European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Mortality from esophagectomy for esophageal cancer across low, middle, and high-income countries: An international cohort study

Oesophago-Gastric Anastomotic Audit (OGAA) Collaborative: Writing Committee, Steering Committee, National Leads, Site Leads, Collaborators

ARTICLE INFO

Article history:
Accepted 9 December 2020
Available online xxx

Keywords:
Global surgery
Esophagectomy
Anastomotic leak
Postoperative mortality

ABSTRACT

Background: No evidence currently exists characterising global outcomes following major cancer surgery, including esophageal cancer. Therefore, this study aimed to characterise impact of high income countries (HIC) versus low and middle income countries (LMIC) on the outcomes following esophagectomy for esophageal cancer.

Method: This international multi-center prospective study across 137 hospitals in 41 countries included patients who underwent an esophagectomy for esophageal cancer, with 90-day follow-up. The main explanatory variable was country income, defined according to the World Bank Data classification. The primary outcome was 90-day postoperative mortality, and secondary outcomes were composite leaks (anastomotic leak or conduit necrosis) and major complications (Clavien-Dindo Grade III - V). Multivariable generalized estimating equation models were used to produce adjusted odds ratios (ORs) and 95% confidence intervals ($CI_{95\%}$).

Results: Between April 2018 to December 2018, 2247 patients were included. Patients from HIC were more significantly older, with higher ASA grade, and more advanced tumors. Patients from LMIC had almost three-fold increase in 90-day mortality, compared to HIC (9.4% vs 3.7%, $p < 0.001$). On adjusted analysis, LMIC were independently associated with higher 90-day mortality (OR: 2.31, $CI_{95\%}$: 1.17–4.55, $p = 0.015$). However, LMIC were not independently associated with higher rates of anastomotic leaks (OR: 1.06, $CI_{95\%}$: 0.57–1.99, $p = 0.9$) or major complications (OR: 0.85, $CI_{95\%}$: 0.54–1.32, $p = 0.5$), compared to HIC.

Conclusion: Resections in LMIC were independently associated with higher 90-day postoperative mortality, likely reflecting a failure to rescue of these patients following esophagectomy, despite similar composite anastomotic leaks and major complication rates to HIC. These findings warrant further research, to identify potential issues and solutions to improve global outcomes following esophagectomy for cancer.

© 2020 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Introduction

Esophageal cancer remains a major cause of cancer mortality and disease burden across the world [1–4], accounting for almost 500,000 deaths in 2017, according to data from the Global Burden of Disease study. Further, these mortality rates are as much as five-fold higher in low/middle income countries (LMIC), compared to high income countries (HIC) [4,5]. Although esophagectomy is the mainstay of curative treatment for esophageal adenocarcinoma, and some with esophageal squamous cell carcinoma (SCC), it remains a technically complex operation associated with high postoperative morbidity, and a 90-day mortality rate as high as 14% [6]. Anastomotic leaks and/or conduit necrosis are common complications, and are associated with high mortality, prolonged hospital stay, reduced quality of life and increased hospital costs [7–10].

Over the last decade, increasing evidence has demonstrated that country income is associated with worse perioperative mortality following surgery [11]. However, there are currently no global data to quantify outcomes of complex cancer surgery, such as esophagectomy for esophageal cancers. Previous multi-center studies

* Corresponding author. Department of Upper Gastrointestinal Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom.

https://doi.org/10.1016/j.ejso.2020.12.006
0748-7983/© 2020 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Please cite this article as: X. Lu, Mortality from esophagectomy for esophageal cancer across low, middle, and high-income countries: An international cohort study, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.12.006

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

have mainly come from high-volume Western centers, hence lack exploratory analyses by country income [6,12]. Understanding these disparities in mortality within cancer surgery will allow for identification of areas for improvement within these healthcare systems, hence improving global cancer outcomes. Therefore, there exists an unmet need to measure outcomes, especially post-operative mortality rates [13], following elective esophagectomy for esophageal cancers.

The Oesophagogastric Anastomosis Audit (OGAA) is an international multi-center collaborative, aiming to evaluate the impact of country income on postoperative mortality following esophagectomy for esophageal cancers. The secondary aims of this study were to evaluate disparities by country income in postoperative outcomes following esophagectomy, such as anastomotic leaks, conduit necrosis and major complications.

Methods

Study design and setting

This study is an analysis of the Oesophagogastric Anastomosis Audit (OGAA) dataset, an international multi-center prospective study including 141 centers across 41 countries [14]. Data were collected prospectively across these centers over a nine-month period from April 1, 2018 to December 31, 2018. All patients were followed-up for 90 days following surgery. The research collaborative model has been described previously, successfully delivering a number of international and national cohort studies [15]. A consultant or attending surgeon supervised data collection at each site, ensuring that it was performed in accordance with a pre-specified protocol.

Ethics and reporting

Ethical approval was dependent on local protocols and was country-specific. It was the responsibility of the local principal investigator of the enrolled unit to ensure appropriate ethical or audit approval was gained prior to commencement of the study. Ongoing study approval was maintained locally throughout the duration of the study. In the UK, the study was registered at each site as either clinical audit or service evaluation, as it was an observational study and was designed to collect routine, anonymized data, with no change to the clinical care pathway.

