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ORIGINAL SCIENTIFIC REPORT

Survival Impacts of Impaired Lung Functions and Comorbidities on Elderly Esophageal Cancer Patients

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Abstract

Background Preoperative physiological assessments are crucial for optimizing clinical outcomes, especially those of elderly esophageal cancer (EC) patients who are generally frail and at the high risk of mortality.
Methods Patients who underwent surgery for EC between 2004 and 2018 were retrospectively reviewed. Patients were categorized into elderly (>70 years) or non-elderly (≤70 years) groups. Various physiological parameters including the Charlson Comorbidity Index (CCI), immunonutritional parameters and pulmonary functions were studied. Pulmonary functions included %vital capacity (VC) and forced expiratory volume in one second (FEV1.0) and FEV1.0%. The thresholds were set as the lowest quartile (100% for %VC and 2L for FEV1.0) in this cohort. Multivariate Cox hazards models were applied to determine independent predictors of non-EC-related deaths.
Results In total, 824 patients were included (elderly; n = 306, non-elderly; n = 518). Elderly patients had a significantly lower 5-year OS rate than non-elderly patients (53.3% vs. 57.2%, *P* = 0.03), mainly due to increased risk of death from non-EC related causes. In the elderly group, multivariate Cox hazards analysis identified 3 independent predictors of non-EC-related deaths; high CCI (HR 1.98, *P*=0.006), low %VC (HR 2.01, *P* = 0.004) and low FEV1.0 (HR 1.6, *P*=0.048). Elderly patients without risk factors had a significantly better 5-year OS rate (63.5%) than those with 1 (50.0%) or 2–3 (36.3%) risk factors (*P* <0.01). Deaths due to pulmonary disease rose significantly as the number of risk factors increased (*P*=0.03).
Conclusions The severity of comorbidities and pulmonary function impairments are useful for predicting long-term outcomes, especially non-EC-related deaths, in elderly EC patients.

Abbreviations

EC	Esophageal cancer
CCI	Charlson comorbidity index
VC	Vital capacity
FEV1.0	Forced expiratory volume in one second
PNI	Prognostic nutritional index
GPS	Glasgow prognostic score
CDDP	Cisplatin
5-FU	5-Fluorouracil
dCRT	Definitive chemoradiotherapy
VATS	Video-assisted transthoracic surgery
C-D	Clavien–Dindo
OS	Overall survival
CSS	Cancer-specific survival
HR	Hazard ratios
CI	Confidence intervals

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Introduction

The recent substantial rise in cancer cases among older adults represents a considerable challenge for healthcare systems worldwide [1]. Declining physiological status, the high prevalence of frailty and short life expectancy of older patients complicate cancer management in this population [2]. In particular, the high possibility of mortality attributable to other causes after surgery largely impacts the survival outcomes of elderly patients with upper gastrointestinal malignancies [3, 4].

Clinicians have little evidence on which to base treatment strategies for this age group due to the limited number of clinical investigations conducted to date. Given that the health status and fitness of elderly patients are heterogeneous, chronologic age alone should not be used as the sole criterion for treatment decision-making [5]. Several geriatric assessment tools have thus been proposed by care providers for the elderly [5, 6].

Esophageal cancer (EC) constitutes the sixth leading cause of cancer deaths worldwide, despite the recent advances in diagnosis and multimodal treatments [7, 8]. Esophagectomy is a highly invasive procedure with considerable morbidity [9], and no consensus has yet been established regarding either age or frailty for identifying candidates who would be medically fit to undergo esophagectomy.

The number of elderly patients with EC has been increasing, and approximately 20% of EC patients in Japan are reportedly ≥75 years of age [10, 11]. Previous studies have revealed advanced age to be significantly associated with high short-term mortality and poor long-term survival [12, 13] and have further suggested esophagectomy to provide a small survival benefit for octogenarians [14]. Given that not only chronological age but also physiological status, as reflected by nutritional status and/or the severity of comorbidities, is reportedly associated with survival outcomes in elderly EC patients [3, 13, 15], therapeutic approaches should be tailored to each patient's condition.

Herein, we studied the survival impact of advanced age in patients undergoing surgery for EC. Furthermore, we investigated clinical factors useful for predicting survival outcomes, especially deaths from causes other than the EC itself, in elderly EC patients.

Patients and methods

Patients

From January 2004 to December 2018, a total of 874 consecutive patients with pathologically confirmed EC underwent esophagectomy at the Saitama Cancer Center. Of the total 874 patients, 33 who died due to postoperative complications, 8 undergoing surgery for remnant EC, 3 with a history of total pharyngolaryngectomy and 6 lacking data on preoperative pulmonary functions were excluded from the analysis. The median follow-up period was 80.2 months for the survivors. This retrospective study was approved by the local ethics committee of the Saitama Cancer Center (ID: 1267).

