy patient
		2: A patient with mild systemic disease
		3: A patient with severe systemic disease
		4: A patient with sever systemic disease that is a constant threat to life
		5: A moribund patient who is not expected to survive without the operation
		6: A declared brain-dead patient whose organs are being removed for donor purposes
CCI	≥ 2/< 2	The sum of scores assigned for several comorbidities based on the below.
		1 Myocardial infarct, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Connective tissue disease, Ulcer disease, Mild liver disease, Diabetes
		2 Hemiplegia, Moderate or severe renal disease, Diabetes with end organ damage, Any tumor, Leukemia, Lymphoma
		3 Moderate or severe liver disease
		6 Metastatic solid tumor, AIDS
Inflammation-based prognostic scores		
PNI	≥ 45/< 45	10 × Albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3)
mGPS	≥ 1/< 1	0: C-reactive protein ≤ 1.0 mg/dL
		1: C-reactive protein > 1.0 mg/dL and albumin ≥ 3.5 g/dL
		2: C-reactive protein > 1.0 mg/dL and albumin < 3.5 g/dL
CAR	≥ 0.026/< 0.026	C-reactive protein (mg/dL)/ Albumin (g/dL)
NLR	≥ 2.24/< 2.24	Neutrophil count/ Lymphocyte count
PLR	≥ 135.29/< 135.29	Platelet count/ Lymphocyte count
Sarcopenia		
PMI (cm^2/m^2)	≤ 6.36 (men) ≤ 3.92 (women)	Manual tracing using plain CT imaging at L3 level was used for measuring the cross-sectional areas of the right and left psoas muscles. PMI was calculated by normalizing the cross-sectional areas for height (cm^2/m^2).

ECOG-PS, Eastern Cooperative Oncology Group performance status; ASA-PS, American Society of Anesthesiologists physical status; CCI, Charlson comorbidity index; AIDS, acquired immunodeficiency syndrome; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; CAR, C-reactive protein/albumin ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PMI, psoas muscle mass index.

them were determined using receiver-operating characteristic (ROC) curve analysis; the values that maximized the sum of sensitivity and specificity for OS were used as the cut-offs. The sex-specific cut-off values of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women for low skeletal muscle mass were used in PMI (Hamaguchi et al. 2016). To evaluate tumor- and treatment-related factors, the variables of categories A to C and additional treatment were also evaluated. Additionally, age, sex, and smoking and drinking history were evaluated. The cut-off for age was determined as 80 years, due to the very small proportion of patients aged over eighty who received curative surgical resection (Bouvier et al. 2005; Ruol et al. 2007), and 85 years, because these patients are classified as "oldest old" and have a tendency to carry a greater burden of disease and disabilities (Wetle 2008; Ling et al. 2010).

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as the number and proportion. OS and DSS curves were calculated according to the Kaplan-Meier

method. Cox proportional hazard regression analysis was used to estimate the univariate and multivariate-adjusted hazard ratio (HR) and 95% confidence intervals (CIs) of mortality. Variables in which the *P* value was < 0.05 in the univariate analysis were entered into the multivariate model. It is recognized that there was multiple testing of outcome data arising from individual patients. The uncorrected *P* values were presented along with the effect of Holm correction whenever that correction removed statistical significance at the $P < 0.05$ level. For each multivariate model, multicollinearity was examined using the variance inflation factors (VIF): A common rule of thumb is that if the VIF is > 5, the multicollinearity is high (Kim 2019). Missing data were imputed using a multiple imputation by a chained equation approach using the "mice" package in R. We created 200 complete datasets by replacing missing values, and the analysis presented is a pooled summary of the results from the 200 datasets. All analyses were computed using the R version.3.6.1 for Windows software (R Foundation for Statistical Computing, Vienna, Austria) and a two-tailed *P* value of < 0.05 was regarded as statistically significant.

Results

Study population

Among 427 patients who underwent ER for ESCC during the study period, 407 patients were enrolled in this study (Fig. 1). The median (IQR) follow-up duration was 69 (40-103) months. The baseline clinicopathological characteristics of the enrolled patients are shown in Table 2, according to three groups: alive, early mortality, and late mortality. In the ROC curve analyses, the areas under the curves of NLR, PLR, and CAR for OS were 0.499, 0.473, and 0.664 respectively, with the best cut-off nodes of 2.24, 135.29, and 0.026, respectively.

