World Journal of Gastrointestinal Surgery

World J Gastrointest Surg 2024 July 27; 16(7): 1956-2364





Published by Baishideng Publishing Group Inc

WJG S

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 16 Number 7 July 27, 2024

EDITORIAL

- 1956 Unveiling the potential of electrocautery-enhanced lumen-apposing metal stents in endoscopic ultrasound-guided biliary drainage Chisthi MM
- 1960 Minimally invasive pelvic exenteration for primary or recurrent locally advanced rectal cancer: A glimpse into the future

Kehagias D, Lampropoulos C, Kehagias I

- 1965 Endoscopic submucosal dissection for early gastric cancer: A major challenge for the west Schlottmann F
- 1969 Impact of immunotherapy on liver metastasis Fu Z, Wang MW, Liu YH, Jiao Y
- 1973 Occurrence and prevention of incisional hernia following laparoscopic colorectal surgery Wu XW, Yang DQ, Wang MW, Jiao Y
- 1981 Role of endoscopic-ultrasound-guided biliary drainage with electrocautery-enhanced lumen-apposing metal stent for palliation of malignant biliary obstruction

Deliwala SS, Qayed E

REVIEW

1986 Pancreatic pseudocyst: The past, the present, and the future

Koo JG, Liau MYQ, Kryvoruchko IA, Habeeb TA, Chia C, Shelat VG

ORIGINAL ARTICLE

Case Control Study

2003 Diagnostic significance of serum levels of serum amyloid A, procalcitonin, and high-mobility group box 1 in identifying necrotising enterocolitis in newborns

Guo LM, Jiang ZH, Liu HZ, Zhang L

Retrospective Cohort Study

2012 Clinical efficacy and safety of double-channel anastomosis and tubular gastroesophageal anastomosis in gastrectomy

Liu BY, Wu S, Xu Y

2023 Application of radioactive iodine-125 microparticles in hepatocellular carcinoma with portal vein embolus Meng P, Ma JP, Huang XF, Zhang KL



Со	nte	nts

R

letros	pective	Study	/
	peccive	ocuu,	,

2031 Reproducibility study of intravoxel incoherent motion and apparent diffusion coefficient parameters in normal pancreas

Liu X, Wang YF, Qi XH, Zhang ZL, Pan JY, Fan XL, Du Y, Zhai YM, Wang Q

- 2040 Weight regain after intragastric balloon for pre-surgical weight loss Abbitt D, Choy K, Kovar A, Jones TS, Wikiel KJ, Jones EL
- 2047 Retrospective analysis based on a clinical grading system for patients with hepatic hemangioma: A single center experience

Zhou CM, Cao J, Chen SK, Tuxun T, Apaer S, Wu J, Zhao JM, Wen H

2054 Spleen volume is associated with overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with portal hypertension

Zhao CJ, Ren C, Yuan Z, Bai GH, Li JY, Gao L, Li JH, Duan ZQ, Feng DP, Zhang H

2065 Evaluation of the clinical effects of atropine in combination with remifentanil in children undergoing surgery for acute appendicitis

Li YJ, Chen YY, Lin XL, Zhang WZ

2073 The combined detection of carcinoembryonic antigen, carcinogenic antigen 125, and carcinogenic antigen 19-9 in colorectal cancer patients

Gong LZ, Wang QW, Zhu JW

2080 Clinical efficacy of laparoscopic cholecystectomy plus cholangioscopy for the treatment of cholecystolithiasis combined with choledocholithiasis

Liu CH, Chen ZW, Yu Z, Liu HY, Pan JS, Qiu SS

2088 Association between operative position and postoperative nausea and vomiting in patients undergoing laparoscopic sleeve gastrectomy

Li ZP, Song YC, Li YL, Guo D, Chen D, Li Y

2096 Preoperative albumin-bilirubin score predicts short-term outcomes and long-term prognosis in colorectal cancer patients undergoing radical surgery

Diao YH, Shu XP, Tan C, Wang LJ, Cheng Y

2106 Association of preoperative antiviral treatment with incidences of post-hepatectomy liver failure in hepatitis B virus-related hepatocellular carcinoma

Wang X, Lin ZY, Zhou Y, Zhong Q, Li ZR, Lin XX, Hu MG, He KL

2119 Effect of rapid rehabilitation nursing on improving clinical outcomes in postoperative patients with colorectal cancer

Song JY, Cao J, Mao J, Wang JL

2127 Interaction between the albumin-bilirubin score and nutritional risk index in the prediction of posthepatectomy liver failure

Qin FF, Deng FL, Huang CT, Lin SL, Huang H, Nong JJ, Wei MJ



Contents	
conten	Monthly Volume 16 Number 7 July 27, 2024
2135	Effectiveness of magnetic resonance imaging and spiral computed tomography in the staging and treatment prognosis of colorectal cancer
	Bai LN, Zhang LX
2145	Correlation between abdominal computed tomography signs and postoperative prognosis for patients with colorectal cancer
	Yang SM, Liu JM, Wen RP, Qian YD, He JB, Sun JS
2157	Study on the occurrence and influencing factors of gastrointestinal symptoms in hemodialysis patients with uremia
	Yuan D, Wang XQ, Shao F, Zhou JJ, Li ZX
2167	"Hepatic hilum area priority, liver posterior first": An optimized strategy in laparoscopic resection for type III-IV hilar cholangiocarcinoma
	Hu XS, Wang Y, Pan HT, Zhu C, Chen SL, Zhou S, Liu HC, Pang Q, Jin H
2175	Impact of nutritional support on immunity, nutrition, inflammation, and outcomes in elderly gastric cancer patients after surgery
	Chen XW, Guo XC, Cheng F
2183	Therapeutic effects of Buzhong Yiqi decoction in patients with spleen and stomach qi deficiency after routine surgery and chemotherapy for colorectal cancer
	Hu Q, Chen XP, Tang ZJ, Zhu XY, Liu C
2194	Influencing factors and risk prediction model for emergence agitation after general anesthesia for primary liver cancer
	Song SS, Lin L, Li L, Han XD
2202	Potential applications of single-incision laparoscopic totally preperitoneal hernioplasty
	Wang XJ, Fei T, Xiang XH, Wang Q, Zhou EC
2211	Clinical significance of preoperative nutritional status in elderly gastric cancer patients undergoing radical gastrectomy: A single-center retrospective study
	Zhao XN, Lu J, He HY, Ge SJ
2221	Establishment and validation of a predictive model for peripherally inserted central catheter-related thrombosis in patients with liver cancer
	Chen XF, Wu HJ, Li T, Liu JB, Zhou WJ, Guo Q
	Observational Study
2232	Effect of information-motivation-behavioral skills model based perioperative nursing on pain in patients with gallstones
	Ma L, Yu Y, Zhao BJ, Yu YN, Li Y
2242	Postoperative body weight change and its influencing factors in patients with gastric cancer
	Li Y, Huang LH, Zhu HD, He P, Li BB, Wen LJ
2255	Cost burden following esophagectomy: A single centre observational study
	Buchholz V, Lee DK, Liu DS, Aly A, Barnett SA, Hazard R, Le P, Kioussis B, Muralidharan V, Weinberg L



Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 7 July 27, 2024

Randomized Controlled Trial

2270 Effectiveness of colonoscopy, immune fecal occult blood testing, and risk-graded screening strategies in colorectal cancer screening

Xu M, Yang JY, Meng T

Clinical and Translational Research

2281 Construction of prognostic markers for gastric cancer and comprehensive analysis of pyroptosis-related long non-coding RNAs

Wang Y, Li D, Xun J, Wu Y, Wang HL

Basic Study

Yangyin Huowei mixture alleviates chronic atrophic gastritis by inhibiting the IL-10/JAK1/STAT3 2296 pathway

Xie SS, Zhi Y, Shao CM, Zeng BF

2308 Impacts of different pancreatic resection ranges on endocrine function in Suncus murinus Li RJ, Yang T, Zeng YH, Natsuyama Y, Ren K, Li J, Nagakawa Y, Yi SQ

SYSTEMATIC REVIEWS

2319 Impact of frailty on postoperative outcomes after hepatectomy: A systematic review and meta-analysis Lv YJ, Xu GX, Lan JR

CASE REPORT

2329 Multidisciplinary management of ulcerative colitis complicated by immune checkpoint inhibitorassociated colitis with life-threatening gastrointestinal hemorrhage: A case report

Hong N, Wang B, Zhou HC, Wu ZX, Fang HY, Song GQ, Yu Y

- 2337 Sequential bowel necrosis and large gastric ulcer in a patient with a ruptured femoral artery: A case report Wang P, Wang TG, Yu AY
- 2343 Colon signet-ring cell carcinoma with chylous ascites caused by immunosuppressants following liver transplantation: A case report

Li Y, Tai Y, Wu H

2351 Misdiagnosis of hemangioma of left triangular ligament of the liver as gastric submucosal stromal tumor: Two case reports

Wang JJ, Zhang FM, Chen W, Zhu HT, Gui NL, Li AQ, Chen HT

LETTER TO THE EDITOR

2358 Revolutionizing palliative care: Electrocautery-enhanced lumen-apposing metal stents in endoscopicultrasound-guided biliary drainage for malignant obstructions

Onteddu NKR, Mareddy NSR, Vulasala SSR, Onteddu J, Virarkar M



a .	World Journal of Gastrointestinal Surgery
Conte	nts Monthly Volume 16 Number 7 July 27, 2024
2362	Preservation of superior rectal artery in laparoscopic colectomy: The best choice for slow transit constipation?
	Liu YL, Liu WC

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 7 July 27, 2024

ABOUT COVER

Peer Reviewer of World Journal of Gastrointestinal Surgery, Hideki Aoki, MD, PhD, Chief Doctor, Surgeon, Department of Surgery, Iwakuni Clinical Center, Iwakuni 740-8510, Japan. aoki.hideki.hy@mail.hosp.go.jp

AIMS AND SCOPE

The primary aim of World Journal of Gastrointestinal Surgery (WJGS, World J Gastrointest Surg) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

INDEXING/ABSTRACTING

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for WJGS as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 123/290 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Zi-Hang Xu; Production Department Director: Xiang Li; Cover Editor: Jia-Ru Fan.