Studied criteria

Demographic data were collected prior to treatment. Comorbidities were categorized according to the Charlson Comorbidity Index (CCI) [16]. Clinical and histological tumor staging was based on the TNM classification (UICC, 8th edition) [17]. As a nutritional parameter, Onodera's prognostic nutritional index (PNI: $10 \times$ albumin $+ 0.005 \times$ total lymphocyte count) was calculated [18]. The Glasgow prognostic score (GPS) was estimated as an inflammatory marker, as previously described [19].

Evaluation of preoperative pulmonary function

Pulmonary functions were measured using spirometry. Vital capacity (VC), as a percent of predicted (%VC), and the forced expiratory volume in one second (FEV1.0)/-forced VC ratio (FEV1.0%) were employed to evaluate ventilatory functions [4, 20]. The cut-off values for %VC and FEV1.0 were set as the lowest quartile (100% for %VC and 2L for FEV1.0) in this cohort.

Treatment strategy

Prior to treatment, the clinical stage was determined by the relevant Multidisciplinary Tumor Board. All patients selected their own treatment modality after consulting with surgeons, medical oncologists and radiologists. Patients were treated according to the Japan Esophageal Society guideline [21]. For patients with T1N1-3 or T2-4a (any N) disease, neoadjuvant chemotherapy followed by surgery was generally performed. As a preoperative treatment, cisplatin (CDDP) plus 5-fluorouracil (5-FU) (CF) therapy was the standard regimen [22], while one consisting of three drugs (CDDP, 5-FU, and docetaxel; DCF therapy) was optional [23]. As chemoradiotherapy (CRT), the CF regimen was added to radiation. For patients clinically diagnosed as having cT4b and/or unresectable lymph node metastasis, definitive CRT (dCRT) was indicated as an initial treatment. dCRT was also administered to those who preferred nonsurgical treatment, regardless of the tumor stage. The patients who failed dCRT were candidates for salvage esophagectomy, if curative resection was considered to be clinically feasible.

Surgical treatment and perioperative management

With the patient under general anesthesia, we placed a single lumen spiral endotracheal tube with a blocker into the right bronchus for one-lung anesthesia to avoid fixing the trachea to the mediastinum. Our standard procedures consisted of subtotal esophagectomy along with en bloc lymph node dissection using a cervico-thoraco-abdominal approach. The operative thoracic approach was by video-assisted thoracoscopic surgery (VATS) or thoracotomy. A gastric conduit was conveyed through the retrosternal or posterior mediastinal route, and esophagogastric anastomosis was usually performed at the neck. The transmediastinal esophagectomy (abdominal-cervical approach) was selected for high-risk patients. Tube duodenostomy was added before abdominal closure to allow early postoperative jejunal feeding. The Clavien–Dindo (C-D) scale was used to grade the severity of all postoperative morbidities [24]. Postoperative surveillance was performed based on the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [21].

Statistical analysis

Categorical variables were expressed in numerical figures and percentages and compared using Fisher's exact test or the χ^2 test, as appropriate. Continuous variables were expressed as the median values (range) and compared using Wilcoxon's rank-sum test (A Mann–Whitney U test). Overall survival (OS) was calculated from the operation date. Cancer-specific survival (CSS) was defined as the period from the date of surgery until death due to EC. Non-EC-related deaths included those from both non-malignant diseases and malignancies other than EC. Survival curves were constructed using the Kaplan–Meier method, and either the log-rank test (for comparisons of 2 groups) or the log-rank test followed by Holm's sequential Bonferroni corrections (for comparisons of $\geq$ 3 groups) was used to determine statistical significance, as appropriate. A multivariate Cox proportional-hazards analysis was performed to identify independent prognostic factors. Clinically meaningful factors with p <0.05 in a Cox proportional hazard model with univariable analysis were regarded as potential risk factors and were further analyzed by applying a multivariable Cox model. Statistical analyses were carried out using JMP 16.0.0 (SAS Institute, Cary, NC, USA).

Results

Survival outcomes according to age

In total, 824 EC patients were included in this study. First, we classified patients into 3 groups according to age (≤70, 71–75 and >75 years of age) and compared the survival outcomes among these 3 groups. OS curves were significantly demarcated according to the age group (*P*=0.02, Fig. 1a); however, the 5-year OS rate of patients 71–75 years of age was essentially equivalent to that of patients ≤70 years of age and also that of patients >75 years of age (57.6% vs. 57.2%, *P*=0.98; 57.6% vs. 48.7%, *P*=0.18). CSS was not significantly demarcated according to age (*P*=0.31, Fig. 1b). In contrast, survival was well-demarcated when death from non-EC-related disease was taken as the event of interest (*P* <0.01, Fig. 1c). Patients >70 years of age had a significantly higher risk of non-EC-related death than those ≤70 years of age (*P*=0.01, Fig. 1c). Overall, advanced age (>70 years) was associated with significantly increased non-EC-related deaths as compared to younger age (≤70 years) in our cohort. We thus subsequently divided our cohort into elderly (>70 years) and non-elderly (≤70 years) EC patients.

