BMC Anesthesiology

RESEARCH

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Impact of the enhanced recovery after surgery (ERAS) protocol on 3-year survival and outcomes following esophagectomy: a retrospective cohort study of 124 patients

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Abstract

Introduction The benefits of the enhanced recovery after surgery (ERAS) protocol across surgeries are well documented, but its impact on esophageal cancer surgery remains understudied. This study compared the 3-year survival rates of esophagectomy patients treated with and without ERAS at a tertiary care hospital.

Methods A retrospective analysis of 124 elective esophagectomy patients (Jan 2017–Jan 2022) was conducted. Patients with distant metastasis or had concurrent hypopharynx cancer that needed pharyngectomy were excluded from analysis. Patients treated before April 2019 received standard care, while those treated from April 2019 followed the ERAS protocol. Multivariate Cox regression analysis identified potential prognostic factors for overall survival. Survival associations were determined using the Kaplan–Meier(K-M) method and log-rank tests. The primary outcome was 3-year overall survival, and the secondary outcomes were postoperative intensive care unit (ICU) stay, hospital length of stay (LOS), and complications.

Results We analyzed 58 patients in the control group and 66 patients in the ERAS group. The ERAS group demonstrated significantly lower 3-year overall mortality compared to the control group in multivariate Cox regression (adjusted hazard ratio: 0.44, 95% CI: 0.22–0.88, $p=0.020$). Advanced pathologic cancer stage and neoadjuvant chemoradiation therapy (CCRT) were independent negative prognostic factors (adjusted hazard ratio for advanced pathological stage: 2.91, 95% CI: 1.27–6.66, $p=0.011$; for neoadjuvant CCRT: 2.73, 95% CI: 1.23–6.08, $p=0.013$). Kaplan-Meier survival analysis showed a significantly higher 3-year survival rate in the ERAS group compared to the control group (70.2% vs. 47.4%, $p=0.043$). Subgroup analysis revealed significant survival benefits of ERAS in patients with preoperative albumin concentration < 4 g/dl, advanced pathological stage and aged < 65 years. Additionally, the ERAS group had significantly shorter ICU stays (mean difference: -2.3 days, $p<0.001$), shorter hospital LOSs (mean difference: -4.9 days, $p<0.001$), while postoperative complication rates were comparable between two groups.

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Conclusions The ERAS protocol in esophagectomy patients was associated with shorter ICU and hospital stays and emerged as an independent positive prognostic factor for 3-year overall survival. These results suggest ERAS might indirectly improve long-term survival by accelerating recovery, thereby enabling patients to better tolerate and complete essential postoperative oncological treatments. Nevertheless, larger prospective studies are required to validate this interpretation conclusively.

Keywords Enhanced recovery after surgery (ERAS), Esophagectomy, 3-year overall survival, Postoperative outcomes

Introduction

Esophagectomy, a complex surgical intervention for esophageal cancer, involves extensive tissue dissection and detailed anatomical reconstruction. This procedure is particularly challenging due to the high incidence of dysphagia and malnutrition in patients, compounded by significant comorbidities associated with the advanced stages of cancer. Compared to other major oncological surgeries, esophagectomy is fraught with a higher rate of perioperative complications and a generally less favorable prognosis [1, 2]. These concerns prompted the development of an international consensus in 2015 [3] and subsequent 2019 guidelines from the Enhanced Recovery After Surgery (ERAS) Society aimed at standardizing care to improve postoperative outcomes [4].

The ERAS protocol represents a multidisciplinary approach for preparing patients for cancer surgeries. It focuses on minimizing surgical tissue trauma and the resultant inflammatory responses. Key components include maintaining an appropriate depth of anesthesia to avoid heavy sedation, employing opioid-sparing multimodal analgesia (MMA), and promoting early enteral feeding along with rapid postoperative mobilization [5, 6]. Although the adoption of ERAS has been shown to reduce postoperative complications and decrease hospital stays in esophagectomy patients [7, 8], its correlation with long-term survival rates, particularly in esophageal cancer surgeries, has been less extensively documented.

This study analyzed ERAS protocol implementation and its 3-year survival outcomes in esophageal cancer patients post-esophagectomy. The focus was on long-term benefits at a high-volume tertiary care center, contributing insights into the sustained advantages of ERAS protocols in oncological surgery, beyond immediate postoperative and short-term survival seen in other cancers [9, 10, 11].

Methods

This retrospective cohort study was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital, and the requirement for informed consent was waived on 7 March 2023 (IRB CE23066C). Items were reported following the STROBE checklist (Supplement File 1).

Surgical approach and patient selection

All esophageal cancer patients who underwent elective esophagectomy and reconstruction at our institution between January 2017 and January 2022 were initially included. To ensure consistency in surgical expertise, only patients operated on by the same surgical team throughout the study period were included. Patients with concurrent hypopharyngeal cancer requiring extrapharyngectomy with jejunal free flap reconstruction were excluded.

Additionally, patients who underwent esophagectomy using an open thoracotomy and laparotomy approach were excluded to minimize confounding, as minimally invasive surgical techniques are a core component of the ERAS protocol and are associated with improved perioperative outcomes. Patients with distant metastasis (postoperative stage IVB) were also excluded to focus the analysis on resectable disease with curative intent, given their inherently poorer prognosis.

Perioperative and postoperative chemotherapy and radiotherapy protocols were consistent and standardized according to institutional guidelines throughout the entire study period for both ERAS and control groups.