Long-term prognoses

Among 106 patients who died during the follow-up period (Table 3), 6 patients died of ESCC. The 3- and 5-year OSs were 92.0% (95% CI, 89.3-94.7) and 83.4% (95% CI, 79.5-87.5) (Fig. 2A). The 3- and 5-year DSSs were 99.5% (95% CI, 98.7-100) and 98.4% (95% CI, 96.9-99.8) (Fig. 2B).

In patients who died of ESCC (Table 4), two patients belonged to category A; one was due to the metachronous advanced ESCC after ER, but the other died of metastases from the primary ESCC.

Additional treatment

One of 55 patients with category B and 21 of 40 patients with category C underwent additional treatment, comprising three with esophagectomy, four with radiation

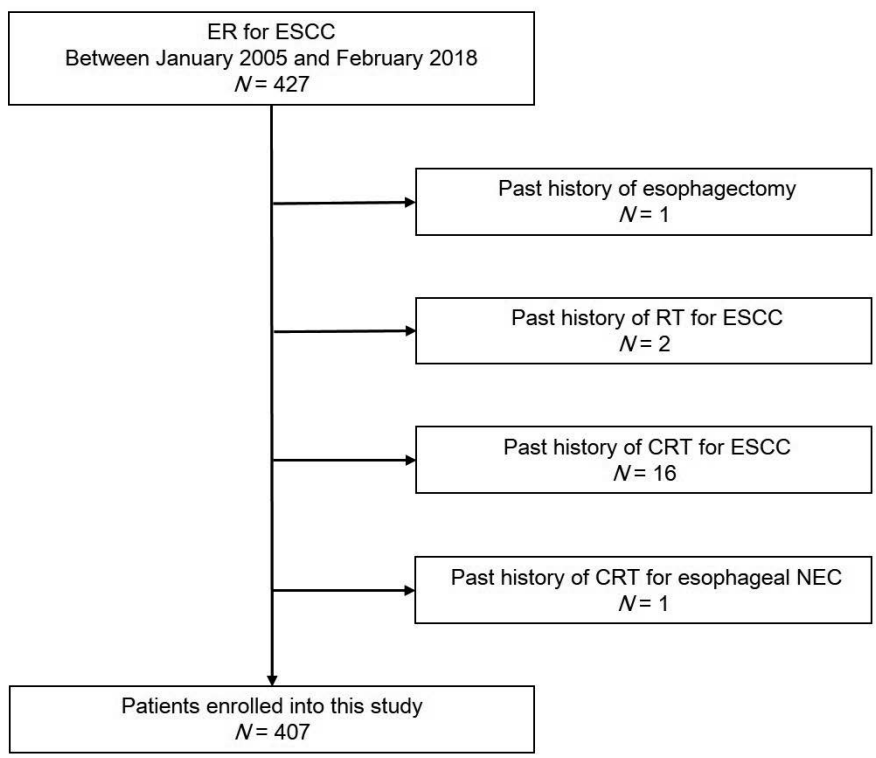

Fig. 1. Flowchart of patient enrollment.
Among 427 patients who underwent ER for ESCC, 20 patients were excluded due to a history of esophagectomy, CRT, or radiation therapy for an esophageal tumor. Finally, 407 were enrolled into this study.
ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; RT, radiation therapy; CRT, chemoradiotherapy; NEC, neuroendocrine carcinoma.

Table 2. Baseline characteristics of the enrolled patients.