Comparison of clinicopathological and demographic characteristics and survival between elderly and non-elderly EC patients

Clinicopathological features according to age are shown in Table 1. Advanced age was significantly associated with poorer pulmonary functions (*P* <0.01), lower PNI (*P* <0.01) and lower rate of pStage III-IV disease (*P*=0.03). OS curves were significantly stratified by age (*P*=0.03, Fig. 2a). Importantly, no significant survival difference was found when the event was EC (*P*=0.19, Fig. 2b), but survival was well-demarcated when death from non-EC-related disease was taken as the event of interest (*P* <0.01, Fig. 2c). Elderly patients had a significantly higher incidence of death due to pulmonary diseases than non-elderly patients (9.5% vs. 3.7%, *P* <0.01, Supplementary Fig. 1).

Predictors of non-EC-related deaths in elderly patients

Univariable analysis and subsequent application of the multivariable Cox proportional hazards model revealed high CCI (≥ 2), low %VC (<100%) and pStage III–IV disease to be independently associated with poor OS

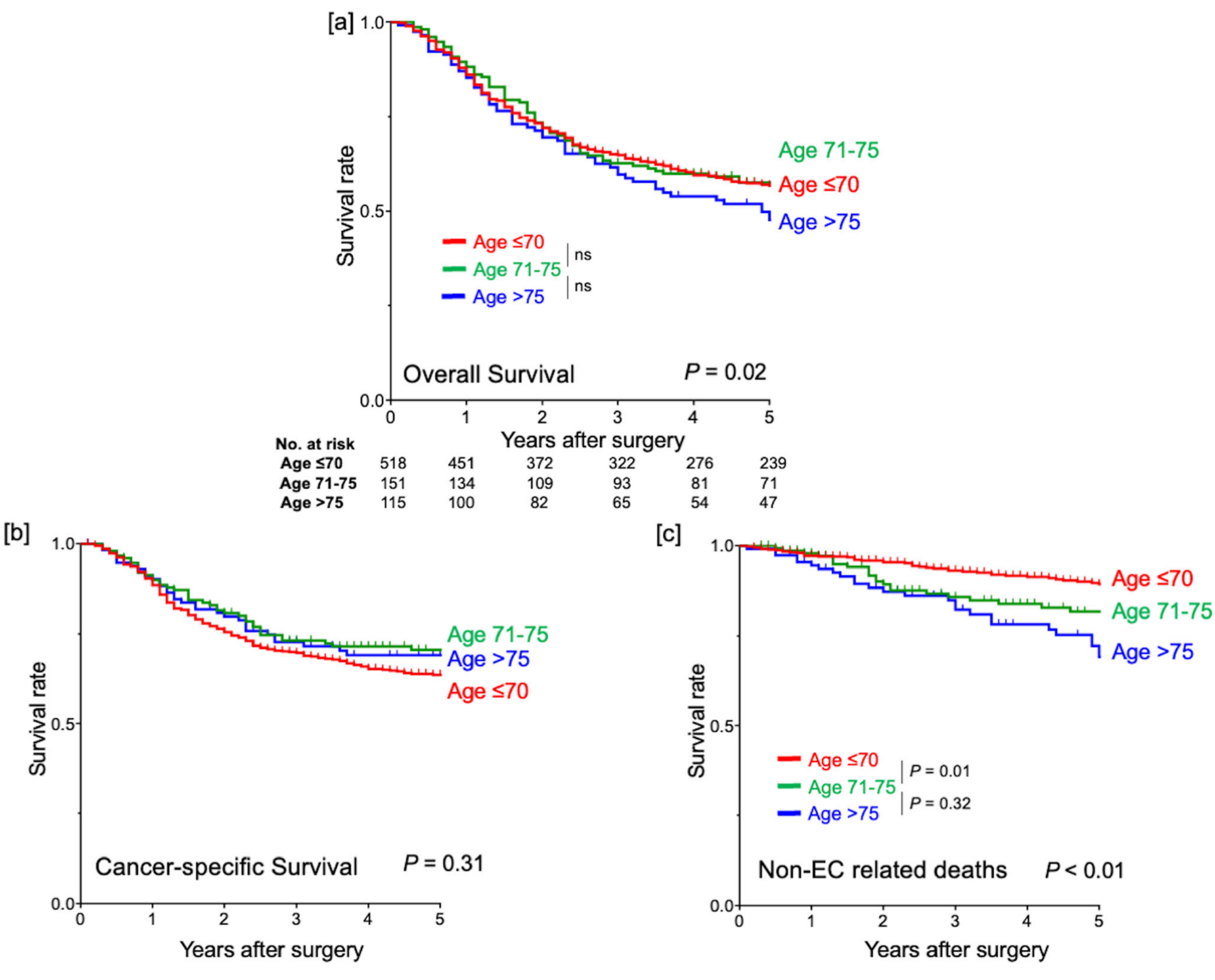

Fig. 1 Survival outcomes according to age. (**a**) Overall survival, (**b**) Cancer-specific survival, and (**c**) Non-EC-related deaths according to age (≤70 vs. 71–75 vs. >75 years of age)