ERAS protocol

The ERAS protocol for esophageal cancer surgery was introduced in April 2019. Patients who underwent minimally invasive esophagectomy prior to this date were categorized as the control group. The ERAS protocol in our institute aligns with the guidelines [4] for perioperative care in esophagectomy established by the ERAS® Society. It is a multidisciplinary care model with a structured framework that includes the following phases:

Preadmission phase Patients in the ERAS group were evaluated at diagnosis to determine whether they were malnourished or frail according to the European Society for Clinical Nutrition and Metabolism (ESPEN) criteria and the Clinical Frailty Scale. Those who were classified as being at high risk of malnutrition or frailty received preoperative nutritional intervention in conjunction with exercise and respiratory rehabilitation to optimize their physical condition for their upcoming neoadjuvant chemotherapy and extensive surgery.

Preoperative phase A reduction in mechanical bowel preparation; the avoidance of prolonged fasting, carbohydrate drink consumption until 2 h prior to esophagectomy; and preemptive analgesia with oral nonsteroidal anti-inflammatory drugs (NSAIDs) were applied for patients.

Intraoperative phase The surgical team utilized a minimally invasive McKeown procedure (thoracoscopic esophageal mobilization, laparoscopic stomach reconstruction, and cervical anastomosis), while the anesthesia team focused on MMA (1) thoracic epidural, (2) dexmedetomidine infusion for analgesia, propofol sparing and anti-inflammatory purposes, (3) regular postoperative acetaminophen administration and nonsteroidal anti-inflammatory drugs (NSAIDs) on an individualized basis), an optimal goal-directed fluid strategy to avoid positive balance, propofol-based total intravenous anesthetic (TIVA) administration for the maintenance of anesthesia under bispectral index (BIS) monitoring, a protective lung ventilation strategy, and the administration of an appropriate dose of intermediate-acting neuromuscular blockers to facilitate immediate extubation after surgery.

Postoperative phase All patients were extubated immediately following surgery and subsequently transferred to the ICU for vigilant monitoring of hemodynamic parameters. Once the patient was deemed stable both hemodynamically and surgically (e.g., SpO2 > 95% at room air, MAP > 65 mmHg, drainage volume less than 300 ml per day), the patient was promptly transferred to the general ward. Elements of the ERAS protocol, such as opioid-sparing analgesia, early enteral feeding, and early mobilization, were implemented. Further details are listed in Supplement File 2.

Audit and compliance In accordance with the consensus checklist published by the TAIWAN CHAPTER ERAS® Society, compliance with ERAS elements was meticulously audited and calculated. The esophagectomy procedure is segmented into four distinct phases: pre-admission (comprising 7 elements), preoperative (7 elements), intraoperative (11 elements), and postoperative (6 elements). The established objective is to achieve an average compliance rate of at least 70% for each phase, as well as for overall adherence.

Patient management before implementation of the ERAS protocol

Patients who underwent esophagectomy and reconstruction before April 2019 at our institution received conventional care. The main differences were as follows: patients who did not receive preoperative rehabilitation or the optimization protocol fasted for up to 8 h without carbohydrate loading before the operation. In terms of perioperative analgesia, the anesthesia department has applied mid-thoracic epidural analgesia as the sole regional analgesia for decades, with intraoperative short-acting opioids (mostly fentanyl) used for analgesia. There was no routine preemptive analgesia, and no routine intravenous dexmedetomidine was used as part of the multimodal analgesia protocol. Arterial line monitoring was performed during surgery but without goal-directed fluid therapy. The maintenance intravenous fluid rate was 6–8 ml/kg/hr with crystalloid solution. At the end of surgery, patients who were transferred to the intensive care unit remained intubated with mechanical ventilation support, and the weaning protocol from the ventilator was initiated at POD 1. Postoperative early mobilization and enteral feeding were embraced but not thoroughly by the medical team at that time, causing some form of variety within postoperative care. A detailed comparison of patient management before and after ERAS protocol implementation is provided in Supplement File 2.

Data collection

Data regarding patient demographics, surgical approach, intraoperative variables, intensive care unit (ICU) stay, hospital length of stay (LOS), complications were gathered through the electronic medical records system of Taichung Veterans General Hospital. Three-year overall survival data was extracted from the National Health Taiwan's National Health Insurance Research Database (NHIRD).

Outcome measurement

The primary objective of this study was to compare the 3-year overall survival rate following esophagectomy between the ERAS and control groups. Factors that differed between the two groups, as well as other potential confounding factors affecting survival, were included and adjusted for in the multivariate analysis. In addition, Kaplan-Meier survival analysis with log-rank testing was performed to evaluate survival differences, and subgroup analyses were conducted based on variables such as preoperative albumin levels, pathological cancer stage (pTNM), age, neoadjuvant chemoradiation therapy (CCRT) and initiation of adjuvant CCRT to determine whether the implementation of the ERAS protocol provided survival benefits in specific patient subgroups.

Secondary outcomes included intensive care unit (ICU) length of stay (LOS), total hospital LOS, and postoperative complications. Postoperative complications were identified through a review of medical records and classified according to the European Perioperative Clinical Outcomes (EPCO) definitions. The severity of complications was graded using the Clavien-Dindo classification.

Statistical analyses

Statistical analysis was performed using SPSS statistical software (IBM® SPSS Statistics 26.0). Categorical variables were compared using Pearson's chi-square test, while Fisher's exact test was used when the frequency was expected to be low. Normally distributed continuous variables were compared using Student's t test and are presented as the mean (standard deviation). Non-normally distributed variables were compared with the Mann–Whitney test and are presented as medians (Q1–Q3).