		Total (N = 407)	Alive (N = 301)	Early mortality (N = 31)	Late mortality (N = 75)
Age (years), median (IQR)		70 (64-74.5)	69 (63-74)	71 (65-74)	73 (67-77)
	< 80, N (%)	375 (92.1)	282 (93.7)	29 (93.5)	64 (85.3)
	80-84, N (%)	24 (5.9)	15 (5.0)	1 (3.2)	8 (10.7)
	≥ 85, N (%)	8 (2.0)	4 (1.3)	1 (3.2)	3 (4.0)
Follow up month, median (IQR)		69 (40-103)	78 (43-109)	25 (19.5-29)	74 (54-95)
Sex, N (%)	Male	356 (87.5)	252 (83.7)	31 (100.0)	73 (97.3)
	Female	51 (12.5)	49 (16.3)	0 (0.0)	2 (2.7)
Smoking history,	No	97 (23.8)	87 (28.9)	3 (9.7)	7 (9.3)
N (%)¶	Yes	307 (75.4)	213 (69.4)	28 (90.3)	66 (88.0)
Drinking history,	No	61 (15.0)	53 (17.6)	0 (0.0)	8 (10.7)
N (%)¶	Yes	344 (84.5)	247 (82.1)	31 (100.0)	66 (88.0)
CCI, N (%)	< 2	176 (43.2)	147 (48.8)	6 (19.4)	23 (30.7)
	≥ 2	231 (56.8)	154 (51.2)	25 (80.6)	52 (69.3)
ASA-PS, N (%)	< 3	350 (86.0)	268 (89.0)	25 (80.6)	57 (76.0)
	≥ 3	57 (14.0)	33 (11.0)	6 (19.4)	18 (24.0)
ECOG-PS, N (%)	< 2	403 (99.0)	300 (99.7)	29 (93.5)	74 (98.7)
	≥ 2	4 (1.0)	1 (0.3)	2 (6.5)	1 (1.3)
mGPS, N (%)¶	< 1	349 (85.7)	261 (86.7)	26 (83.9)	62 (82.7)
	≥ 1	17 (4.2)	9 (3.0)	3 (9.7)	5 (6.7)
NLR, median (IQR)¶		1.94 (1.48-2.68)	1.93 (1.49-2.64)	2.24 (1.64-2.94)	1.93 (1.40-2.75)
CAR, median (IQR)¶		0.026 (0.023-0.050)	0.025 (0.023-0.039)	0.028 (0.026-0.071)	0.028 (0.025-0.068)
PLR, median (IQR)¶		124.86 (96.78-164.72)	124.63 (100.32-164.12)	135.62 (102.6-173.51)	118.93 (87.73-163.07)
PNI, median (IQR)¶		49.35 (45.63-52.16)	49.66 (46.13-52.77)	47.06 (44.42-50.25)	48.54 (44.35-50.52)
PMI, median (IQR)¶		6.84 (5.76-7.83)	6.89 (5.77-7.79)	6.59 (5.85-8.27)	6.44 (5.61-7.86)
Histopathological category, N (%)					
A		312 (76.7)	238 (79.1)	23 (74.2)	51 (68.0)
B		55 (13.5)	40 (13.3)	3 (9.7)	12 (16.0)
C		40 (9.8)	23 (7.6)	5 (16.1)	12 (16.0)
Additional treatment, N (%)					
No		385 (94.6)	288 (95.7)	28 (90.3)	69 (92.0)
Esophagectomy		3 (0.7)	1 (0.3)	0 (0.0)	2 (2.7)
CRT		15 (3.7)	10 (3.3)	2 (6.5)	3 (4.0)
Radiation therapy		4 (1.0)	2 (0.7)	1 (3.2)	1 (1.3)

IQR, interquartile range; CCI, Charlson comorbidity index; ASA-PS, American Society of Anesthesiologists physical status; ECOG-PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; CAR, C-reactive protein/albumin ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; PMI, psoas muscle mass index; CRT, chemoradiotherapy.

¶There were missing data (3 cases in smoking history, 2 cases in drinking history, 41 cases in mGPS, 1 case in NLR, 43 cases in CAR, 1 case in PLR, 3 cases in PNI, and 50 cases in PMI).

therapy, and 15 with CRT (Fig. 3). Two patients died of CRT-related adverse events (Table 4); among them, one patient received prophylactic CRT (41.4 Gy), which is recognized as lower-dose CRT and less-invasive approach than definitive CRT (50-60 Gy).

Predictors of early mortality after ER for ESCC

Thirty-one patients died within 3 years. In the univariate analysis, high CCI, high ECOG-PS, and high CAR were significantly associated with early mortality after ER for ESCC (Table 5). Other factors, however, including age, were not significantly correlated with early mortality. Multivariate analyses revealed that independent risk factors for early mortality were high ECOG-PS [HR (95% CI) = 7.21 (1.71-30.37), P = 0.007], high CCI [2.97 (1.21-7.28), P = 0.017], and high CAR [2.18 (1.01-4.69), P = 0.047]; however, the P value of < 0.025 should be regarded as significant in the variable of CAR after Holm correction for multiple testing of the outcome data and this correction removed the significance of high CAR (Table 5). Testing for multicollinearity revealed satisfactory values of the VIF (1.00-1.02); thus, this multivariate model was appropriate.