outcomes in the elderly group (Table 2). Notably, multivariate Cox hazards model analysis focusing on non-EC-related deaths showed high CCI (≥2) (HR 1.98, 95% CI 1.22–3.22, *P*=0.006), low %VC (<100%) (HR 2.01, 95% CI 1.24–3.24, *P*=0.004) and low FEV1.0 (<2L) (HR 1.6, 95% CI 1.00–2.57, *P*=0.048) to be independent predictors of non-EC-related deaths (Table 3).

Next, we stratified patients into 3 groups according to the number of the 3 identified variables present (high CCI, low %VC and low FEV1.0; 0, low risk; 1, intermediate risk; 2–3, high risk). Age and the rate of female sex increased as the number of risk factors increased in the elderly group (Table 3). Neither the incidence of postoperative complications nor pStage differed significantly among the 3 groups (Table 4).

Survival outcomes according to the number of factors predicting non-EC-related deaths

Patients without risk factors had a significantly better 5-year OS rate (63.5%) than those with 1 (50.0%) or 2–3 (36.3%) risk factors (*P*<0.01, Fig. 3a). The survival difference among the 3 groups was attributable mainly to non-EC-related deaths (Fig. 3b, c). The incidence of deaths due to pulmonary disease rose significantly as the number of risk factors increased in the elderly group (*P* = 0.03, Supplementary Figure 2).

Table 1 Characteristics of 824 patients according to age

Variables	Age ≤70 (n = 518)	Age >70 (n = 306)	*P* value
Sex, male/female	446 (86.1)/72 (13.9)	257 (84.0)/49 (16.0)	0.41
Comorbidity (CCI ≥ 2)	91 (17.6)	60 (19.6)	0.47
Pulmonary functions			
VC, L Median (range)	3.82 (1.31–6.35)	3.33 (1.28–5.46)	<0.01
%VC, % Median (range)	114.8 (52.2–168.6)	110.4 (56.8–153.1)	<0.01
%VC <100%	99 (19.1)	86 (28.1)	<0.01
FEV1.0, L Median (range)	2.73 (1.03–4.97)	2.23 (0.75–3.67)	<0.01
FEV1.0 <2L	53 (10.2)	99 (32.4)	<0.01
FEV1.0%, % Median (range)	74.3 (36.6–100)	71.3 (39.5–100)	<0.01
BMI, kg/m^2 Median (range)	21.1 (14.1–36.8)	21.5 (13.2–35.6)	0.54
Location, Lt-Ae/Mt/Ut-Ce	202 (39.0)/213 (41.1)/103 (19.9)	133 (43.5)/124 (40.5)/49 (16.0)	0.28
cStage, 0–II/III–IV	237 (45.8)/281 (54.3)	156 (51.0)/150 (49.0)	0.15
dCRT	25 (4.8)	18 (5.9)	0.51
NAC(RT)	271 (52.3)	145 (47.4)	0.17
Preoperative laboratory data			
PNI, Median (range)	42.1 (25.1–54.1)	41.1 (28–50.1)	<0.01
GPS, 0/1–2	454 (87.6)/64 (12.4)	264 (86.3)/42 (13.7)	0.57
MIE	442 (85.3)	258 (84.3)	0.69
Complications (≥ Grade III[†])	180 (34.8)	95 (31.1)	0.27
Tissue type, SCC/AC/Others	459 (88.6)/51 (9.9)/8 (1.5)	278 (90.9)/19 (6.2)/9 (2.9)	0.08
pStage, 0–II/III–IV	253 (48.8)/265 (51.2)	173 (56.5)/133 (43.5)	0.03

CCI Charlson comorbidity index; *VC* vital capacity; *FEV* forced expiratory volume; *BMI* body mass index; *dCRT* definitive chemoradiotherapy; *NAC(RT)* neoadjuvant chemo(radio)therapy; *PNI* prognostic nutritional index; *GPS* Glasgow prognostic score; *MIE* minimally invasive esophagectomy; *SCC* squamous cell carcinoma; *AC* adenocarcinoma; *C-D* Clavien–Dindo

[†]Clavien–Dindo classification

Discussion

This study demonstrated poor survival outcomes of elderly EC patients to be attributable mainly to the high incidence of death from non-EC-related causes in this population. We identified several physiological parameters which were useful for predicting non-EC-related deaths in elderly EC patients, and devised a novel tool applicable to stratifying the survival outcomes of elderly EC patients.