To identify factors potentially influencing overall survival, we used univariate and multivariate Cox proportional hazards regression models. Confounding factors with a p-value less than 0.05 in the univariate analysis were included in the multivariate Cox regression, which was conducted using the Enter method. The Kaplan–Meier method was used to compare the 3-year survival rate between patients in the ERAS group and patients in the control group.

Furthermore, a subgroup analysis was conducted to explore variations in survival across distinct patient categories. Subgroups were identified based on significant multivariate regression findings or relevant cofactors affecting survival differences. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and compliance with ERAS

A total of 124 patients were included and analyzed in this study, with 66 patients receiving the ERAS protocol and the other 58 patients managed with standard care as the control group. A total of 113 of our patients had squamous cell esophageal carcinoma, and most of these patients had advanced cancer according to the 8th edition AJCC/UICC clinical staging (cTNM) (stage I (7.9%), stage II (20.4%), stage III (65.5%), and stage IVA (5.5%)). The remaining 11 patients were diagnosed with adenocarcinoma or other types: 3 had stage IIB disease (27.3%), and the other 3 had stage III disease (27.3%). The detailed tumor stage distribution can be found in Supplement File 3.

Nearly 70% of our patient cohort received preoperative neoadjuvant CCRT before the operation. Pathologic staging after surgery demonstrated a tumor downstaging effect from preoperative therapy, resulting in more than half of the patients having pathologic stage I esophageal cancer immediately after surgery. One third of patients in our cohort initiated adjuvant CCRT. Among them, the ERAS group had significant higher adjuvant CCRT completion rate than the control group (ERAS vs. control, 100% vs. 63.2%, $p = 0.003$). Detailed reasons for incompletion are listed in Supplement File 4.

Comparative analysis between the two groups revealed no statistically significant differences in variables such as body mass index (BMI), percentage of patients with diabetes mellitus, preoperative estimated glomerular filtration rate (eGFR), preoperative clinical stage, or postoperative pathological stage. However, patients in the ERAS group were older (ERAS vs. control, 59.5 ± 8.6 vs. 56.4 ± 8.5, $p = 0.044$), had a greater percentage of hypertension (34.9% vs. 17.2%, $p = 0.028$) and had a higher preoperative serum albumin level (4.1 ± 0.4 vs. 3.9 ± 0.4 g/dL, $p = 0.010$) than did those in the control group. Detailed demographic characteristics of the patients in both groups are listed in Table 1. In terms of fidelity to the ERAS protocol, the cumulative compliance rate was 80.8%, distributed across the different phases as follows: 75% preadmission, 88% preoperative, 89% intraoperative, and 71% postoperative.

Intraoperative variables

The anesthesia duration and consumption of ephedrine and norepinephrine were not significantly different. However, the ERAS group received significantly less crystalloid and colloid fluids than did the control group (ERAS vs. control, 2802.5 (2467–3280) ml vs. 3725 (3000–4350) ml, $p < 0.001$ and 500 (500–500) ml vs. 1000 (500–1000), $p = 0.001$, respectively). Additionally, the ERAS group had less blood loss (0 (0-100) ml vs. 130 (0-200) ml, $p = 0.002$) and less urine output (700 (500–900) ml vs. 1200 (700–1600) ml, $p < 0.001$) than the control group (Table 2).

Postoperative variables

Postoperatively, the ERAS group had a significantly shorter ICU LOS (2 (2–3) days vs. 5 (4–6) days, $p < 0.001$) and shorter hospital LOS (8 (7–9) days vs. 10 (8–12) days, $p < 0.001$) than did the control group (Table 3). No significant differences were observed in the overall incidence of complications. Most of the complications were mild according to the Clavien–Dindo classification (grades I and II), but the control group had a slightly greater percentage of complications categorized as major according to the Clavien–Dindo classification, without reaching statistical significance. We also compared the incidence of postoperative pulmonary complications (PPCs), which are composite outcomes including pneumonia, pulmonary edema, and respiratory failure. Patients in the ERAS group had significantly fewer PPCs than did those in the control group (ERAS vs. control, 0% vs. 8.6%, $p = 0.015$). The incidence of pneumonia was lower in the ERAS group than in the control group (ERAS vs. control 0% vs. 8.6%, $p = 0.015$). The incidences of the remaining postoperative complications were comparable between the two groups.

Table 1 Demographics of the ERAS group and control group

	ERAS($n=66$)		Control($n=58$)		*p* value
Age	59.5	±8.6	56.4	±8.5	0.044
Sex					
Male	60	(90.9%)	53	(91.1%)	0.927
Female	6	(9.1%)	5	(8.2%)	
BMI, kg/cm^2	26.9	±26.4	22.2	±2.7	0.180
Neoadjuvant CCRT	48	(72.7%)	37	(63.8%)	0.287
Adjuvant CCRT					
Initiated	22	(33.3%)	19	(32.8%)	0.946
Completed [†]	22	(100%)	12	(63.2%)	0.002
Preoperative PEG	39	(59.0%)	27	(46.6%)	0.164
Hypertension	23	(34.9%)	10	(17.2%)	0.028
Diabetes Mellitus	6	(9.1%)	9	(15.5%)	0.275
Serum Albumin, g/dl	4.1	±0.4	3.9	±0.4	0.010
eGFR, ml/min/1.73m^2	86.7	±21.9	92.8	±25.6	0.158
Tumor Type					0.882
Squamous Cell Carcinoma	60	(90.9%)	53	(91.4%)	
Adenocarcinoma	4	(6.1%)	4	(6.9%)	
Other	2	(3%)	1	(1.7%)	
Operation Approach					0.004
Minimal Invasive [a]	66	(100%)	51	(87.9%)	
Hybrid [b]	0	(0%)	7	(12.1%)	
Preoperative clinical Stage(cTNM)					0.943
Carcinoma In Situ	1	(1.5%)	1	(1.7%)	
Stage I	5	(7.7%)	6	(10.3%)	
Stage II	16	(24.6%)	11	(19.0%)	
Stage III	39	(60%)	36	(62.1%)	
Stage IV	4	(6.2%)	3	(5.2%)	
Postoperative pathologic Stage(pTNM)					0.628
Carcinoma In Situ	2	(3.0%)	1	(1.7%)	
Stage I	33	(50.0%)	34	(58.6%)	
Stage II	12	(18.2%)	8	(13.8%)	
Stage III	17	(25.8%)	11	(19.0%)	
Stage IV	2	(3.0%)	4	(6.9%)	