NAME OF JOURNAL	INSTRUCTIONS TO AUTHORS
World Journal of Gastrointestinal Surgery	https://www.wjgnet.com/bpg/gerinfo/204
ISSN	GUIDELINES FOR ETHICS DOCUMENTS
ISSN 1948-9366 (online)	https://www.wjgnet.com/bpg/GerInfo/287
LAUNCH DATE	GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
November 30, 2009	https://www.wjgnet.com/bpg/gerinfo/240
FREQUENCY	PUBLICATION ETHICS
Monthly	https://www.wjgnet.com/bpg/GerInfo/288
EDITORS-IN-CHIEF Peter Schemmer	PUBLICATION MISCONDUCT https://www.wjgnet.com/bpg/gerinfo/208
EDITORIAL BOARD MEMBERS	ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/1948-9366/editorialboard.htm	https://www.wjgnet.com/bpg/gerinfo/242
PUBLICATION DATE	STEPS FOR SUBMITTING MANUSCRIPTS
July 27, 2024	https://www.wjgnet.com/bpg/GerInfo/239
COPYRIGHT	ONLINE SUBMISSION
© 2024 Baishideng Publishing Group Inc	https://www.f6publishing.com

© 2024 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA E-mail: office@baishideng.com https://www.wjgnet.com



W C

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2024 July 27; 16(7): 2255-2269

DOI: 10.4240/wjgs.v16.i7.2255

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study Cost burden following esophagectomy: A single centre observational study

Vered Buchholz, Dong Kyu Lee, David S Liu, Ahmad Aly, Stephen A Barnett, Riley Hazard, Peter Le, Benjamin Kioussis, Vijayaragavan Muralidharan, Laurence Weinberg

Specialty type: Gastroenterology	Vered Buchholz, Department of Surgery, Austin Health, Melbourne 3084, Victoria, Australia
and hepatology	Dong Kyu Lee, Department of Anesthesiology and Pain Medicine, Dongguk University Ilsan
Provenance and peer review:	Hospital, Seoul 14566, Goyang, South Korea
Unsolicited article; Externally peer reviewed.	David S Liu, Ahmad Aly, Stephen A Barnett, Vijayaragavan Muralidharan, Department of Surgery, Austin Health, The University of Melbourne, Melbourne 3084, Victoria, Australia
Peer-review model: Single blind	Riley Hazard, Peter Le, Benjamin Kioussis, Department of Anesthesia, Austin Health, Melbourne
Peer-review report's classification	3084, Victoria, Australia
Scientific Quality: Grade C	Laurence Weinberg, Department of Anesthesia, Austin Hospital, Heidelberg 3084, Victoria,
Novelty: Grade C	Australia
Creativity or Innovation: Grade C	
Scientific Significance: Grade B	Laurence Weinberg, Department of Critical Care, The University of Melbourne, Melbourne 3084, Victoria, Australia
P-Reviewer: Liang P	Corresponding author: Laurence Weinberg, BSc, MBChB, MD, MRCP, PhD, Director, Full
Received: April 25, 2024	Professor, Department of Anesthesia, Austin Hospital, 145 Studley Road, Heidelberg 3084,
Revised: June 16, 2024	Victoria, Australia. laurence.weinberg@austin.org.au
Accepted: July 1, 2024	
Published online: July 27, 2024	
Processing time: 88 Days and 0.3	Abstract
Hours	BACKGROUND
	Cost analyses of patients undergoing esophagectomy is valuable for identifying modifiable expenditure drivers to target and curtail costs while improving the quality of care. We aimed to define the cost-complication relationship after esophagectomy and delineate the incremental contributions to costs.

AIM

To assess the relationship between the hospital costs and potential cost drivers post esophagectomy and investigate the relationship between the cost-driving variables (predicting variables) and hospital costs (dependent variable).

METHODS

In this retrospective single center study, the severity of complications was graded using the Clavien-Dindo (CD) classification system. Key esophagectomy complications were categorized and defined according to consensus guidelines. Raw



costing data included the in-hospital costs of the index admission and any unplanned admission within 30 postoperative days. We used correlation analysis to assess the relationship between key clinical variables and hospital costs (in United States dollars) to identify cost drivers. A mediation model was used to investigate the relationship between these variables and hospital costs.

RESULTS

A total of 110 patients underwent primary esophageal resection. The median admission cost was \$47822.7 (interquartile range: 35670.2-68214.0). The total effects on costs were \$13593.9 (95%CI: 10187.1-17000.8, *P* < 0.001) for each increase in CD severity grade, \$4781 (95%CI: 3772.7-5789.3, P < 0.001) for each increase in the number of complications, and \$42552.2 (95% CI: 8309-76795.4, P = 0.015) if a key esophagectomy complication developed. Key esophagectomy complications drove the costs directly by \$11415.7 (95%CI: 992.5-21838.9, P = 0.032).

CONCLUSION

The severity and number of complications, and the development of key esophagectomy complications significantly contributed to total hospital costs. Continuous institutional initiatives and strategies are needed to enhance patient outcomes and minimize costs.

Key Words: Anesthesia; Esophagectomy; Complications; Cancer; Surgery

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Our findings show that complications following esophagectomy are common, with most patients experiencing at least one complication, and over 40% of patients developing a major complication. Moreover, we have demonstrated that the severity, number of complications and the presence of esophagectomy key complications significantly contributed to total hospital costs. Reoperation, prolonged intensive care stay and hospital stay were major drivers of hospital costs. This study highlights the importance of a continuous institutional quality review to prevent and mitigate complications, and the need for improved intervention strategies to enhance patient outcomes and minimize costs.

Citation: Buchholz V, Lee DK, Liu DS, Aly A, Barnett SA, Hazard R, Le P, Kioussis B, Muralidharan V, Weinberg L. Cost burden following esophagectomy: A single centre observational study. World J Gastrointest Surg 2024; 16(7): 2255-2269 URL: https://www.wjgnet.com/1948-9366/full/v16/i7/2255.htm

DOI: https://dx.doi.org/10.4240/wjgs.v16.i7.2255

INTRODUCTION

Esophagectomy is a complex surgical procedure and the keystone of multimodal treatment for locally advanced esophageal cancer. It is associated with significantly high postoperative morbidity. The delivery of high-standard and innovative treatment, particularly in the context of esophagectomy, can drive steep increases in health expenditures, undermining the economic sustainability of cancer healthcare systems. Simultaneously, healthcare systems strive to maintain performance standards without compromising cancer treatment outcomes[1].

Postoperative complications are indicators of surgical quality and performance. Their effect on the surgical cost of care has been established in previous studies assessing the costs of major procedures[2-4]. Consequently, cost analysis of patients undergoing esophagectomy is valuable for identifying modifiable expenditure drivers to target and curtail costs while improving the quality of care.

Although a few studies have explored the economic effects of post-esophagectomy complications [5-8], the literature on this topic remains scarce and inconsistent in relation to data sourcing, definitions of complications, and severity grading. Therefore, we aimed to define the cost-complication relationship after esophagectomy and delineate the incremental contributions to costs.

MATERIALS AND METHODS

Logistics and setting

This study was conducted at Austin Health, a university-affiliated tertiary referral center for upper gastrointestinal conditions. The Human Research Ethics Committee of Austin Hospital approved this retrospective observational study as a clinical audit, and the protocol was registered with the Australian New Zealand Clinical Trials Registry. Given that this was a retrospective observational audit, trial registration of this study was undertaken after ethics approval and data collection. There were no changes to the original study protocol at any stage. Data analysis was only undertaken after trial registration. The key timelines for the study are as follows: (1) September 23, 2019: Study protocol approved by the



Austin Health Office for Human Research (approval No. Audit/19/Austin/103); (2) October 10, 2019: Data collection following ethics approval; (3) November 19, 2020: Data collection completed; and (4) December 22, 2020: Retrospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001377921). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies[9,10].

Participants

We included patients aged \geq 18 years who underwent esophagectomy between January 2010 and December 2019. Patients were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision and codes specific to esophagectomy. Surgical procedures consisted of two- or three-stage esophagectomy performed using an open, laparoscopic, or hybrid approach for esophageal cancer, benign tumors, and motility disorders. All surgical procedures were performed by eight surgeons from the upper gastrointestinal and thoracic surgery units.