Previous studies have highlighted the relatively poor short- and long-term outcomes of elderly EC patients as compared with their non-elderly counterparts [11, 12, 25]. It is noteworthy that the survival impacts of physiological status, as reflected by frailty, nutritional status, comorbidities and/or BMI outside of normal range, are more evident in elderly than in non-elderly patients [3, 13, 15, 26]. As such, preoperative evaluation of multi-dimensional health status is of major importance for improving the survival outcomes of elderly EC patients [2].

The present study showed the poor survival outcomes of elderly EC patients to be attributable mainly to the high probability of non-cancer-related deaths. Therefore, we performed multivariable Cox hazards analysis focusing on non-EC-related deaths and identified three physiological factors (low %VC, low FEV1.0 and comorbidity) impacting non-EC-related deaths. Only a few studies have focused on non-cancer-related deaths in EC patients [20, 27], although this is a highly relevant issue from a public health perspective [28]. Our newly proposed tool based on physiological status is useful for stratifying long-term outcomes of elderly EC patients, especially predicting the risk of non-cancer mortality.

Lung elasticity and intercostal muscle mass both deteriorate with advancing age, resulting in lung function impairments in the elderly population [29]. Notably, the presence of impaired lung functions is reportedly associated with high general mortality [30], and poor survival outcomes of patients who underwent surgery for upper gastrointestinal malignancies [4, 20]. Furthermore, a recent study highlighted the survival impacts of the difference between lung age and chronological age in EC patients [31]. Our observations, together with those made in previous studies, suggest pulmonary function evaluation to be useful for predicting frailty in elderly patients [4, 20, 32].