[†] Percentage calculated from those who initiated adjuvant CCRT. Reasons for incompletion of CCRT are detailed in Supplement File 4. Continuous variables were compared with Student's t test and are presented as the mean ± SD. Categorical variables were compared with the chi-square test and are presented as the number (%). BMI, body mass index; CCRT, chemoradiation therapy; eGFR, estimated glomerular filtration rate; clinical stage, 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction; a: thoracoscopic + laparoscopic, b: thoracoscopic + converted to mini-laparotomy due to previous abdominal surgery

Table 2 Intraoperative variables of the ERAS group and control group

	ERAS($n=66$)		Control($n=58$)		*p* value
Total Anesthesia time (hr)	9.04	(8.50–9.58)	8.79	(8.25–9.58)	0.171
Ephedrine (mg)	10	(10–20)	15	(9.3–20.0)	0.757
Norepinephrine (mcg)	49	(15.75-136.94)	55	(20-271.6)	0.685
Crystalloid (ml)	2802.5	(2467–3280)	3725	(3000–4350)	< 0.001
Colloid (ml)	500	(500–500)	1000	(500–1000)	0.001
Blood Loss (ml)	0	(0-100)	130	(0-200)	0.002
Urine Output(ml)	700	(500–900)	1200	(700–1600)	< 0.001

Continuous variables were compared with the Mann–Whitney test and are presented as the median (IQR). Ephedrine, intraoperative amount in mg; norepinephrine, intraoperative amount in mcg; crystalloid, intraoperative intravenous crystalloid volume; colloid, intraoperative colloid (Voluven 6% or Gelofusion) volume

Factors affecting overall 3-year mortality

We used univariate and multivariate Cox regression to examine and display the factors affecting overall mortality, as shown in Table 4. The analysis included ERAS protocol implementation and other relevant cofactors such as neoadjuvant CCRT, preoperative serum albumin level, surgical approach, pathological cancer stage, adjuvant CCRT, postoperative complications and tumor

Table 3 Postoperative variables of the ERAS group and control group

	ERAS	(*n* = 66)	Control	(*n* = 58)	*p* value
ICU stay, days	2	(2–3)	5	(4–6)	< 0.001
Hospital length of stay, days	8	(7–9)	10	(8–12)	< 0.001
Postoperative complications	23	(34.8%)	28	(48.3%)	0.131
Minor (Grade I & II)	22	(95.7%)	22	(79.0%)	0.081
Major (Grade III & VI)	1	(4.3%)	6	(21.0%)	0.081
Grade					0.323
Grade I	8	(34.8%)	4	(14.3%)	
Grade II	14	(60.9%)	18	(64.3%)	
Grade IIIa	0	(0%)	1	(3.6%)	
Grade IIIb	1	(4.3%)	4	(14.3%)	
Grade IV	0	(0%)	1	(3.6%)	
Patients with PPCs	0	(0%)	5	(8.6%)	0.015
Complications					
Pneumonia	0	(0%)	5	(8.6%)	0.015
Pulmonary edema	0	(0%)	1	(1.7%)	0.286
Respiratory failure	0	(0%)	1	(1.7%)	0.286
Chylothorax	0	(0%)	3	(5.2%)	0.063
Acute kidney injury	3	(4.5%)	0	(0.0%)	0.102
Arrhythmia	9	(13.6%)	6	(10.3%)	0.577
Wound infection	6	(9.1%)	9	(15.5%)	0.276
Vocal cord injury	10	(15.2%)	8	(13.8%)	0.831
Neck anastomosis leakage	4	(6.1%)	9	(15.5%)	0.088
Urine retention	2	(3.0%)	4	(6.9%)	0.319

Continuous variables were compared with the Mann–Whitney test and are presented as the median (IQR). Categorized variables were compared with the chi-square test and are presented as numbers (%). Hospital length of stay, from the day of the surgery to the day of discharge; Grade, Clavien–Dindo classification; PPCs, postoperative pulmonary complications, including pneumonia, pulmonary edema, and respiratory failure

histology. Age and hypertension were also included as potential confounding factors due to baseline differences between the ERAS and control groups. Adjuvant CCRT completion showed only a trend toward significance (HR 1.82, $p = 0.062$) and was therefore not included in multivariate analysis.

Univariate Cox regression revealed that ERAS protocol implementation (hazard ratio: 0.52, 95% CI: 0.27–0.99, $p = 0.046$), preoperative neoadjuvant CCRT (hazard ratio: 2.88, 95% CI: 1.34–6.22, $p = 0.007$), preoperative serum albumin level < 4 g/dL (hazard ratio: 0.35, 95% CI: 0.16–0.78, $p = 0.010$), minimally invasive surgical approach (hazard ratio: 0.45, 95% CI: 0.18–1.14, $p = 0.009$), advanced pathological cancer stage (hazard ratio: 3.07, 95% CI: 1.68–5.64, $p < 0.001$), and initiation of adjuvant CCRT (hazard ratio: 2.23, 95% CI: 1.23–4.05, $p = 0.008$) were significant predictors of overall 3-year mortality.