Preoperative optimization

All patients, independent of the treating surgical unit, underwent an enhanced recovery after surgery (ERAS) program aligned with international guidelines[11], which included a comprehensive pre-optimization program for smoking and alcohol cessation. As part of our institution's diabetes discovery initiative, all patients with an HbA1c level of 8.3% (67 mmol/mol) had a personalized plan for glycemia and were managed according to the hospital's perioperative guidelines for patients with diabetes, with an inpatient blood glucose target of 5-10 mmol/L based on the Australian Diabetes Society guidelines. All participants underwent a comprehensive multidisciplinary assessment, with optimization of nutrition, medical comorbidities, and hemoglobin levels, based on the National Blood Authority of Australia's Patient Blood Management Initiative^[12]. Standard perioperative care included strict transfusion practices following these guidelines. General anesthesia was managed using an ERAS protocol designed to standardize care.

Postoperatively, all patients were admitted to the intensive care unit (ICU) for at least one overnight stay and discharged to a dedicated surgical ward by a multidisciplinary team of surgeons, anesthetists, perioperative physicians, and pain clinicians. Analgesia was optimized by an acute pain service that reviewed all patients twice daily.

Data collection

All data were sourced directly by the authors using prospectively recorded patient variables from the hospital's electronic health records (Cerner Millennium, KS, United States). Preoperative patient parameters included demographic information, body mass index, history of smoking and alcohol abuse, American Society of Anesthesiologists (ASA) score, comorbidities, Carlson comorbidity index (CCI), history of previous abdominal or thoracic surgery, preoperative blood values, pathological diagnosis, and neoadjuvant treatment.

Intraoperative parameters included the type of surgery (open or minimally invasive laparoscopy & thoracoscopy), the surgical approach (transthoracic, 3-stage or transhiatal), the operative time, the volume of transfused crystalloids, colloids, and blood products, the use of vasoactive medications, and the intraoperative complications. Postoperative variables included ICU admission and care duration, postoperative blood values, blood product transfusion, histopathology, American Joint Committee on Cancer pathologic stage group (8th edition)[13], length of hospital stay, discharge destination, and readmissions (30 days, 90 days, and one year). Postoperative complications were derived directly from patient files.

The severity of complications was graded using the Clavien-Dindo (CD) classification system[14]. Major complications were defined as CD III-IV. Key complications of esophagectomy (anastomotic leak, conduit necrosis, chyle leak, and vocal cord palsy) were categorized and defined according to the Esophagectomy Complications Consensus Group (ECCG) definitions[15]. Raw costing data were provided by the hospital's clinical informatics and costing center and included the in-hospital costs of the index admission under the surgical service and the costs of any unplanned admission within 30 days. The clinical-based cost buckets included anesthesia, ICU, medical emergency team call, operating theater (including endoscopy), allied health, pharmacy, radiology, pathology, medical consult, blood product, and ward costs (e.g., costs of the hospital bed, nursing, and catering). Costs were inflated to June 30, 2022 values based on the end-of-fiscal-quarter Australian Consumer Price Index and converted to United States dollars (USD) based on the market rate on June 30, 2022.

Statistical analysis

Statistical analysis was performed using the R software (version 4.2.1; 2022, R Core Team, Vienna, Austria). The normality of continuous variables was evaluated using the Shapiro-Wilk test and a visual check of the Q-Q plot. Data are presented as mean ± SD, median [interquartile range (IQR)], (minimum, maximum), or number (percentile). An unadjusted cost analysis was performed using Wilcoxon and Kruskal-Wallis rank-sum tests. Pairwise comparisons using the Wilcoxon rank-sum test with continuity correction were also performed. The P value was adjusted using the method of Benjamini and Hochberg during multiple pairwise comparisons.

Correlation analysis was used to assess the relationship between the measured variables and hospital costs and identify potential cost drivers. The correlations among the likely cost drivers were visualized as a correlation matrix (R package "Performance Analytics," ver. 2.0.4)[16]. The complex relationship between the hospital cost and measured variables was investigated using a correlation data frame network plot with various coefficient limits and the incorporated function of R package "corrr" ver. 0.4.4[17].

We used a mediation model to investigate the relationship between the cost-driving variables (predicting variables) and hospital costs (dependent variable). The model clarifies situations where a total exposure-outcome effect is identified, but a direct causal effect between the predictor and dependent variables is not apparent. The mediation model suggests

that the mediating variable transmits the effect of the predicting variable on the dependent variable [18,19]. The mediator variable's transmittance effect (indirect effect) is then quantified and can be complete or partial (Figure 1).

Multiple mediation effect analyses were performed to evaluate the direct and indirect effects of the severity and number of complications and the presence of key esophagectomy complications on hospital costs using generalized linear models (R package "mma" ver. 10.6-1)[20]. The 95% CI of the estimated effects were calculated using the nonparametric bootstrap method with 1000 repetitions. The expected mortality was estimated using Kaplan-Meier survival analysis. Statistical significance was determined using a two-sided *P* value below 0.05.

RESULTS

A total of 110 patients underwent primary esophageal resection for benign and malignant diseases during the study period. Baseline patient characteristics are summarized in Table 1. The study population was predominantly male (83%), with a mean age of 64.5 years. The mean CCI score was 4.4. Eighty (72.7%) patients were current or past smokers with an average smoking history of 20 pack years. Ninety-four patients (85.4%) underwent open surgery, and 16 (14.5%) underwent hybrid or minimally invasive esophagectomy. The most prevalent procedure was the two-stage esophagectomy (61.8%). The full datasheet of deidentified patient information can be found in the Supplementary Table 1.

Of the 104 patients (94.5%) who underwent surgery for esophageal malignancy, 76 (69%) received neoadjuvant chemotherapy or chemoradiotherapy before the operation, and four (3.6%) underwent salvage esophagectomy more than 12 months after completing definitive chemoradiotherapy. The median length of stay in the ICU was 2.7 days (1.6-6.3), and the median length of hospital stay was 18 days (13-27). In total, 89 patients (80%) were discharged home, and 19 patients (17.3%) were transferred to a rehabilitation or nursing facility.

Postoperative complications

In total, 658 complications were recorded. All but two patients had at least one complication. Sixty-two (56.3%) patients had minor complications, while 46 (41.8%) experienced major complications (Table 2). Two patients died during the index admission (1.8%). A detailed breakdown of complications is summarized in the Supplementary Table 2. The most common complications were electrolyte imbalance (n = 93, 84.5%), hypotension requiring intervention (n = 67, 60.9%), atrial fibrillation (n = 37, 33.6%), pneumonia (n = 36, 32.7%), and anemia requiring transfusion (n = 31, 28.2%). Key complications of esophagectomy (anastomotic leak, conduit necrosis, chyle leak, and recurrent nerve palsy) occurred in 47 (42.7%) patients. Twenty patients (18%) experienced an anastomotic leak, with severity varying from CD-II to CD-IVb. Three patients experienced conduit necrosis; all three required surgery, and one required diversion surgery (Table 3).

Unadjusted cost analysis

The median admission cost was USD 47822.7 (IQR 35670.2-68214.0). The highest expenditures were for the ICU stay, the operating theater, and ward care (Supplementary Table 3). An unadjusted analysis of complications and hospital costs demonstrated a significant association between the severity of complications and cost increments, with cost increments increasing as the CD severity grade advanced. For example, hospital costs doubled for patients with CD grades IV-V compared with patients without complications or with CD grade I (Figure 2A and Table 4).

The number of complications per patient similarly influenced admission costs. The median admission cost for patients with seven or more complications of any grade was 2.5 times that for patients with 0-3 complications (Figure 2B and Table 4). Likewise, key complications of esophagectomy were associated with high additional costs. The median overall admission cost for patients who experienced any of the four key complications was USD 75517.0 compared to USD 42937.5 for patients without esophagectomy-specific complications (Figure 2C and Table 4).

Adjusted cost analysis

Spearman's correlation analysis was performed to identify the relationships between various perioperative parameters, complications, and total costs (Supplementary Table 4). The severity (CD grade) of complications, the number of complications, and the presence of esophagectomy key complications were moderately or highly related to the total hospital cost [Spearman's correlation coefficient P = 0.585, 0.670, and 0.576, respectively; P < 0.001, 0.001, and 0.004 (P < 0.001), respectively].

The duration of ICU or high-dependency unit (HDU) stay, length of hospital stay, emergency reoperation, ASA classification, CCI score, history of previous laparotomy, surgery time, postoperative lowest albumin level, postoperative creatinine level, total red blood cell units given during the admission, and readmission within 90 days after discharge were significantly correlated with the hospital cost as well as the CD severity grade and the number of complications. Using a network matrix of the correlation data frame, we identified several of the parameters listed above as potential mediator variables in the relationship between complications and costs (Supplementary Figure 1). These variables were related to each other over the hospital cost and complications. The visual checking of a network plot of a correlation data frame showed the possible mediation effects of several variables listed above from postoperative complications to the hospital cost (Supplementary Figure 2).