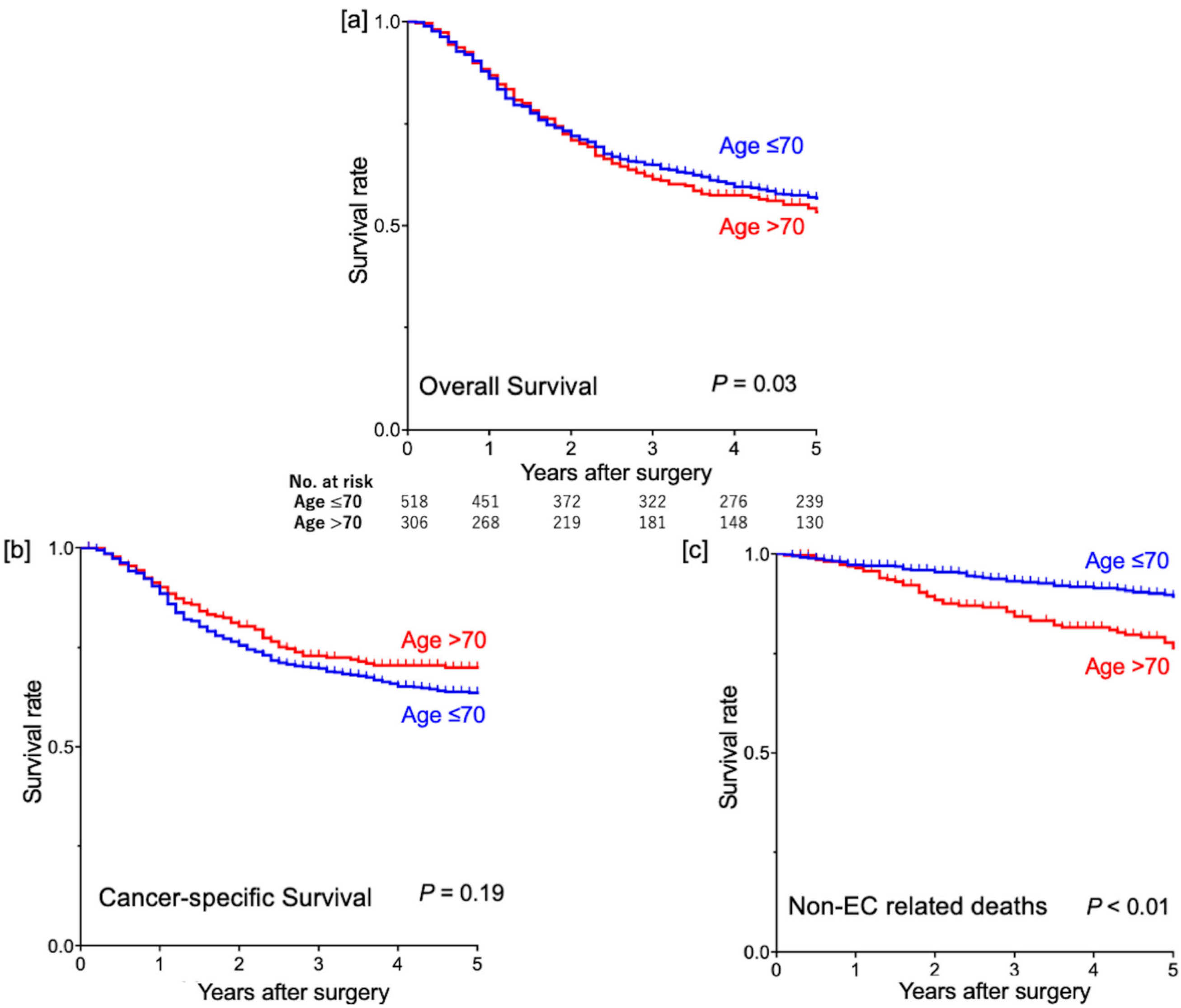

Fig. 2 Comparison of survival outcomes between elderly and non-elderly patients. (**a**) Elderly (>70 years of age) patients had significantly poorer OS than non-elderly patients (P=0.03). (**b**) No significant survival difference was found when the event was EC (P = 0.19), but (**c**) Survival was well-demarcated when death from non-EC-related disease was taken as the event of interest (P <0.01)

The severity of comorbidities is also reportedly associated with survival outcomes and non-cancer mortality of EC patients undergoing surgery [27, 33, 34]. Overall, our observation that elderly patients with both lung function impairments and high CCI have very poor survival outcomes is reasonable.

In our present study, oncological outcomes did not differ significantly between elderly and non-elderly patients. Previous studies have shown less aggressive treatments, such as omission of neoadjuvant chemotherapy or limited lymphadenectomy, to often be applied to the elderly, leading to poor oncological outcomes for these patients [13, 35]. In our present study, however, the NAC administration rates did not differ significantly between the elderly and the non-elderly, possibly accounting for the similar oncological outcomes of these two groups. On the other hand, a recent study suggested the negative survival impact of postoperative complications to be particularly apparent in elderly patients who received triplet chemotherapy [36]. Further investigation is required to determine the optimal treatment intensity for elderly patients. Taken together, these observations highlight why the individual oncological impacts of age remain controversial in ESCC patients.

The incidence of postoperative complications did not rise significantly as the number of risk factors increased. This observation, together with a recent study which showed frailty to not necessarily be associated with

Table 2 Cox hazards model for OS in elderly patients

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age >75	1.33	0.99–1.78	0.06			
Male	1.25	0.83–1.89	0.28			
CCI≥ 2 (vs. 0–1)	1.64	1.1702.31	0.004	1.58	1.11–2.26	0.01
%VC <100%	1.92	1.42–2.59	<0.001	1.41	1.01–1.97	0.045
FEV1.0 <2L	1.63	1.21–2.19	0.001	1.29	0.93–1.79	0.12
FEV1.0% <70%	1.02	0.76–1.37	0.91			
BMI <18	1.88	1.31–2.69	<0.001	1.24	0.85–1.81	0.27
NAC(RT)	0.82	0.61–1.10	0.19			
Renal dysfunction	1.13	0.79–1.61	0.48			
PNI <40	1.42	1.05–1.91	0.02	1.35	0.99–1.84	0.06
Complications (≥ C-D Grade III)	1.09	0.80–1.49	0.56			
pStage						
Stage 0–I	Ref			Ref		
Stage II	1.21	0.77–1.89	0.42	1.07	0.67–1.69	0.79
Stage III–IV	3.04	2.05–4.51	<0.001	2.82	1.89–4.22	<0.001

CCI Charlson comorbidity index; *VC* vital capacity; *FEV* forced expiratory volume; *BMI* body mass index; *NAC(RT)* neoadjuvant chemo(radio)therapy; *PNI* prognostic nutritional index; *MIE* minimally invasive esophagectomy; *C-D* Clavien–Dindo

Table 3 Cox hazards model for non-EC-related death in elderly patients

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age >75	1.59	1.05–2.42	0.03	1.28	0.81–2.00	0.28
Male	0.98	0.58–1.67	0.95			
CCI ≥ 2 (vs. 0–1)	2.34	1.49–3.69	<0.001	1.98	1.22–3.22	0.006
%VC <100%	2.54	1.67–3.85	<0.001	2.01	1.24–3.24	0.004
FEV1.0 <2L	2.32	1.54–3.51	<0.001	1.6	1.00–2.57	0.048
FEV1.0% <70%	1.03	0.68–1.57	0.87			
BMI <18	1.76	1.03–2.99	0.04	0.96	0.52–1.75	0.89
NAC(RT)	0.72	0.47–1.10	0.13			
Renal dysfunction	0.89	0.52–1.54	0.68			
PNI <40	1.48	0.97–2.24	0.06	1.36	0.87–2.13	0.17
Complications (≥ C-D Grade III)	1.27	0.83–1.95	0.28			
pStage						
Stage 0–I	Ref					
Stage II	1.08	0.65–1.79	0.76			
Stage III–IV	1.12	0.67–1.88	0.67			