Multivariate Cox regression demonstrated that ERAS protocol implementation remained an independent positive predictor of mortality (adjusted hazard ratio: 0.44, 95% CI: 0.22–0.88, $p = 0.020$). Conversely, receiving neoadjuvant CCRT (adjusted hazard ratio: 2.73, 95% CI: 1.23–6.08, $p = 0.013$) and advanced pathological cancer stage (adjusted hazard ratio: 2.91, 95% CI: 1.27–6.66, $p = 0.011$) were independent negative predictors of 3-year overall mortality.

Kaplan-meier survival analysis

Kaplan−Meier survival analysis revealed that the 3-year survival rate was significantly greater in the ERAS group than in the control group (ERAS vs. control, 70.2% vs. 47.4%, $p = 0.043$) (Fig. 1).

For the subgroup analyses shown in Fig. 2, patients were further divided based on serum albumin level ($<$ 4 g/dl, $\geq$ 4 g/dl), pathological cancer stage (early stage, advanced stage), age ($<$ 65 years old, $\geq$ 65 years old) and neoadjuvant CCRT to compare the difference in 3-year survival between the ERAS and control groups. We found out that in subgroup Kaplan-Meier survival analysis, ERAS group had higher survival than the control group among patients with lower albumin levels (ERAS vs. control, 81.1% vs. 33.3%, $p = 0.035$) (Fig. 2a), advanced pathological stage (ERAS vs. control, 61.1% vs. 13.3%, $p = 0.008$)(Fig. 2d) and younger patients (ERAS vs. control, 76.8% vs. 42.7%, $p = 0.037$) (Fig. 2e).

Discussion

In this study, conducted at a high-volume tertiary care center, we evaluated the influence of the ERAS protocol on postoperative outcomes and long-term survival in esophagectomy patients. The ERAS group demonstrated significantly shorter ICU and hospital stays and a higher 3-year overall survival rate compared to the control group. In multivariate analysis, ERAS protocol implementation emerged as an independent positive prognostic factor, associated with a 51% lower risk of death within three years. Subgroup analysis further indicated survival benefits in patients with hypoalbuminemia, advanced pathological cancer stage, and those younger than 65 years. These findings support the potential role of ERAS protocols in improving both short-term recovery and long-term outcomes in complex surgical procedures such as esophagectomy.

Prognostic factors for three-year mortality analysis

Traditionally, ERAS protocols have been associated predominantly with short-term clinical benefits. However, we hypothesize that ERAS may indirectly enhance long-term prognosis by reducing surgical stress, decreasing postoperative complications, and enhancing patient physical resilience for adjuvant therapies. Our analysis showed superior adjusted 3-year survival outcomes in the ERAS cohort. Although postoperative complication rates were comparable between groups, the significantly reduced length of ICU and hospital stays observed

Table 4 Univariate and multivariate regression analyses of 3-year mortality in esophagectomy patients

	Univariate			Multivariate		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
ERAS	0.52	(0.27–0.99)	0.046*	0.44	(0.22–0.88)	0.020*
Neoadjuvant CCRT	2.88	(1.34–6.22)	0.007*	2.73	(1.23–6.08)	0.013*
Yes vs. no						
Preop albumin	0.35	(0.16–0.78)	0.010*	0.52	(0.20–1.35)	0.178
Surgical approach	0.45	(0.18–1.14)	0.009*	0.43	(0.06–3.39)	0.424
Minimal invasive vs. Hybrid						
Pathologic cancer stage	3.07	(1.68–5.64)	< 0.001**	2.91	(1.27–6.66)	0.011*
Advanced vs. early						
Adjuvant CCRT initiated	2.23	(1.23–4.05)	0.008*	1.39	(0.64–3.04)	0.405
Yes vs. no						
Adjuvant CCRT completed	1.82	(0.99–3.36)	0.062			
Yes vs. no						
Postoperative complication	2.28	(0.75–6.95)	0.148			
Major (Grade III & IV) vs. mild (Grade I & II))						
Age	1.01	(0.98–1.05)	0.560			
Hypertension	1.19	(0.61–2.32)	0.602			
Tumor type	0.60	(0.19–1.95)	0.399			
SCC vs. others						

Factors that were statistically significant ($p < 0.05$)in univariate Cox regression were selected into multivariate Cox regression. * $p < 0.05$, ** $p < 0.001$

Minimally invasive, thoracoscopic + laparoscopic; Hybrid, thoracoscopic + converted to mini-laparotomy due to previous abdominal surgery; Pathologic Cancer Stage, 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction; SCC, squamous cell carcinoma; CCRT, chemoradiation therapy; Complication, Graded by Clavien–Dindo classification

in the ERAS group indicated faster recovery after esophagectomy.

Significantly, among patients who initiated adjuvant chemoradiotherapy (CCRT), completion rates were notably higher in the ERAS group (100% vs. 63.2%, $p = 0.003$). This aligns with the emerging concept of Return to Intended Oncologic Therapy (RIOT), whereby rapid postoperative recovery under ERAS facilitates timely initiation and successful completion of subsequent cancer treatments. Recent evidence corroborates this, demonstrating improved adjuvant chemotherapy adherence in non-small cell lung cancer patients undergoing ERAS-based thoracic surgery [12]. Additionally, ERAS has been independently associated with improved long-term survival in bladder and colorectal cancer surgery, attributed to fewer complications and accelerated initiation of adjuvant therapy [13, 14, 15].