Mediation effect analysis

We first established that the complication severity grade, number of complications, and key esophagectomy complications were significant predictors of costs (linear regression coefficients: USD 19176, 95% CI: 12972.6-25379.4; USD 7648, 95% CI: 5809.5-9486.5; USD 40086, 95% CI: 28206.4-51965.6, respectively; all P < 0.001). These results imply that all three



Table 1 Baseline characteristics, surgical and oncological da	ata, n (%)
Variable	<i>n</i> = 110
Demographics	
Sex	
Male	91 (82.7)
Female	19 (17.3)
Age (years)	64.47 ± 9.694
Body mass index (kg/m ²)	27.0 ± 4.9
Smoking	
Never	30 (27.3)
Active	12 (10.9)
Quit < 6 weeks prior to surgery	5 (4.5)
Quit 6 weeks to 90 days prior to surgery	4 (3.6)
Quit > 90 days prior to surgery	59 (53.6)
Pack year history	20 (0-40)
Alcohol consumption > 4 standard drinks	13 (11.8)
Risk classification	
ASA	
1	2 (1.8)
2	35 (31.8)
3	68 (61.8)
4	5 (4.5)
ECOG	
0	78 (70.9)
1	28 (25.5)
2	3 (2.7)
ACCI (median)	4 (3-5)
Comorbidities	
Coronary artery disease	3 (2.7)
Myocardial infarction	6 (5.5)
Congestive heart failure	1 (0.9)
Peripheral vascular disease	7 (6.4)
Cerebrovascular accident	5 (4.5)
Chronic pulmonary disease	11 (10)
Diabetes mellitus (uncomplicated)	13 (11.8)
Diabetes mellitus (end-organ damage)	2 (1.8)
Moderate to severe renal disease	1 (0.9)
Synchronous malignancy (solid tumor)	2 (1.8)
Past malignancy	16 (14.5)
Previous laparotomy	13 (11.8)
Previous thoracotomy	8 (7.3)
Previous hiatal operation	4 (3.6)
Laboratory tests	

Buchholz V et al. Cost burden after esophagectomy

<table-container>Headquidy120,120,130What qu'ny (not (not (not (not (not (not (not (not</table-container>		
Plack(10 ¹ /1)210(10,400)GR4(1/2) attract(1/2) attract(1/2)25(30,40)GR4(1/2) attract(1/2) attract(1/2)26(30,40)GR4(1/2) attract	Hemoglobin (g/L)	132 (90, 176)
Cardinine (main(n))P(24,27)cCR (minuch(27)m)P(30,30)All-main(1)P(30,40)Pari-inter (main(1))P(40,40)Pari-inter (main(1))P(30,40)Pari-inter (main(1))P(30,40)P(41,40)P(41,40)<	White cell (10 ⁹ /L)	6.6 (3, 13)
SR (n (, n ())))))))))	Platelet (10 ⁹ /L)	231.5 (110, 541)
<table-container>Alwaia(j1)8(2,4)Huniq(j1)1045,1Haipan1045,1Baipan1045,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,1Saysan10,2Saysan</table-container>	Creatinine (mmol/L)	79.5 (44, 72)
<table-container>Netropological set of the set of the</table-container>	eGFR (mL/minute/1.73 m ²)	87 (33, 91)
<table-container>Alignent104(45)Beige65)Serger Jerrock9(5)Verte9(6)Net103)Conserve Serve Ser</table-container>	Albumin (g/L)	38 (27, 44)
Inemin(5)Gerigat approact4(54)Urgat approact4(54)Urgat approact10.10Urgat approact10.10Urgat approact10.10Conversion to open0.60Conversion to open0.60Urgat approact10.10Urgat approact0.60Urgat approact0.60<	Principal diagnosis (indication for surgery)	
<table-container>SiguifyrainingSignifyraining99991010101010101010101010101010101010101110111012101310141014101510161016101710181019101910<</table-container>	Malignant	104 (94.5)
Npmqls3,Miminul invasive (dupanoscopy thoracoscopy)3 (27)Harring to end to end to add	Benign	6 (5.5)
<table-container>Minimuly unserve function opposedSecond second second</table-container>	Surgical approach	
<table-container>Here[10]Correr50.5Automatical50.5Correr60.60.5Correr60.60.5Correr60.60.5Correr10.07.00.5Correr10.07.00.5Correr10.07.00.5Image60.27.00.5Image10.07.00.5Image10.07.00.5Image10.07.00.5Image10.00.5Image</table-container>	Open	94 (85.4)
<table-container>Cerver of the server of the</table-container>	Minimally invasive (laparoscopy & thoracoscopy)	3 (2.7)
<table-container>Anatomic setCircle6(6).5Net6(6).5Set6(2).5Set10(7).5Circle10(7).5I6(2).5I6(2).5I10(2).5I10(2).5I10(2).5I10(2).5IBA2(2).5INA2(2).5INA2(3).5INA2(3).5INA2(3).5INA10(2).5INA10(2).5INA10(2).5INA10(2).5INA2(2).5INA2(3).5INA2(4).5INA2(</table-container>	Hybrid (chest or abdomen)	13 (11.8)
<table-container>Chet866.8Nek2682Seture1097.3Seture30.7Clar1097.3Autor362.7I36.27I36.27I36.27I36.27IA36.27IA36.27IA36.27IA36.27IA36.27IA36.27IA36.27IA36.27IA36.27IA36.24IA36.24IA36.24IA36.24IA36.24IA36.40IA<td< td=""><td>Conversion to open</td><td>5 (4.5)</td></td<></table-container>	Conversion to open	5 (4.5)
<table-container>Nek[4082]Berlow1073]Some1073]Color027]Auge102]I102]I102]IA102]IB2043]IVA2043]IVA2043]IVA2043]IVA2043]IVA2014]I</table-container>	Anastomosis site	
Isophagel conduit 10703) Soma 10703) Image: Soma (abult) 3(27) Image: Soma (abult) 3(28)	Chest	68 (61.8)
Nome10Color202202202201201020<	Neck	42 (38.2)
Colorj27AUTj27Ij28I <td< td=""><td>Esophageal conduit</td><td></td></td<>	Esophageal conduit	
k 3627; k 3630; k	Stomach	107 (97.3)
I96,27,00000000000000000000000000000000000	Colon	3 (2.7)
II 4 (27) IIA 0 (9) IIB 2 (24.5) IVA 3 (1.8) IVB 3 (27) IVB 3 (27) Restrictmargin 97 (88.1) Restrictmonergin 10 (9) Instruction details 10 (9) Instructin detailsontin facility (9) 10 (9) <td>AJCC staging (8th edition)</td> <td></td>	AJCC staging (8 th edition)	
IIA10IIB27(24.5)IIA30(1.8)IVA30.7)IVB30.7)Re-rearry97(88.1)Re-rearry10.9)Re-rearry10.9)Ad-rearry10.9)Ad-rearry10.9)III length of stay (days) n = 10850.40.7)Ingth of stay (days) n = 10850.64.0.7)Ingth of stay (days) n = 10850.40.7)Ingth of stay (days) n = 10810.9)Ingth of stay (days) n = 10850.40.7)Ingth of stay (days) n = 10850.40.7)Ingth of stay (days) n = 10810.9)Ingth of stay (days) n = 10810.9)Ing	Ι	36 (32.7)
IIB 2 (24.5) IVA 3 (31.8) IVB 3 (2.7) Re-reserve 9 (98.1) Re-reserve 10 (9) Re-reserve 10 (2)	П	14 (12.7)
IVA 13 (1.8) IVB 3 (27) Reservance 3 (27) Reservance 9 (98.1) Restronmargin 10 (9) Restroncopic positive 10 (9) Restroncopic positive 10 (9) Variation details 27 (16-6.3) ICU length of stay (days) n = 108 27 (16-6.3) IPU length of stay (days) n = 108 50 (0.40.7) IPU length of stay (days) n = 108 10 (30.2) IPU length of stay (days) n = 108 10 (30.2) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (30.40.7) IPU length of stay (days) n = 108 10 (17.3) IPU length of stay (days) n = 108 10 (13.2) IPU length of stay (days) n = 108 10 (13.2) IPU length of stay (days) n = 108	ША	10 (9)
IVB3(27)R-Vertice margin9(28)R-Neqative9(28)R-Neqative10(9)R-Necocopic positive10(9)R-Vertice Mathematication10(1)R-Urlength of stay (days) n = 10%27 (16-6.3)R-DU length of stay (days) n = 17%15 (0.40.7)R-Du length of stay (days) n = 17%16 (0.40.7)R-Du length of stay (days)	ШВ	27 (24.5)
Resection margin 708.1 R0: Negative 97 (88.1) R1: Microscopic positive 10 (9) R2: Macroscopic positive 10.9 R2: Macroscopic positive 10.9 Adwission details 27 (1.6-6.3) ICU length of stay (days) n = 108 27 (1.6-6.3) IDU length of stay (days) n = 108 27 (1.6-6.3) IDU length of stay (days) n = 108 20 (0.4-0.7) Length of hospital stay 0.5 (0.4-0.7) Iconge destination 18 (1.3-2.7) Home 81 (3-2.7) I conge destination 18 (1.3-2.7) I conge destination 19 (1.3) I conge destination 19 (1.3) I conge destination facility/subacute care 9 (10.3) I conge destination facility/subacute care 19 (1.3) I conge destination 2 (1.8) Retabilitation facility/subacute care 10 (1.8) I conge destination 2 (1.8) Retabilitation facility/subacute care 2 (1.8) I conge destination 2 (1.8) I conge destination 2 (2.8)	IVA	13 (11.8)
R0: Negative 97 (88.1) R1: Microscopic positive 10.9) R2: Macroscopic positive 10.9) Ad	IVB	3 (2.7)
R1: Microscopic positive 10 (9) R2: Macroscopic positive 27 (16-6.3) IDU length of stay (days) n = 108 0.5 (0.4 · 0.7) I Length of hospital stay 0.5 (0.4 · 0.7) I Length of hospital stay 18 (13-27) I Length of hospital stay 84 (66.4) I Home 84 (66.4) I Rospital at home 54.5) I Rohabilitation facility/subacute care 9107.3) I Dath 21 (8) I Dath 21 (8) I Jourgandinsion 62 (36.6)	Resection margin	
R2: Macroscopic positive 10.9 Attristion details 2.7 (16-6.3) ICU length of stay (days) n = 108 2.7 (16-6.3) HDU length of stay (days) n = 17 0.5 (0.4-0.7) Length of hospital stay 0.5 (0.4-0.7) Icongen of hospital stay 18 (13-27) Foreign of hospital stay 18 (13-27) Home 84 (76.4) Icongen of hospital staphome 5 (45.7) Icongen of hospital staphome 5 (45.7) Icongen of hospital staphome 19 (17.3) Icongen of hospital staphome 2 (18.7) Icongen of hospital staphome 2 (18.7) Icongen of hospital staphome 2 (19.7) Icongen of hospital staphome 2 (10.7) Icongen of hospital staphome	R0: Negative	97 (88.1)
All I clu length of stay (days) n = 1082.7 (1.6-6.3)HDU length of stay (days) n = 170.5 (0.4-0.7)I rength of hospital stay0.5 (0.4-0.7)I rength of hospital stay18 (13-27)Home84 (76.4)I fonpial at home54.5I rength of inclinity/subacute care19 (17.3)I path2.1 (3.2)I path2.1 (3.2)<	R1: Microscopic positive	10 (9)
ICU length of stay (days) n = 108 2.7 (1.6-6.3) IDU length of stay (days) n = 17 0.5 (0.4-0.7) Length of hospital stay 18 (13-27) I-ungth of hospital stay 18 (13-27) I-ungth of hospital stay 18 (16-2.7) I-ungth of hospital stay 18 (13-27) I-ungth of hospital stay 19 (13-20) I-ungth of hospital stay 19 (17.3) I-ungth of hospital stay 19 (13.2)	R2: Macroscopic positive	1 (0.9)
HDU length of stay (days) n = 17 0.5 (0.4-0.7) Length of hospital stay 18 (13-27) Discharge destination 19 (17.3) Home 64 (56.4) Hospital at home 5 (4.5) Rehabilitation facility/subacute care 19 (17.3) Death 2 (1.8) Readmission 2 (1.8)	Admission details	
Length of hospital stay 18 (13-27) Discharge destination 84 (76.4) Home 84 (76.4) Hospital at home 5 (4.5) Rehabilitation facility/subacute care 19 (17.3) Death 2 (1.8) Retaction 30-day readmission	ICU length of stay (days) $n = 108$	2.7 (1.6-6.3)
Distribution 84 (76.4) Home 84 (76.4) Hospital at home 5 (4.5) Rehabilitation facility/subacute care 19 (17.3) Death 2 (1.8) Reserve 30-day readmission	HDU length of stay (days) $n = 17$	0.5 (0.4-0.7)
Home84 (76.4)Hospital at home5 (4.5)Rehabilitation facility/subacute care19 (17.3)Death2 (1.8)Re-initiation facility/subacute careJo-day readmission26 (23.6)	Length of hospital stay	18 (13-27)
Hospital at home 5 (4.5) Rehabilitation facility/subacute care 19 (17.3) Death 2 (1.8) Readmission 2 (2.8)	Discharge destination	
Rehabilitation facility/subacute care19 (17.3)Death2 (1.8)Readmission30-day readmission26 (23.6)	Home	84 (76.4)
Death2 (1.8)Readmission30-day readmission30-day readmission26 (23.6)	Hospital at home	5 (4.5)
Readmission 26 (23.6)	Rehabilitation facility/subacute care	19 (17.3)
30-day readmission 26 (23.6)	Death	2 (1.8)
	Readmission	
90-day readmission 47 (42.7)	30-day readmission	26 (23.6)
	90-day readmission	47 (42.7)