Table 3. Causes of death.

	All	Early mortality	Late mortality
All causes, *N*	106¶	31	75
Malignant disease	52	18	34
Pharyngeal cancer	13	5	8
Lung cancer	12	2	10
Esophageal cancer	6	2	4
Hepatocellular cancer	5	0	5
Oral cancer	4	2	2
Gastric cancer	3	2	1
Pancreatic cancer	2	1	1
Prostate cancer	2	2	0
Other	5	2	3
Non-malignant disease	44	13	31
Cardiovascular disease	9	3	6
Pneumonia	8	0	8
Non-infectious respiratory disease	5	2	3
Old age	4	1	3
Kidney disease	2	0	2
Additional treatment-related	2	2	0
Choking on food	2	2	0
Other accidents	5	1	4
Other	7	0	7
Unknown	10	2	8

¶In 41 cases, cause of death was obtained by telephone interview.

Predictors of late mortality after ER for ESCC

After the exclusion of 31 patients who had died within 3 years and 58 patients whose follow up duration had been within 3 years, a total of 318 patients including 75 patients who died more than 3 years after ER were evaluated for the analysis of late mortality. Univariate analysis showed that predictors of late mortality were age (80-84, ≥ 85 years), male, smoking history, high CCI, high ECOG-PS, high ASA-PS, high CAR, low PNI, low PMI, and category C (Table 6). In the multivariate analyses, age ≥ 85 years [8.38 (2.37-29.64), $P < 0.001$], age of 80-84 years [3.08 (1.32-7.20), $P = 0.010$], high CCI [1.90 (1.11-3.24), $P = 0.019$], high ECOG-PS [15.62 (1.51-161.50), $P = 0.021$], and high CAR [1.99 (1.07-3.69), $P = 0.029$] were independent risk factors for late mortality; however, as with the analysis for early mortality, Holm correction for multiple testing of the outcome data about high CAR removed the significance (Table 6). Smoking history [2.17 (0.93-5.11)] tended to be associated with late mortality, but it did not reach statistical significance ($P = 0.075$). The values of the VIF (1.08-1.52) clarified no multicollinearity, and this multivariate model was appropriate.

Discussion

This study firstly revealed predictors of early and late mortality in patients who underwent ER for ESCC. High ECOG-PS and high CCI were independent risk factors for both early and late mortality, whereas age (80-84, ≥ 85 years) was an independent risk factor only for late mortality.

Several studies have evaluated patient-related factors, such as nutritional status, comorbidity, and physical condi-