Despite the identified survival advantage associated with ERAS, determining the most influential individual component within this multifaceted protocol remains challenging. Each element, from preoperative optimization to postoperative analgesia, contributes synergistically to improved outcomes. Nonetheless, variables such as compliance with ERAS components and institutional expertise significantly influence outcomes. Protocol adherence exceeding 77% has consistently been associated with favorable outcomes [15, 16, 17], and our institutional adherence rate of 80.8% likely contributed to the improved survival observed in the ERAS group. Moreover, our analysis revealed that neoadjuvant CCRT and advanced pathological cancer stages were associated with poorer survival, reflecting the advanced disease burden and inherent prognostic disadvantage in these patient subgroups. This contrasts with findings from large-scale trials like the CROSS study [18, 19], where neoadjuvant CCRT improved survival outcomes. The observed discrepancy underscores the complexities of clinical practice, where higher disease burden, treatment-related toxicity, and postoperative complications may collectively influence outcomes [20, 21]. The retrospective design, limited sample size, and potential confounding further complicate interpretation, emphasizing the need for prospective, large-scale studies.

Specific cohorts that may benefit from the ERAS protocol

Our Kaplan–Meier survival analysis highlighted a survival advantage in the ERAS group, particularly in patients with hypoalbuminemia and advanced cancer stages. Patients with advanced esophageal cancer and hypoalbuminemia typically experience compromised physical status, increasing susceptibility to surgical stress [22]. The ERAS protocol components— reducing surgical-related tissue injury and inflammation, goal-directed fluid therapy to avoid over-hydration and subsequent tissue edema, and protective lung ventilation strategy to mitigate postoperative pulmonary complications— may mitigate these vulnerabilities.

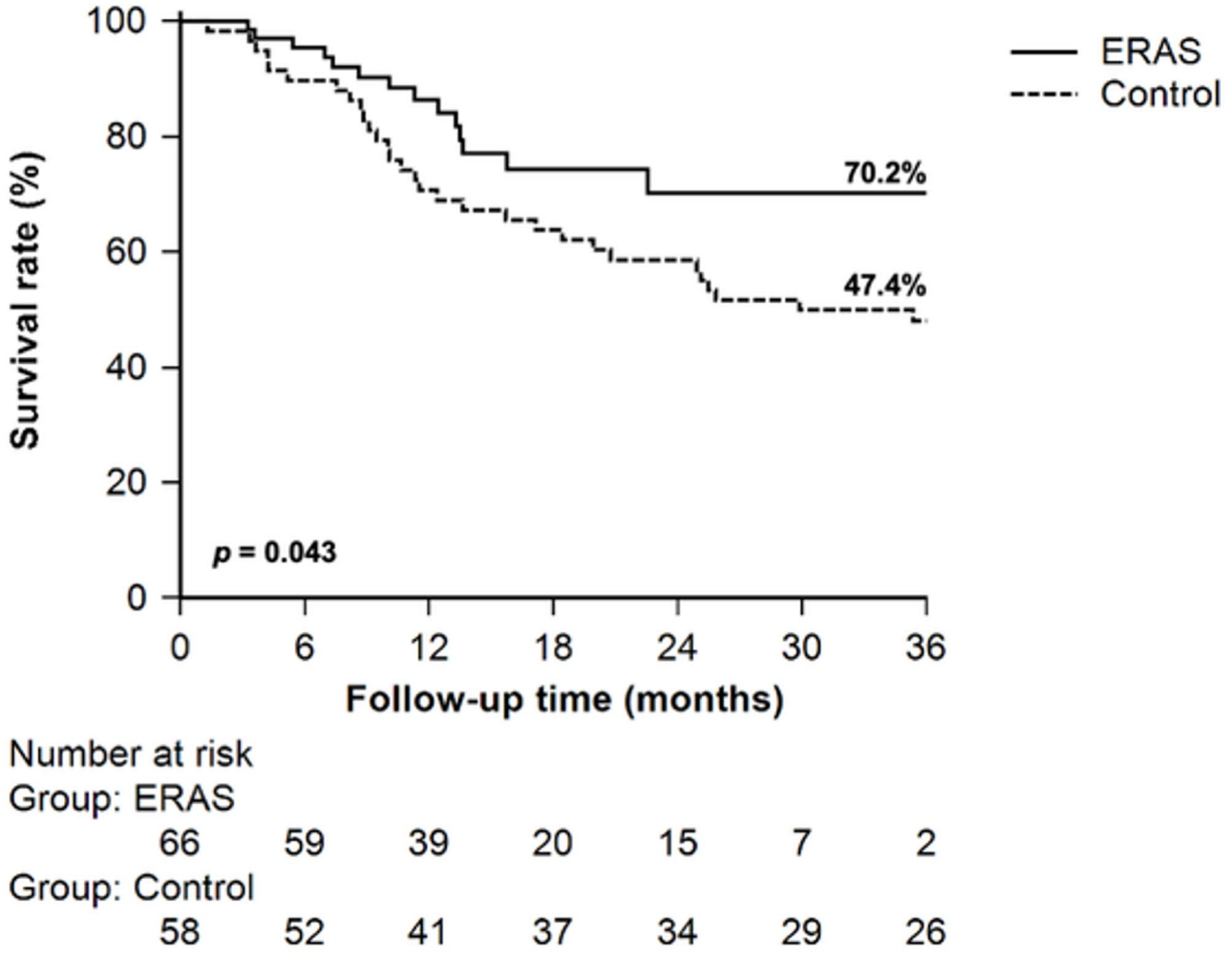

Fig. 1 Kaplan–Meier 3-year survival curves for the ERAS and control groups following esophagectomy. Figure 1 displays the Kaplan–Meier 3-year survival curves for the ERAS (solid line) and control (dotted line) groups up to 3 years after esophagectomy. The x-axis represents the follow-up months (0, 6, 12, 18, 24, 30, and 36), and the y-axis indicates the survival rate (0-100%). The 3-year survival rate was 70.2% in the ERAS group and 47.4% in the non-ERAS group ($p = 0.043$). The number at risk during survival analysis for each time point is provided below the graph. ERAS, Enhanced recovery after surgery