Jaisbideng® WJGS | https://www.wjgnet.com

Data are presented as count (proportion), mean ± SD, and median (interquartile range). ASA: American Society of Anesthesiology; ACCI: Age-related Charlson Comorbidity Index; ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer; ICU: Intensive care unit; HDU: High dependency unit; eGFR: Estimate glomerular filtration rate.

Table 2 Complications summary, severity grade and number, n (%)		
Clavien-Dindo highest grade	<i>n</i> = 110	
None	2 (1.8)	
I	4 (3.6)	
П	58 (52.7)	
IIIa	9 (8.2)	
Шь	13 (11.8)	
IVa	19 (17.3)	
IVb	3 (2.7)	
V	2 (1.8)	
Number of complications per patient		
0-2	10 (9)	
3-6	58 (52.7)	
>7	42 (38.1)	
Complications per patient (mean SD)	6.0 ± 2.9	

Data are presented as count (proportion) and mean ± SD.

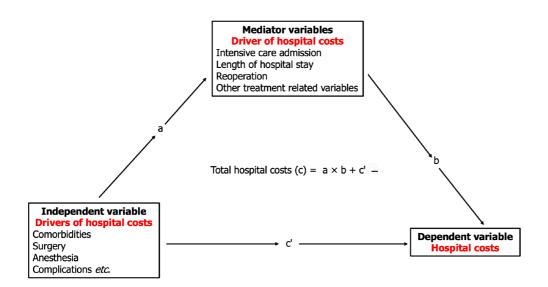


Figure 1 Mediation effects analysis model. a: The effect of drivers of hospital costs on other drivers of hospital costs; b: The effect on hospital costs; c': The direct effect of drivers of hospital costs on hospital costs adjusted to the mediator (c - ab); c: The total hospital costs, including the mediator variables. The indirect effect is the product of coefficients a and b (ab) and the difference between the c coefficient and c' coefficient (c-c').

variables have direct, indirect, and combined effects on costs.

Multiple mediation effect analyses using the generalized linear model revealed that the complications' CD severity grade (Figure 3A), the number of complications (Figure 3B), and the presence of esophagectomy key complications (Figure 3C) had significant total effects on admission cost (Supplementary Table 5). The total effects on costs were USD 13593.9 (95%CI: 10187.1-17000.8, P < 0.001) for each increase in CD severity grade, USD 4781 (95%CI: 3772.7-5789.3, P < 0.001) for each increase in the number of complications, and USD 42552.2 (95%CI: 8309.0-76795.4, P = 0.015) for key esophagectomy complications.

Table 3 Esophagectomy key complications, <i>n</i> (%)		
Complications	Grade	<i>n</i> = 110
Anastomotic leak: Full-thickness GI defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification	Type I: Local defect requiring no change in therapy or treated medically or with dietary modification	11 (10.0)
	Type II: Localized defect requiring interventional but not surgical therapy	5 (4.5)
	Type III: Localized defect requiring surgical therapy	4 (3.64)
Subtotal		20 (18.2)
Conduit necrosis/failure: Postoperative identification of conduit necrosis	Type I: Focal conduit necrosis identified endoscopically requiring monitoring or non-surgical therapy	0 (0)
	Type II: Focal conduit necrosis focal identified endoscopically and not associated with free anastomotic or conduit leak, requiring surgical therapy without esophageal diversion	2 (1.8)
	Type III: Conduit necrosis extensive requiring with conduit resection with diversion	1 (0.9)
Subtotal		3 (2.7)
Chyle leak: Milky discharge upon initiation of enteric feeds and/or	Type Ia: < 1 L output, Treatment-enteric dietary 3 modifications	3 (2.7)
pleural fluid analysis demonstrating triglyceride level > 100 mg/dL and/or chylomicrons in pleural fluid	Type Ib: > 1 L output, treated with enteric dietary modifications	0 (0)
	Type IIa: < 1 L output, treated with total parenteral nutrition	1 (0.9)
	Type IIb: > 1 L output, treated with total parenteral nutrition	0 (0)
	Type IIIa: < 1 L output, treated with interventional or surgical therapy	2 (1.8)
	Type IIIb: > 1 L output, treated with interventional or surgical therapy	5 (4.5)
Subtotal		11 (10)
	Type Ia: Unilateral injury transient injury requiring no therapy (dietary modification aloud)	5 (4.5)
	Type Ib: Bilateral injury transient injury requiring no therapy (dietary modification aloud)	0 (0)
	Type IIa: Unilateral injury requiring elective surgical procedure, for example thyroplasty or medialization procedure	3 (2.7)
	Type IIb: Unilateral injury requiring elective surgical procedure for example thyroplasty or medialization procedure	0 (0)
	Type IIIa: Unilateral injury requiring acute surgical intervention (due to aspiration or respiratory issues), for example, thyroplasty or medialization procedure	2 (1.8)
	Type IIIb: Bilateral Injury requiring acute surgical intervention (due to aspiration or respiratory issues), for example, thyroplasty or medialization procedure	3 (2.7)
Subtotal		13 (11.8)
Total		47 (42.7)

Complications are defined and graded as per the Esophageal Complications Consensus Group[19]. GI: Gastrointestinal.