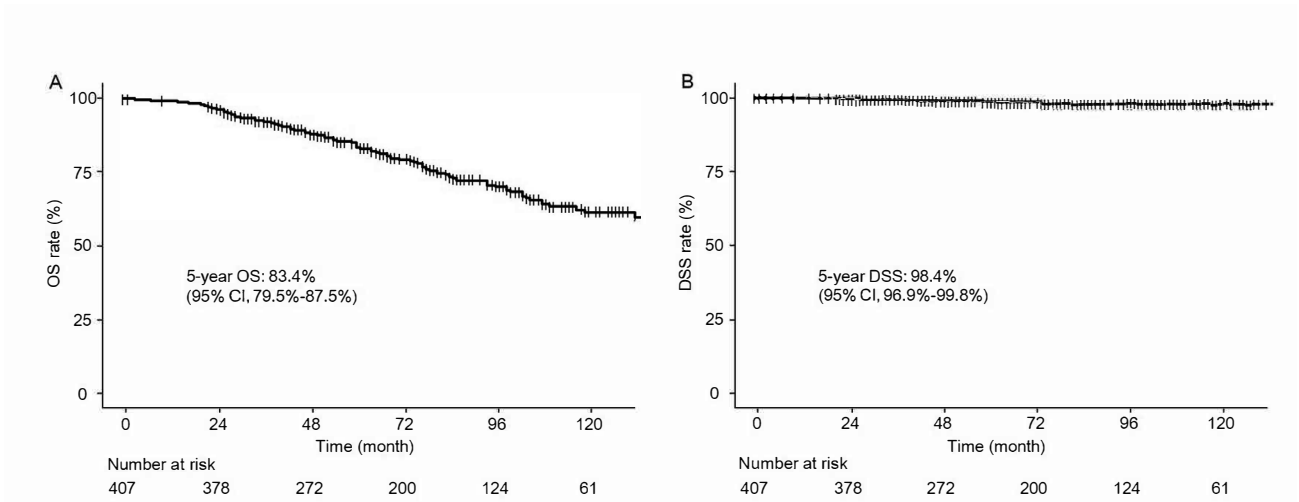

Fig. 2. Prognosis in patients who underwent ER for ESCC.
A. OS
B. DSS
The 5-year OS and DSS, which is an indicator of ESCC-related mortality, in patients who underwent ER for ESCC were 83.4% and 98.4%, respectively, indicating that most mortalities were not caused by ESCC. Number at risk is the number of patients with event-free and uncensored at each time. Censored subjects are indicated on the Kaplan-Meier curves as tick marks.
ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; OS, overall survival; DSS, disease-specific survival; CI, confidence interval.

Table 4. Summary of cases with ESCC-related and treatment-related mortality.

	Case no.	Age/Sex	CCI	ECOG-PS	Histopathological category	Additional treatment	Survival time (month)	Site of recurrence
ESCC-related mortality	1	64/male	0	0	C	CRT (60.0 Gy)	39	Lymph node, Lung
	2	74/male	2	0	C	None¶	27	Lymph node
	3	68/male	3	1	A	None	74	Lymph node, Brain
	4	74/male	2	0	A	None†	59	Esophagus (metachronous)
	5	60/male	0	0	B	None	20	Lymph node
	6	81/male	1	2	C	None	47	Esophagus
								Causes of death
Treatment-related mortality	1	67/male	0	0	C	CRT (60.0 Gy)	31	Radiation pericarditis and pleuritis
	2	67/male	2	0	C	CRT (41.4 Gy)	17	Radiation pneumonitis

ESCC, esophageal squamous cell carcinoma; CCI, Charlson comorbidity index; ECOG-PS, Eastern Cooperative Oncology Group performance status; CRT, chemoradiotherapy.
¶This patient received CRT after the development of metachronous advanced ESCC.
†This patient received chemotherapy after the development of lymph node metastases.