CCI Charlson comorbidity index; *VC* vital capacity; *FEV* forced expiratory volume; *BMI* body mass index; *NAC(RT)* neoadjuvant chemo(radio)therapy; *PNI* prognostic nutritional index; *MIE* minimally invasive esophagectomy; *C-D* Clavien–Dindo

morbidity [26], suggests esophagectomy to potentially be feasible even for frail patients. However, the survival benefit of esophagectomy remains controversial in elderly patients with EC [14], especially those with significant comorbidities [37]. While less invasive treatment strategies, such as endoscopic resection or chemoradiotherapy, are reportedly indicated for frail elderly patients [38, 39], the benefit of CRT remains controversial, especially for

Table 4 Characteristics of 306 elderly patients according to number of risk factors

Variables	No risk factors (n = 147)	1 risk factor (n = 88)	2–3 risk factors (n = 71)	*P* value
Age, y Median (range)	73 (70–88)	74 (70–82)	75 (70–87)	0.006
Sex				
Male	135 (91.8)	68 (77.3)	54 (76.1)	0.001
vFemale	12 (8.2)	20 (22.7)	17 (23.9)	
Location				
Ut-Ce	23 (15.6)	12 (13.6)	14 (19.7)	0.84
Mt	62 (42.2)	35 (39.8)	27 (38.0)	
Lt-Ae	62 (42.2)	41 (46.6)	30 (42.3)	
cStage				
0–I	41 (27.9)	28 (31.8)	16 (22.5)	0.55
II	35 (23.8)	16 (18.2)	20 (28.2)	
III–IV	71 (48.3)	44 (50.0)	35 (49.3)	
NAC(RT)	82 (55.8)	40 (45.5)	23 (32.4)	0.004
Complications (≥ Grade III†)	40 (27.2)	28 (31.8)	27 (38.0)	0.27
pStage				
0–I	43 (29.3)	24 (27.3)	14 (19.7)	0.56
II	43 (29.3)	28 (31.8)	21 (29.6)	
III–IV	61 (41.4)	36 (40.9)	36 (50.7)	

NAC(RT) neoadjuvant chemo(radio)therapy

†Clavien–Dindo classification

super-elderly patients with EC [40]. In general, surgical indications should not be determined based solely on chronological age [14], although optimal selection criteria have yet to be established [10]. Whether our newly proposed survival prediction model is useful for determining surgical indications merits further study.

Our model might help clinicians optimize perioperative managements for patients with impaired physiological functions. Pharmacological interventions are reportedly useful for improving the survival of patients with pulmonary diseases [41]. High-risk patients might be good candidates for long-term rehabilitation programs. Notably, recent randomized trails revealed a supervised exercise program and a health education informatics program to improve both cardiorespiratory fitness and quality of life for EC patients after esophagectomy [42, 43]. The combination of pre-habilitation and pre-nutrition therapy reportedly improves perioperative functional capacity, thereby reducing the incidence of postoperative complications [44].

Pulmonary morbidity after esophagectomy can be avoided by perioperative management strategies such as pre-operative smoking cessation, respiratory rehabilitation, maintaining oral hygiene, perioperative nutritional interventions and applying less invasive surgery [45]. In our institution, all patients start a rehabilitation program and visit a dentist at the outpatient clinic. Furthermore, MIE was generally performed (85%) during the study period, and enteral nutrition was given via the jejunostomy postoperatively. In addition to these managements, further surgical approaches can be modified in frail patients. Transmediastinal esophagectomy can avoid one-lung ventilation and can be performed on frail people, such as the elderly or patients with pulmonary comorbidities [46]. Also, robot-assisted minimally invasive esophagectomy can reportedly improve postoperative outcomes [47].

Our study has limitations. First, we did not include patients who underwent dCRT, which is reportedly a less-invasive and efficacious treatment option for elderly EC patients [39]. Accordingly, our cohort included only patients deemed fit for an esophagectomy. Although the proportion of ESCC patients who received dCRT did not differ according to the age category in our study (data not shown), selection bias might influence the results. Second, the definition of elderly differs among investigations. We defined advanced age as >70 years considering that patients older than 70 had significantly poorer survival outcomes. Several prior investigations have employed the same age threshold [13, 15, 25], while others used different cut-off values [12, 35]. A recent study suggested that rather than >70 years, >75 years would be the most useful age cut-off value for indicating poor survival [12]. Differences