The severity of complications did not have a significant direct effect on costs (P = 0.991). The total effect was partially mediated by ICU/HDU stay time (USD 7658.9, 95%CI: 5130.3-10187.6, P < 0.001), length of hospital stay (USD 4239.6, 95% CI: 2520.2-5959.0, *P* < 0.001), and emergency reoperation (USD 2381.7, 95% CI: 2011.4-2752.0, *P* < 0.001). Similarly, the direct effect of the number of complications on costs was insignificant (P = 0.889), and the total effect of each complication number increase on costs was partially mediated by the emergency reoperation variable (USD 911.6, 95% CI: 6.4-1816.9, P = 0.048).

In contrast, key esophagectomy complications significantly drove the costs directly by USD 11415.7 (95%CI: 992.5-21838.9, P = 0.032). Additionally, the total effect on costs was partially mediated by ICU/HDU stay time (USD 6951, 95% CI: 6703.9-7198.2, P < 0.001), length of hospital stay (USD 5248.1, 95% CI: 3701.4-6794.7, P < 0.001), surgery time (USD 2056.6, 95%CI: 2045.7-2067.4, *P* < 0.001), and the postoperative lowest albumin level (USD 1122.4, 95%CI: 782.8-1462.0, *P* < 0.001; Figure 3C).

Raishideng® WJGS | https://www.wjgnet.com

Table 4 Complications costs analysis - Clavien-Dindo severity grade, number of complications and esophagectomy key complication	Table 4 Complications costs an	vsis - Clavien-Dindo severit	ity grade, number of comp	lications and esophagecte	omv key complications
---	--------------------------------	------------------------------	---------------------------	---------------------------	-----------------------

	Median cost USD (IQR)
CD grade	
No complication or CD I	37427.94 (34277.96-42283.38)
CD II	43174.77 (29114.99-49366.61)
CD III	54454.79 (43421.93-78679.18) ^{a,b}
CD IV & V	76 063.38 (61 579.73-114 664.51) ^{a,b,c}
Number of complications	
0-3	29629.58 (25592.76-41683.1)
4-7	46666.14 (36410.33-58611.02) ^d
>7	75516.55 (56456.86-136612.02) ^{d,e}
Esophagectomy key complication	
No	42937.5 (29992.1-49629.0)
Yes	75516.6 (53544.1-101343.0) ^f

 $^{a}P < 0.05 vs$ no complications or Clavien-Dindo (CD) I.

 $^{b}P < 0.05 vs$ CD grade II.

 $^{c}P < 0.05 vs$ CD III.

 ${}^{d}P < 0.05 vs 0.3$ complications. ${}^{e}P < 0.05 vs 4.7$ complications.

 $^{f}P < 0.05 vs$ no key complications.

CD: Clavien-Dindo; USD: United States dollars.

DISCUSSION

This study presents a detailed cost analysis of the postoperative costs associated with esophagectomy and demonstrates the economic burden of complications on hospital costs. We found a high incidence of complications following esophagectomy, with almost all patients experiencing at least one complication and over 40% developing a major complication. In addition, one-third of the patients experienced esophagectomy-specific complications, most of which required intervention. However, despite the high rate of complications, in-hospital mortality remained low at 1.8% and below international standards[21], indicating that esophagectomy is a safe procedure when performed in a specialized center.

Relation to the literature

Our study's high overall complication rate likely reflects our meticulous perusal of patient medical records. We used a comprehensive rather than selective approach for data collection, including minor complications often neglected in other studies, and adhered strictly to the CD classification. The lack of consensus regarding the assessment of complications hampers the comparison of our results with those of previous studies. First, the studies followed a selected or elaborate repertoire of complications. For example, Carrott *et al*[22] tracked a list of 29 complications, whereas Low *et al*[21], in their multicenter benchmark study, followed a list of 48 different complications[21]. We tracked all the reported complications. Thus, we provided an accurate assessment of patients' postoperative course.

Second, studies differ in their choice of complication severity grading system. Such severity grading systems include the accordion system[22], the Society of Thoracic Surgeons consensus guidelines[23], and the CD grading system[5-7,21]. We followed the widely used and validated therapy-oriented CD grading system in alignment with the international ECCG[15]. Lastly, the authors differed in their categorization of minor and major complications. While Goense *et al*[7] defined major complications as CD grade IIIb and above, we and others[5,6], considered CD grade IIIa the cutoff for major complications. Our major complication rate (41.8%) is similar to that reported in recent studies that applied the same grading system and severity criteria[5,11].

The total admission cost for esophagectomy at our institution is comparable to the cost data reported by other international centers[5,7,22]. We used an activity-based costing methodology to underline the proportional expense components. Operating theater, intensive care, and ward care were the top contributors to total costs. These findings align with those of previous publications[5-7], and reflect the surgical and anaesthetic complexity of the operation and the high level of intensive care and ward care support required following esophagectomy.

We found that hospital costs escalate with the increasing severity of complications. Most studies have used dichotomized cost analysis to compare the costs of minor and major complications. An exception is a study by Carrott *et al*[22], which explored the gradual cost increase for each accordion severity grade. We applied a similar high-resolution approach and demonstrated that cumulative costs increase with each CD severity grade. We showed that cost increments

Raisbideng® WJGS | https://www.wjgnet.com

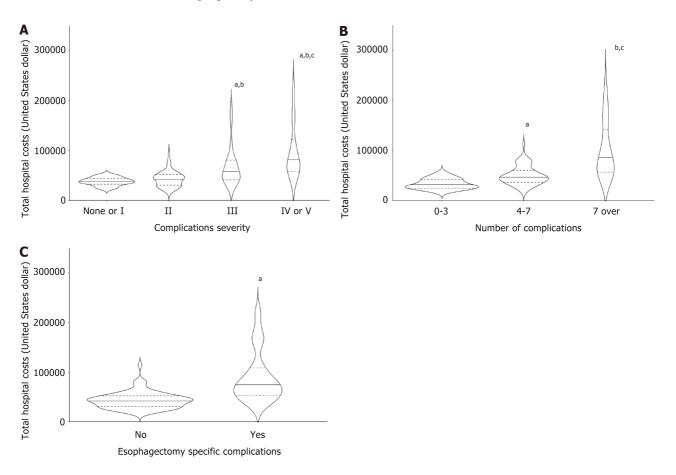


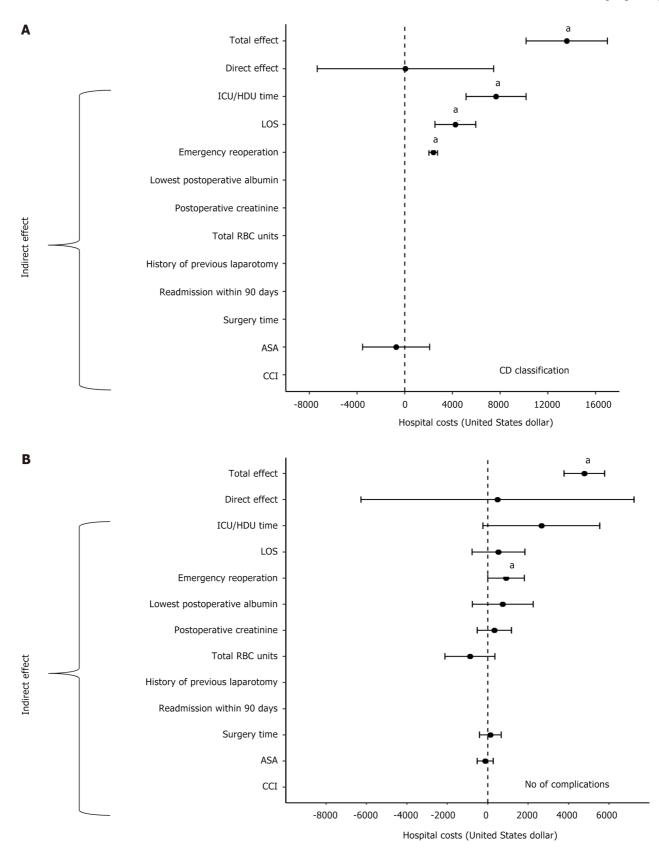
Figure 2 Unadjusted cost. A: Unadjusted cost comparison by the severity of complications. A line indicates the median, and a dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates the maximum cost range, and the width of each graph plots the kernel density estimate. Kruskal-Wallis rank sum test: $X^2 = 37.843$, df = 3, P < 0.001. Pairwise comparisons using the Wilcoxon rank sum test with continuity correction. ^aP < 0.05 vs no complication or CD I, ^bP < 0.05 vs CD II, ^bP < 0.05 vs CD III; B: Unadjusted cost comparison by the number of complications. A line indicates the median, and a dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates the maximum cost range, and the width of each graph plots the kernel density estimate. Kruskal-Wallis rank sum test: $X^2 = 47.606$, df = 2, P < 0.001. Pairwise comparisons using the Wilcoxon rank sum test with continuity correction. ^aP < 0.05 vs 0-3 complications, ^bP < 0.05 vs 4-7 complications, ^cP < 0.05 vs higher number of complications more than 7; C: Unadjusted hospital costs between the patients with and without esophagectomy specific complications. A line indicates the median and dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates the median and dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates the median and dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates maximum cost range, and the width of each graph plots the kernel density estimate. Wilcoxon rank sum test with continuity correction. ^aP < 0.05 vs 0-3 complications, ^bP < 0.05 vs higher number of complications more than 7; C: Unadjusted hospital costs between the patients with and without esophagectomy specific complications. A line indicates the median and dashed line indicates the 1st and 3rd quartiles. The height of each graph indicates maximum cost range, and the width of each graph plots the

were profoundly higher as the severity grade advanced, with the most substantial cost addition noted between CD grades III and IV-V. Likewise, an increasing number of complications induced a marked cost escalation, particularly in patients with seven or more complications. The rise in cost associated with the increased number of complications has been explored in other major procedures[2-4], but has not yet been quantified in the context of esophagectomy.