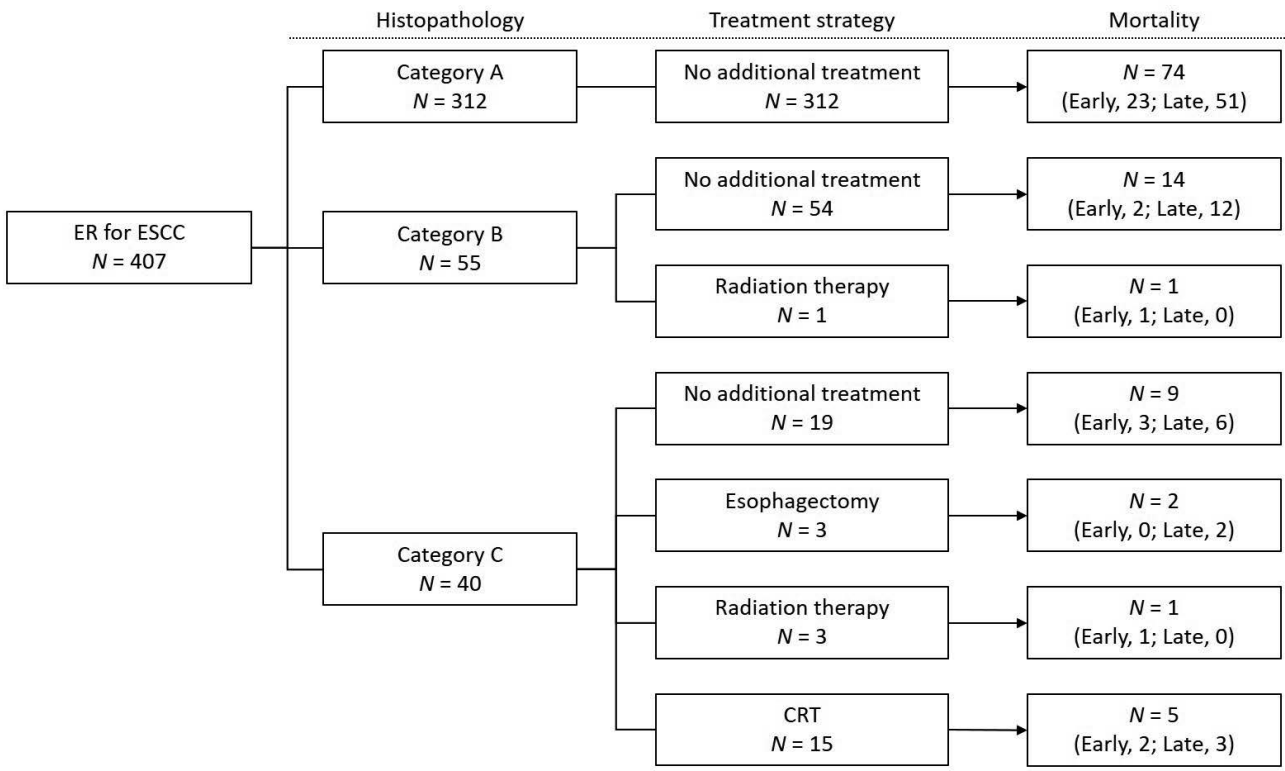

Fig. 3. Summary of additional treatment after ER for ESCC.
Most patients (54/55) with histopathological category B underwent no additional treatment after ER for ESCC. In histopathological category C, over half of patients (21/40) underwent additional treatment; however, esophagectomy was performed only in three cases. Although additional treatment was recommended for those with categories B or C, whether to undergo additional therapy depended on the risk of LNM, patient's condition, age, and patients' preference.
ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; CRT, chemoradiotherapy; LNM, lymph node metastasis.

tion, in attempts to predict the prognosis in patients who underwent ER for early gastric cancer (Sekiguchi et al. 2017; Iwai et al. 2018). By contrast, few studies have evaluated prognostic predictors after ER for ESCC. Although Nakajo et al. (2019) clarified CCI (≥ 2) as being a significant prognostic predictor in elderly patients with ESCC treated by endoscopic submucosal dissection, this study evaluated only ASA-PS and CCI among patient-related prognostic indices. In addition, no study has focused on predictors of early and late mortality in such patients.

Table 5. Predictors of early mortality after ER for ESCC.

Variables		Person-month	No. of mortality	Univariate		Multivariate	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	< 80	12,617	29	1 (Reference)			
	80-84	792	1	0.55 (0.07-4.03)	0.556		
	≥ 85	275	1	1.59 (0.22-11.66)	0.650		
Sex	Female	1,781	0	1 (Reference)			
	Male	11,903	31	–	–		
Smoking history¶	No	3,348	3	1 (Reference)			
	Yes	10,228	28	3.11 (0.95-10.23)	0.062		
Drinking history¶	No	2,132	0	1 (Reference)			
	Yes	11,480	31	–	–		
CCI	< 2	6,015	6	1 (Reference)		1 (Reference)	
	≥ 2	7,669	25	3.31 (1.36-8.08)	0.008	2.97 (1.21-7.28)	0.017
ASA-PS	< 3	11,812	25	1 (Reference)			
	≥ 3	1,872	6	1.53 (0.63-3.73)	0.351		
ECOG-PS	< 2	13,561	29	1 (Reference)		1 (Reference)	
	≥ 2	123	2	8.13 (1.94-34.07)	0.004	7.21 (1.71-30.37)	0.007
mGPS¶	< 1	11,686	26	1 (Reference)			
	≥ 1	543	3	2.37 (0.72-7.82)	0.156		
NLR¶	< 2.24	8,615	16	1 (Reference)			
	≥ 2.24	5,033	15	1.63 (0.81-3.30)	0.174		
CAR¶	< 0.026	6,843	10	1 (Reference)		1 (Reference)	
	≥ 0.026	5,314	19	2.38 (1.11-5.11)	0.026	2.18 (1.01-4.69)	0.047*
PLR¶	< 135.29	8,079	15	1 (Reference)			
	≥ 135.29	5,569	16	1.56 (0.77-3.16)	0.215		
PNI¶	≥ 45	10,698	22	1 (Reference)			
	< 45	2,878	9	1.52 (0.70-3.30)	0.291		
PMI¶	High†	8,391	14	1 (Reference)			
	Low	3,616	10	1.57 (0.72-3.40)	0.254		
Histopathological category	A	10,487	23	1 (Reference)			
	B	1,852	3	0.74 (0.22-2.48)	0.631		
	C	1,345	5	1.70 (0.64-4.46)	0.284		
Additional treatment	No	12,936	28	1 (Reference)			
	Yes	748	3	1.86 (0.56-6.10)	0.309		

ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; ASA-PS, American Society of Anesthesiologists physical status; ECOG-PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; CAR, C-reactive protein/albumin ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; PMI, psoas muscle mass index.