Interestingly, our subgroup analysis indicated survival benefits predominantly in younger patients, whereas elderly patients showed limited differentiation. Age has been identified as an independent prognostic factor for postoperative survival in cancer patients [23, 24]. Younger patients typically exhibit superior baseline resilience, enabling effective utilization of ERAS interventions such as early mobilization and nutritional optimization, facilitating prompt initiation of postoperative oncological therapies. Although elderly patients also benefited from ERAS, their survival outcomes may have been modulated by age-related physiological constraints and comorbidities, which might diminish long-term ERAS benefits. Additionally, the small elderly cohort size ($n = 29$) could account for the lack of statistical significance in this subgroup.

Shorter LOS and fewer PPCs

In our ERAS cohort, a significant reduction in LOS and PPCs was observed, consistent with prior research indicating that ERAS protocols lead to reduced post-esophagectomy hospital stays [25, 26]. There are several key factors that may elucidate our outcomes:

Impact of perioperative fluid management on LOS and PPCs In line with the 2019 ERAS guidelines [4], our goal-directed fluid therapy, which focuses on optimizing stroke volume and refraining an overall fluid balance > 2 L at the end of surgery, could lead to improved outcomes. The relevance of this finding is underscored by studies indicating that excessive perioperative fluid is a significant indicator of PPCs and anastomosis leakage after esophagectomy [27, 28], and others have reported that managing fluid overload can reduce major morbidity and decrease the LOS after major abdominal surgeries by up to 33% [29, 30].