We applied mediation analysis to expose the underlying mechanism by which severity and the number of complications (independent variables) drive costs (dependent variable)[18]. Mediation analysis decomposes the effect of the severity and number of complications into their direct effect on costs and the indirect effect through a mediator cost driver variable. Our results suggest that the severity of complications does not have a significant direct effect on total costs. Instead, the effect is indirect and mediated by ICU/HDU stay, length of hospital stay, and emergency reoperation. Similarly, the cumulative effect of each increase in the number of complications on total admission costs was indirectly mediated by emergency reoperation.

Several factors could explain our findings. First, the post-esophagectomy complication rate is high, and many patients experience major complications. Therefore, the cost increase is generated by the consecutive economic burden of the medical activity required for their treatment: Readmission to the ICU, reoperation, and prolonged hospital stay. Further, reoperation and intensive care were the most significant contributors to the overall cost, and as others showed previously, expenditure for both rose drastically in patients with major complications[9-11]. Finally, as demonstrated by Goense *et al* [7], the length of stay is significantly prolonged once a patient experiences a complication, leading to further expenses for multiple medical activities.

The documentation of four key complications is considered essential for quality and outcome monitoring in centers performing esophagectomy[15]. Each of the four complications was individually evaluated in previous cost analyses. Complications found to significantly increase costs (in both univariate and multivariate analyses) included anastomotic leak[7,22], chyle leak[7], and laryngeal nerve palsy[6]. Our study examined all four complications as a group. We illustrated the substantial contribution of esophagectomy-specific complications to total hospital costs, adding USD 46417 to the mean cost for patients without these key complications. Our mediation analysis confirmed that key esophagectomy



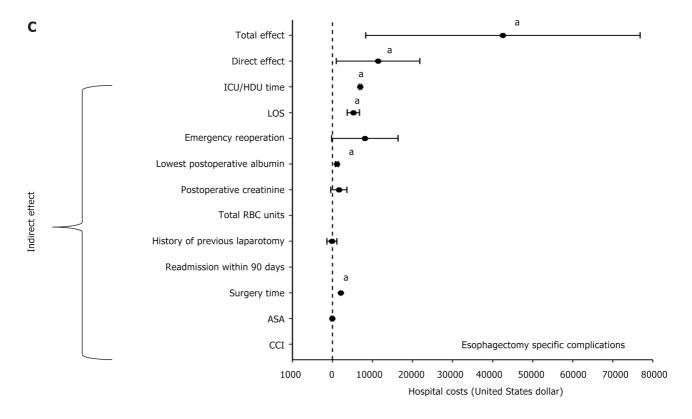


Figure 3 Mediation analyses for complications. A: Mediation analyses for severity of complications. The indirect, mediator adjusted direct, and the total effects are presented; B: Mediation analyses for the number of complications. The indirect, mediator adjusted direct, and the total effects are presented; C: Mediation analyses for esophagectomy key complications. The indirect, mediator adjusted direct, and the total effects are presented. ^a*P* < 0.05; ICU: Intensive care unit; HDU: High dependency unit; LOS: RBC: ASA: American Society of Anesthesiology; CCI: Charlson comorbidity index; CD: Clavien-Dindo.

complications directly increase the total costs while also partially driving costs through various mediator variables, mainly ICU/HDU time and length of hospital stay and, to a lesser extent, surgery time and lowest albumin levels. These findings indicate that preventing esophagectomy-specific complications is an important target when developing a cost-effective intervention strategy.

Study implications

Our findings highlight the need to monitor and optimize the outcomes of patients undergoing esophageal resection. To achieve this objective, it is necessary to minimize the number of complications and mitigate their severity. Complications were linked to reduced quality of life and survival[6,22,24]. Therefore, targeting complications will diminish expenditure while promoting better short- and long-term outcomes. Proactive interventions to improve patients' ability to withstand surgical stress and modify postoperative morbidity include smoking cessation, optimization of background comorbidities, and preoperative exercise. All these interventions were undertaken in our patient cohort as part of an ERAS program. Recent data showed that the use of personalized, non-selective multimodal prehabilitation for all esophagectomy candidates (regardless of frailty status), including aerobic and strength exercise, nutritional optimization, and psychological support (to improve patient wellbeing and engagement), reduced pulmonary complications and length of stay[25]. However, the incidence and severity of complications were not significantly different, indicating that further research is needed to optimize esophagectomy outcomes.

The benefits of ERAS programs in reducing morbidity are now established across multiple surgical procedures, including esophagectomy[26]. A meta-analysis from 2017 reviewing ERAS for esophagectomy showed reduced non-surgical complications and length of stay but not reduced surgical complications[27]. The ERAS Society Guidelines statement from 2019 addressed these issues and provided evidence-based recommendations for preoperative, operative, and postoperative care[11]. A recent study showed that the successful application of the revised ERAS reduced the number and severity of complications (both surgical and medical), the reoperation rate, and the length of stay. However, adherence to the protocol was most affected by postoperative complications[26]. The development of ERAS protocol modifications for patients with complications may help moderate their consequences.

Prevention and management of the four key esophagectomy complications are challenging. The optimization of surgical techniques can reduce their prevalence. In addition, high suspicion, early diagnosis, and prompt intervention can preclude patient decompensation[27]. Prevention and intervention strategies have been thoroughly discussed in the literature. Examples include avoidance or judicious use of vasopressors, operative optimization of conduit blood supply, tension-free anastomosis to reduce anastomotic leak and conduit necrosis[28], thoracic anastomosis to reduce recurrent laryngeal nerve injury and early medialization to prevent aspiration[29], and selective thoracic duct ligation for patients with positive intraoperative provocative chyle leak test[30]. Studies investigating superior techniques and technique

[®] WJGS https://www.wjgnet.com

optimization continue to be paramount.

Surgical volume is linked to a reduced complication rate and severity when comparing high-volume units to lowvolume units and high-volume vs low-volume surgeons within a high-volume unit[31,32]. Most centers in Australia, including ours, are medium-volume centers based on international standards. Therefore, reduced morbidity and consequent cost savings may be achieved by centralizing esophagectomy.

Strengths and limitations

Applying actual financial costs using hospital data and activity-based methodology rather than registers or insurance claims[6], provided an accurate account of the financial burden associated with all treatment components of esophagectomy and allowed us to identify the costliest medical interventions. We applied the widely used and validated CD complication severity grading system^[14], and extracted data directly from patient files to ensure accuracy in the classification of severity. Lastly, we provide a unique insight into the complex effect of complications on admission costs, being the first to use mediation analysis.

The limitations of our study include its retrospective design and the relatively small sample size of a single center setup. A multicenter analysis could validate our findings and guide future interventions. Most of the procedures were open, and a comparative analysis of the minimally invasive approach was not performed. Additionally, we focused on short-term costs and outcomes during index admission or readmission within 30 days. Therefore, the financial implications of late- or long-term clinical and economic outcomes were not assessed and are areas for future research.

CONCLUSION

Complications after esophagectomy are common, resulting in a heavy financial burden and compromising patient outcomes. Our findings demonstrated that the severity and number of complications and the presence of key complications of esophagectomy significantly contributed to total hospital costs. We showed that the effect of the severity and the number of complications on admission cost was mediated through the costs of reoperation, prolonged ICH/HDU stay, and prolonged hospital stay, namely, activities known for their highest resource use. The effect of the presence of esophagectomy key complications was partially mediated but retained a significant direct effect on costs. This study highlights the importance of a continuous institutional quality review to prevent and mitigate complications, and the need for improved intervention strategies to enhance patient outcomes and minimize costs. Additionally, our analysis of cost drivers may shed insights into standardizing the way cost outcomes should be measured.

FOOTNOTES

Author contributions: Buchholz V and Weinberg L designed the research study and wrote the paper; Lee DK analyzed the data; Liu DS, Aly A, Barnett SA, Hazard R, Kioussis B, Le P and Muralidharan V assisted with data collection and wrote the study; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Austin Health Human Research Ethics Committee, Approval No. Audit/19/Austin/103.

Informed consent statement: A waiver of participant consent was provided by the Austin Health Research Ethics Committee.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The full dataset is available as a Supplementary material.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/

Country of origin: Australia

ORCID number: Vijayaragavan Muralidharan 0000-0001-8247-8937; Laurence Weinberg 0000-0001-7403-7680.

Corresponding Author's Membership in Professional Societies: Australian & New Zealand College of Anaesthetists, 15766; Medical Practitioners Board of Australia, MED0001200466.