¶There were missing data (3 cases in smoking history, 2 cases in drinking history, 41 cases in mGPS, 1 case in NLR, 43 cases in CAR, 1 case in PLR, 3 cases in PNI and 50 cases in PMI).

†The sex-specific cut-off values of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women for the low skeletal muscle mass were used in PMI.

*Nominal significance for this *P* value in a single Cox regression; however, correction for multiple testing of outcome data removes this significance.

Hence, we investigated multiple patient-related indices to reveal such factors.

The present study has two clinical implications. First, we revealed risk factors for early and late mortality; high ECOG-PS and high CCI for both early and late mortality, and age (80-84, ≥ 85 years) only for late mortality. We confirmed high CCI as a prognostic predictor and, additionally, we found that this factor was associated with both early and late mortality. Furthermore, we firstly clarified that high ECOG-PS had the highest HR for both early and late mortality, which indicates the importance of evaluating ECOG-PS in deciding the treatment strategy after ER for

Table 6. Predictors of late mortality after ER for ESCC.

Variables		Person-month	No. of mortality	Univariate		Multivariate	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	< 80	26,202	64	1 (Reference)		1 (Reference)	
	80-84	1,290	8	3.42 (1.62-7.20)	0.001	3.08 (1.32-7.20)	0.010
	≥ 85	278	3	9.36 (2.84-30.90)	< 0.001	8.38 (2.37-29.64)	< 0.001
Sex	Female	3,848	2	1 (Reference)		1 (Reference)	
	Male	23,922	73	5.61 (1.38-22.87)	0.016	2.11 (0.46-9.79)	0.339
Smoking history¶	No	7,512	7	1 (Reference)		1 (Reference)	
	Yes	20,082	66	3.51 (1.61-7.64)	0.002	2.17 (0.93-5.11)	0.075
Drinking history¶	No	4,776	8	1 (Reference)			
	Yes	22,861	66	1.62 (0.78-3.37)	0.200		
CCI	< 2	13,398	23	1 (Reference)		1 (Reference)	
	≥ 2	14,372	52	2.30 (1.42-3.81)	< 0.001	1.90 (1.11-3.24)	0.019
ASA-PS	< 3	24,249	57	1 (Reference)		1 (Reference)	
	≥ 3	3,521	18	2.38 (1.40-4.06)	0.001	1.58 (0.89-2.81)	0.121
ECOG-PS	< 2	27,683	74	1 (Reference)		1 (Reference)	
	≥ 2	87	1	22.08 (2.81-173.43)	0.003	15.62 (1.51-161.50)	0.021
mGPS¶	< 1	23,120	62	1 (Reference)			
	≥ 1	927	5	1.79 (0.72-4.50)	0.213		
NLR¶	< 2.24	18,407	44	1 (Reference)			
	≥ 2.24	9,277	30	1.47 (0.92-2.33)	0.105		
CAR¶	< 0.026	13,316	21	1 (Reference)		1 (Reference)	
	≥ 0.026	10,604	45	2.74 (1.64-4.59)	< 0.001	1.99 (1.07-3.69)	0.029*
PLR¶	< 135.29	16,620	42	1 (Reference)			
	≥ 135.29	11,064	32	1.14 (0.72-1.81)	0.566		
PNI¶	≥ 45	22,147	48	1 (Reference)		1 (Reference)	
	< 45	5,410	25	2.30 (1.42-3.74)	< 0.001	1.50 (0.84-2.67)	0.168
PMI¶	High†	16,681	34	1 (Reference)		1 (Reference)	
	Low	6,884	25	1.71 (1.02-2.86)	0.043	1.24 (0.71-2.15)	0.453
Histopathological category	A	21,583	51	1 (Reference)		1 (Reference)	
	B	3,416	12	1.57 (0.84-2.95)	0.161	1.73 (0.90-3.34)	0.097
	C	2,771	12	1.90 (1.01-3.57)	0.045	1.22 (0.61-2.47)	0.556
Additional treatment	No	26,328	69	1 (Reference)			
	Yes	1,442	6	1.69 (0.73-3.91)	0.218		

ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; ASA-PS, American Society of Anesthesiologists physical status; ECOG-PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; CAR, C-reactive protein/albumin ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; PMI, psoas muscle mass index.