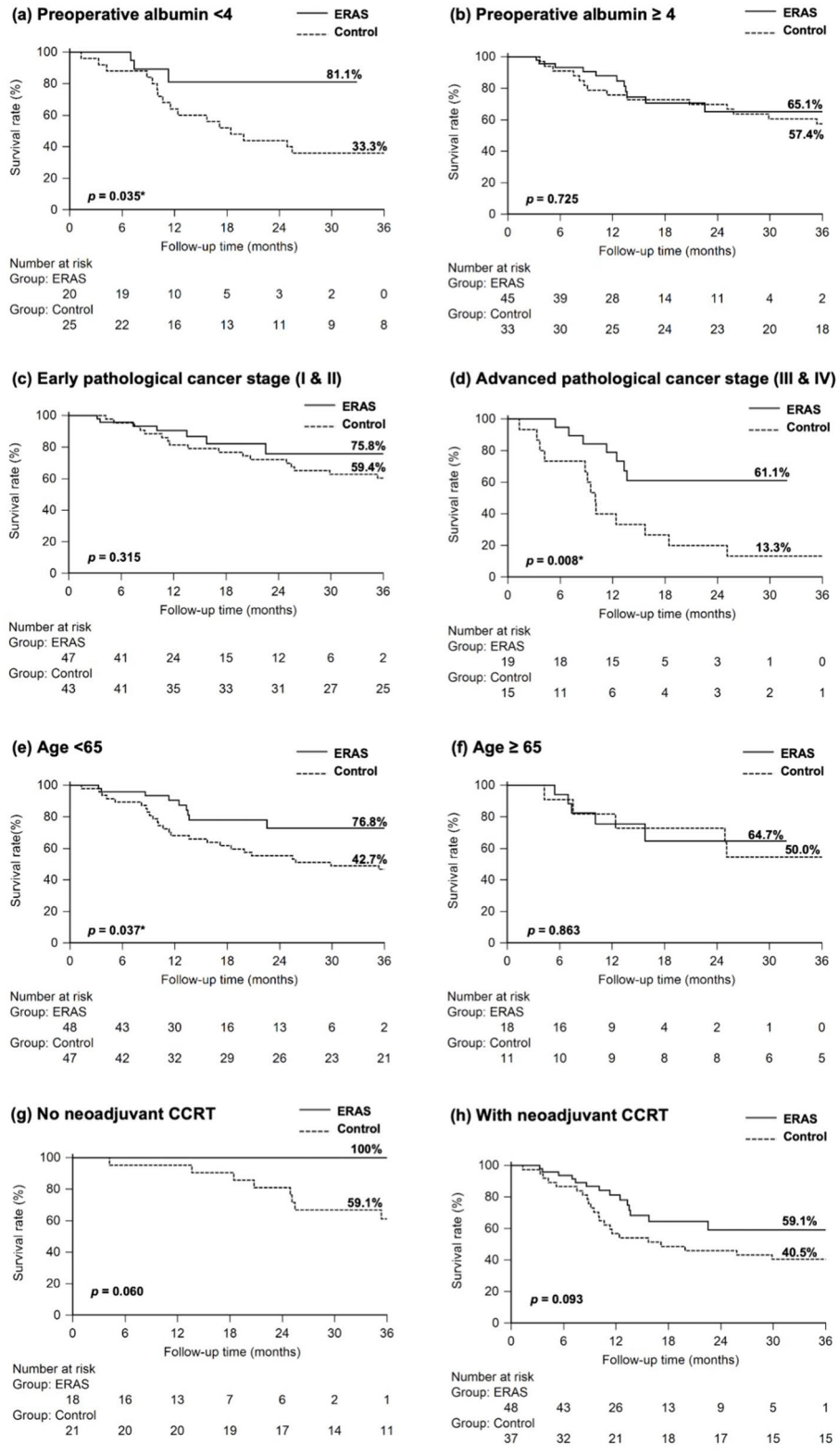

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Kaplan–Meier subgroup survival analysis for the ERAS and control groups following esophagectomy. Figure 2 consists of eight panels (2a-2 h) illustrating the Kaplan–Meier survival curves for various subgroups in the ERAS (solid line) and control (dotted line) groups: 2**a** - patients with preoperative Albumin < 4 g/dl; 2b - patients with preoperative Albumin ≥ 4 g/dl; 2**c** - patients with early pathologic cancer stages (Stage I & II); 2**d** - patients with advanced pathologic cancer stages(Stage III & IV); 2**e** - patients aged < 65 years; 2f - patients aged ≥ 65 years; 2 **g**- Patients who did not receive neoadjuvant chemoradiation therapy (CCRT); 2 **h**- patients who received neoadjuvant chemoradiation therapy (CCRT); The x-axis represents the follow-up months (0, 6, 12, 18, 24, 30, and 36), and the y-axis indicates the survival rate (0-100%). Each panel shows the 3-year survival rates and *p* values for the respective subgroups. pathologic cancer stage was defined according to 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction, after the final report of postoperative pathology reports

Moreover, while the multicenter FEDORA trial showed a significant reduction in complications and length of stay with the implementation of a goal-directed hemodynamic strategy in low- to moderate-risk surgical patients [31], one recent large multicenter randomized controlled trial reported that goal-directed fluid therapy was independently associated with mortality and morbidity reduction in transthoracic esophagectomy patients [32].

Role of low-dose vasopressors in mitigating TEA-induced hypotension There is increasing evidence that even a short duration of intraoperative hypotension, defined as a mean blood pressure less than 65 mmHg, is associated with postoperative morbidity [33, 34, 35, 36]. Our institutional practice of employing thoracic epidural analgesia (TEA) for esophagectomy necessitates counteracting potential hypotension while avoiding overhydration while restoring blood pressure. For euvolemic patients, we administer low-dose norepinephrine rather than phenylephrine due to its efficiency in maintaining cardiac output and splanchnic circulation. Both approaches capitalize on the benefits of TEA, such as mesenteric vasodilatation, safeguarding against complications such as conduit ischemia [37, 38] and preventing anastomosis leakage caused by overhydration [27, 39].

Contribution of protective lung ventilation to reducing PPCs Given the prolonged use of one-lung ventilation (OLV) in esophagectomy, implementing a protective lung ventilation strategy is paramount, especially in our ERAS cohort. Utilizing techniques such as low tidal volumes, individualized PEEP, and intermittent lung recruitment not only minimizes OLV-induced atelectrauma but also diminishes the risks associated with mechanical ventilation [40].

Early mobilization and reduced PPCs Early mobilization postsurgery is a cornerstone of enhanced recovery after surgery (ERAS) protocols. Multiple studies have shown that mobilization on postoperative day 1 (POD 1) is inversely associated with the incidence of lung atelectasis and is correlated with a decrease in pulmonary complications and a reduced duration of hospitalization [41, 42, 43]. In our cohort, approximately 75% of patients adhering to the ERAS protocol achieved the predetermined mobilization benchmarks by POD 1, which ranged from passive limb exercises while in bed to sitting upright or transitioning to a seated position at the edge of the bed. By POD 2 or 3, these patients typically advanced to standing or ambulatory activities. Such mobilization milestones may have contributed to the observed decrease in the number of PPCs within the ERAS group. Other elements of the ERAS protocol synergistically support this outcome, including tailored intraoperative goal-directed fluid therapy to prevent peripheral edema secondary to fluid overload and a multimodal analgesia approach designed to minimize opioid-related adverse effects that could impede patient mobilization efforts.

Limitations

Our study has several inherent limitations. Its retrospective design introduces potential residual confounding, limiting causal inferences. While the control and ERAS groups were contemporaneously managed by the same surgical team, retrospective biases persist. The analysis lacked certain prognostic variables, including tumor differentiation and R0 resection status, due to data constraints. Moreover, the small cohort size limits subgroup analyses and statistical power, particularly regarding unexpected findings such as the impact of neoadjuvant CCRT. Furthermore, the absence of detailed cause-specific mortality limits oncological outcome assessment. Future studies should prospectively evaluate detailed recurrence and cause-specific mortality to delineate ERAS's oncological impact better.

Conclusion

We observed an association between ERAS protocol implementation and improved 3-year survival among patients underwent esophagectomy. However, these results must be cautiously interpreted given the study's retrospective nature, potential residual confounding, and limited cohort size. Our findings indicate a correlation rather than direct causation and underline the need for prospective randomized studies to validate the observed survival benefit conclusively.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03124-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements
The authors would like to thank the Biostatistics Task Force of Taichung Veterans General Hospital for their statistical support. This study received no funding. No authors have any relevant competing interests to declare.

Author contributions
SJC, collected the data and write the manuscript draft; CHS, supervise the study, data analysis; CYC, study design and supervise; YTC: study design, data analysis, writing and editing the manuscript. All authors reviewed the manuscript.

Funding
No funding.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study received approval from the Institutional Review Board (IRB) of Taichung Veterans General Hospital with a waiver of the requirement for informed consent on 7 March 2023 (IRB CE23066C).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 29 October 2023 / Accepted: 8 May 2025
Published online: 21 May 2025

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