S-Editor: Li L L-Editor: A P-Editor: Zhang XD



REFERENCES

- 1 Porter ME. What is value in health care? N Engl J Med 2010; 363: 2477-2481 [PMID: 21142528 DOI: 10.1056/NEJMp1011024]
- Cosic L, Ma R, Churilov L, Debono D, Nikfarjam M, Christophi C, Weinberg L. The financial impact of postoperative complications 2 following liver resection. Medicine (Baltimore) 2019; 98: e16054 [PMID: 31277099 DOI: 10.1097/MD.000000000016054]
- Johnston SA, Louis M, Churilov L, Ma R, Marhoon N, Bui A, Christophi C, Weinberg L. The financial burden of complications following 3 rectal resection: A cohort study. Medicine (Baltimore) 2020; 99: e20089 [PMID: 32384480 DOI: 10.1097/MD.000000000020089]
- Short MN, Aloia TA, Ho V. The influence of complications on the costs of complex cancer surgery. Cancer 2014; 120: 1035-1041 [PMID: 4 24382697 DOI: 10.1002/cncr.28527]
- 5 Browning AF, Chong L, Read M, Hii MW. Economic burden of complications and readmission following oesophageal cancer surgery. ANZ J Surg 2022; 92: 2901-2906 [PMID: 36129457 DOI: 10.1111/ans.18062]
- Löfgren A, Åkesson O, Johansson J, Persson J. Hospital costs and health-related quality of life from complications after esophagectomy. Eur J 6 Surg Oncol 2021; 47: 1042-1047 [PMID: 33032864 DOI: 10.1016/j.ejso.2020.09.032]
- 7 Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol 2017; 43: 696-702 [PMID: 28012715 DOI: 10.1016/j.ejso.2016.11.013]
- Park MG, Haro G, Mabeza RM, Sakowitz S, Verma A, Lee C, Williamson C, Benharash P. Association of frailty with clinical and financial 8 outcomes of esophagectomy hospitalizations in the United States. Surg Open Sci 2022; 9: 80-85 [PMID: 35719414 DOI: 10.1016/j.sopen.2022.05.003
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of 9 Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335: 806-808 [PMID: 17947786 DOI: 10.1136/bmj.39335.541782.AD]
- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. 10 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007; 18: 805-835 [PMID: 18049195 DOI: 10.1097/EDE.0b013e3181577511]
- Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, Law S, Lindblad M, Maynard N, Neal J, Pramesh CS, Scott M, 11 Mark Smithers B, Addor V, Ljungqvist O. Guidelines for Perioperative Care in Esophagectomy: Enhanced Recovery After Surgery (ERAS(®)) Society Recommendations. World J Surg 2019; 43: 299-330 [PMID: 30276441 DOI: 10.1007/s00268-018-4786-4]
- National Blood Authority. Blood Management Guidelines: Module 2, Perioperative. 2012. [cited 23 June 2024]. Available from: https:// 12 20Perioperative.PDF
- Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to 13 clinical practice. Ann Cardiothorac Surg 2017; 6: 119-130 [PMID: 28447000 DOI: 10.21037/acs.2017.03.14]
- 14 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
- 15 Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, Griffin SM, Hölscher AH, Hofstetter WL, Jobe BA, Kitagawa Y, Kucharczuk JC, Law SY, Lerut TE, Maynard N, Pera M, Peters JH, Pramesh CS, Reynolds JV, Smithers BM, van Lanschot JJ. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015; 262: 286-294 [PMID: 25607756 DOI: 10.1097/SLA.000000000001098]
- 16 Peterson BG, Boudt K, Bennett R, Ulrich J, Zivot E, Cornilly D, Hung E, Lestel M, Balkissoon K, Wuertz D, Christidis AA, Martin, Zeheng RD, Zhou ZZ, Shea JM. Performance Analytics: Econometric Tools for Performance and Risk Analysis. R package version 2.0.4. Feb 6, 2020. [cited 23 June 2024]. Available from: https://cran.r-project.org/web/packages/PerformanceAnalytics/index.html, 2020
- Kuhn M, Jackson S, Cimentada J. corrr: Correlations in R, version 0.4.4. 2022. [cited 23 June 2024]. Available from: https://corrr.tidymodels. 17 org
- 18 Rijnhart JJM, Lamp SJ, Valente MJ, MacKinnon DP, Twisk JWR, Heymans MW. Mediation analysis methods used in observational research: a scoping review and recommendations. BMC Med Res Methodol 2021; 21: 226 [PMID: 34689754 DOI: 10.1186/s12874-021-01426-3
- MacKinnon DP, Pirlott AG. Statistical approaches for enhancing causal interpretation of the M to Y relation in mediation analysis. Pers Soc 19 Psychol Rev 2015; 19: 30-43 [PMID: 25063043 DOI: 10.1177/1088868314542878]
- Yu QZ, Li B. mma: Multiple Mediation Analysis. R package version 10.6-1. "mma" is an R package for mediation analysis with multiple 20 mediators that produces complex mediation models and functioans to identify mediators and statistical inference on mediation effects. 2022. [cited 23 June 2024]. Available from: https://cran.r-project.org/web/packages/mma/index.html
- 21 Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, Davies A, D'Journo XB, Gisbertz SS, Griffin SM, Hardwick R, Hoelscher A, Hofstetter W, Jobe B, Kitagawa Y, Law S, Mariette C, Maynard N, Morse CR, Nafteux P, Pera M, Pramesh CS, Puig S, Reynolds JV, Schroeder W, Smithers M, Wijnhoven BPL. Benchmarking Complications Associated with Esophagectomy. Ann Surg 2019; 269: 291-298 [PMID: 29206677 DOI: 10.1097/SLA.00000000002611]
- Carrott PW, Markar SR, Kuppusamy MK, Traverso LW, Low DE. Accordion severity grading system: assessment of relationship between 22 costs, length of hospital stay, and survival in patients with complications after esophagectomy for cancer. J Am Coll Surg 2012; 215: 331-336 [PMID: 22683069 DOI: 10.1016/j.jamcollsurg.2012.04.030]
- Geller AD, Zheng H, Gaissert H, Mathisen D, Muniappan A, Wright C, Lanuti M. Relative Incremental Cost of Postoperative Complications 23 of Esophagectomy. Semin Thorac Cardiovasc Surg 2019; 31: 290-299 [PMID: 30391498 DOI: 10.1053/j.semtcvs.2018.10.010]
- Rutegård M, Lagergren P, Rouvelas I, Mason R, Lagergren J. Surgical complications and long-term survival after esophagectomy for cancer 24 in a nationwide Swedish cohort study. Eur J Surg Oncol 2012; 38: 555-561 [PMID: 22483704 DOI: 10.1016/j.ejso.2012.02.177]
- Halliday LJ, Doganay E, Wynter-Blyth VA, Hanna GB, Moorthy K. The Impact of Prehabilitation on Post-operative Outcomes in 25 Oesophageal Cancer Surgery: a Propensity Score Matched Comparison. J Gastrointest Surg 2021; 25: 2733-2741 [PMID: 33269459 DOI: 10.1007/s11605-020-04881-3]
- Puccetti F, Klevebro F, Kuppusamy M, Han S, Fagley RE, Low DE, Hubka M. Analysis of Compliance with Enhanced Recovery After 26 Surgery (ERAS) Protocol for Esophagectomy. World J Surg 2022; 46: 2839-2847 [PMID: 36138318 DOI: 10.1007/s00268-022-06722-7]
- 27 Pisarska M, Małczak P, Major P, Wysocki M, Budzyński A, Pedziwiatr M. Enhanced recovery after surgery protocol in oesophageal cancer



surgery: Systematic review and meta-analysis. PLoS One 2017; 12: e0174382 [PMID: 28350805 DOI: 10.1371/journal.pone.0174382]

- Fabian T. Management of Postoperative Complications After Esophageal Resection. Surg Clin North Am 2021; 101: 525-539 [PMID: 28 34048771 DOI: 10.1016/j.suc.2021.03.013]
- Friedman AD, Burns JA, Heaton JT, Zeitels SM. Early versus late injection medialization for unilateral vocal cord paralysis. Laryngoscope 29 2010; 120: 2042-2046 [PMID: 20824787 DOI: 10.1002/lary.21097]
- Lin Y, Li Z, Li G, Zhang X, Deng H, Yang X, Liu L. Selective En Masse Ligation of the Thoracic Duct to Prevent Chyle Leak 30 After Esophagectomy. Ann Thorac Surg 2017; 103: 1802-1807 [PMID: 28385376 DOI: 10.1016/j.athoracsur.2017.01.025]
- Munasinghe A, Markar SR, Mamidanna R, Darzi AW, Faiz OD, Hanna GB, Low DE. Is It Time to Centralize High-risk Cancer Care in the 31 United States? Comparison of Outcomes of Esophagectomy Between England and the United States. Ann Surg 2015; 262: 79-85 [PMID: 24979602 DOI: 10.1097/SLA.000000000000805]
- Dolan D, White A, Lee DN, Mazzola E, Polhemus E, Kucukak S, Wee JO, Swanson SJ. Short and Long-term Outcomes Among High-Volume 32 vs Low-Volume Esophagectomy Surgeons at a High-Volume Center. Semin Thorac Cardiovasc Surg 2022; 34: 1340-1350 [PMID: 34560249 DOI: 10.1053/j.semtcvs.2021.09.007]





Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: office@baishideng.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