¶There were missing data (3 cases in smoking history, 2 cases in drinking history, 41 cases in mGPS, 1 case in NLR, 43 cases in CAR, 1 case in PLR, 3 cases in PNI and 50 cases in PMI).

†The sex-specific cut-off values of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women for the low skeletal muscle mass were used in PMI.

*Nominal significance for this *P* value in a single Cox regression; however, correction for multiple testing of outcome data removes this significance.

ESCC. On the other hand, ages of 80-84 years and ≥ 85 years were, unexpectedly, not associated with early mortality; these were related only to late mortality. In Japan, the mean life expectancies in 80-year-old men and women were 9.06 and 11.91 years, respectively, and even in 90-year-old men and women were 4.33 and 5.66 years, respectively (Ministry of Health, Labour and Welfare of Japan (MHLW) 2019), which may be associated with our results. Considering their predictive ability for early mortality, ECOG-PS and/or CCI might be prior to age in deciding treatment strategy after ER for ESCC. In particular, elderly patients, such as age ≥ 85 years, with low ECOG-PS and low CCI might not be regarded as having a short life expectancy in such situation.

In the second clinical implication, additional treatment did not always contribute to longer life expectancy when ESCCs did not meet the curability criteria. A previous study showed that, in patients with category C, 0% (0/32) and 2.4% (1/41) of patients with and without additional treatment, respectively, died of ESCC (Nakajo et al. 2019). In this study, these rates were 4.8% (1/21) and 10.5% (2/19), respectively, but additional treatment was not significantly associated with either early or late mortality. Furthermore, although most patients underwent radiation therapy or CRT as an additional treatment after ER in patients with category C, 11.1% (2/18) of such patients died of radiation-related adverse events. This rate is similar to that in a previous report (10.6%) (Kawaguchi et al. 2015); however, one of these patients in the present study received 41.4 Gy, which was reported to be minimally invasive radiation therapy with no severe adverse events in a previous multicenter study (Minashi et al. 2019). Although a large-scale study is required to reach a definitive conclusion about the benefit and harm of additional treatment, this study suggests that additional treatment after ER for ESCC has a certain risk of adverse event-related and tumor-related mortality.

The present study has two strengths. This study obtained long-term follow-up data; the median follow-up duration was 69 months. In addition, we evaluated simultaneously multiple prognostic predictors, such as nutritional status indices, comorbidity, physical condition, and sarcopenia, in addition to histopathological factors. These strengths would make our study results reliable.

We acknowledge that there are several limitations in this study. First, as the present study is a single-center retrospective cohort study design, selection bias cannot be excluded and some cases had missing data. However, the missing data were imputed using a multiple imputation. Second, the sample size in the present study is not sufficient, leading to lower events per variable in the analysis for late mortality (75/12 = 6.3) than the preferable value (≥ 10) (Peduzzi et al. 1996); thus, a type II error may have occurred. Third, we did not investigate the alcohol flushing response which is the risk for ESCC. Fourth, we did not include patients with other treatment methods, i.e., esophagectomy, CRT, and radiation therapy, for early-stage ESCC as an initial treatment, although histopathology is not obtained in CRT or radiation therapy. Furthermore, there are inevitable selection biases of treatment selection before and after ER. Although it is difficult to overcome the fourth limitation, a well-designed, prospective, multi-institutional cohort study with larger numbers of patients is required to overcome the first and second limitations and for confirming our study results.

In conclusion, high ECOG-PS and high CCI were associated with both early and late mortality after ER for ESCC, while old age was associated with only late mortality. In deciding the treatment strategy after ER for ESCC, ECOG-PS and CCI might be regarded as better indices for a relatively shorter life expectancy than age. Further large-scale multicenter prospective studies are warranted to confirm our findings.

Conflict of Interest

The authors declare no conflict of interest.

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