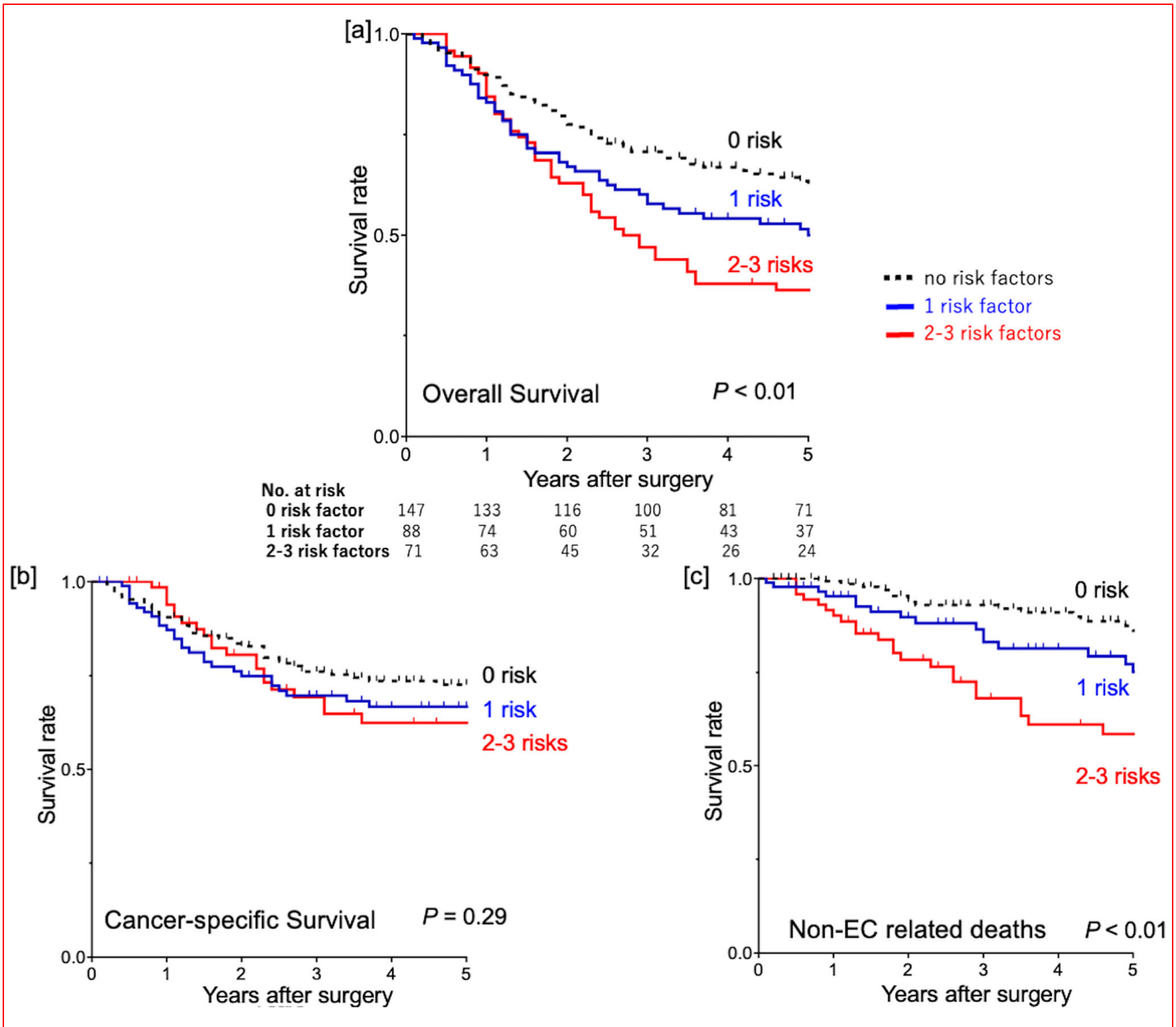

Fig. 3 Survival outcomes according to the number of risk factors. (**a**) Patients without risk factors had a significantly better 5-year OS rate (63.5%) than those with 1 (50.0%) or 2–3 (36.3%) risk factors (P <0.01). (**b**) Cancer-specific survival and (**c**) non-EC-related deaths according to the number of risk factors

in standard care regimens during the study period, the NAC administration rate and tumor histology might have influenced the survival impacts of aging. The optimal age cut-off in EC patients merits further research. Third, the thresholds for %VC and FEV1.0 were set as the lowest quartile (100% for %VC and 2L for FEV1.0) in our cohort. In general, pulmonary dysfunction is defined as %VC <80% or FEV1.0%<70%. In our cohort, the proportion of patients with %VC <80% was very small (3.3%), a finding consistent with prior studies [48], because thoracic surgery is not feasible for patients with extremely poor pulmonary functions. Finally, this was a single-institution study with a relatively small number of patients. Further studies with larger cohorts are needed to achieve more convincing results.

In conclusion, elderly EC patients are at high risk of death from non-EC-related causes, which worsens the overall survival outcomes of this population. A survival prediction model based on physiological status is useful for stratifying the survival outcomes of elderly EC patients, thus aiding clinicians in optimizing treatment strategies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00268-023-07195-y.

Author contributions The contributions of the authors to this study are as follows: K.S. and T.F. are the authors mainly responsible for the study's conception and design, acquisition of data, and analysis and interpretation of data. H.H., T.Y. and D.O. contributed mainly to the drafting of the article and to revising it critically for important intellectual content. All authors have no conflicts of interest or financial ties to disclose.

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Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical approval All procedures were 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 Informed consent was obtained from all individual participants in the form of opt-out on the website. Those who rejected participation were excluded.

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