Inclusion and exclusion criteria

During the pre-defined data collection period, all consecutive adult patients undergoing elective (planned) esophagectomy for esophageal cancer were included. All surgical approaches (two-stage Ivor Lewis, three-stage McKeown, thoracoabdominal, transhiatal using any combination of open, robotic or standard minimal access approaches) were included, as were thoracic and cervical anastomotic locations. Exclusion criteria were: (i) extended total gastrectomy; (ii) pharyngolaryngo-esophagectomy; (iii) colonic interposition or small bowel jejunal interposition reconstructions; (iv) emergency resections; and (v) resections for benign disease, as previously described [16,17].

Outcome measures

The primary outcome was 90-day postoperative mortality, with the day of index operation taken as day zero. The secondary outcomes were a composite outcome of anastomotic leak or conduit necrosis, major complications, length of stay (both in the intensive care unit [ICU] and overall), return to theatre, and 30-day mortality. Anastomotic leaks were defined as a full thickness GI defect involving the oesophagus, anastomosis, staple line, or conduit, irrespective of presentation or method of identification, and classified as Grade 1, 2 or 3, in accordance with the ECCG framework [6]. Conduit necrosis was also defined in accordance to the ECCG framework [6]. Major complications were defined as those of Clavien-Dindo Grade III-V [17].

Explanatory variable

The main explanatory variable was country income, with

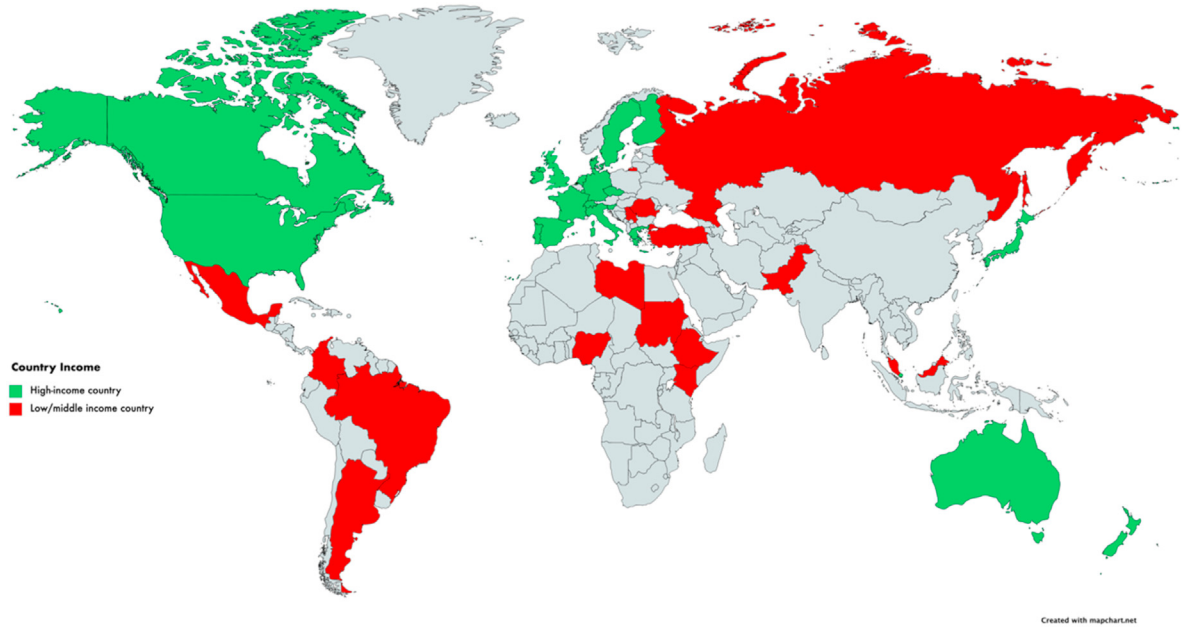

Fig. 1. Distribution of countries involved in the study by high income and low/middle income.

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

Table 1
Center-level factors associated with low/middle income and high-income countries of patients undergoing esophagectomy for esophageal cancers.

	Number of Centers	LMIC	HIC	p-value
Number of Patients	137			**<0.001**
During Study Period*		4 (3–10)	13 (7–27)	
Estimated Number per Year**		5 (4–13)	17 (9–36)	
Number of Consultants	134	3 (2–4)	3 (2–5)	0.1
Number of Beds	134	330 (195–731)	800 (450–1086)	**<0.001**
Number of ICU Beds	134	20 (11–40)	24 (16–36)	0.4
On-Call Rota	134			0.8
None		3 (10%)	14 (13%)	
Weekdays - Daytime Only		2 (7%)	11 (11%)	
Weekdays - 24 h		1 (3%)	2 (2%)	
Every Day - Daytime Only		2 (7%)	4 (4%)	
Every Day - 24 h		22 (73%)	73 (70%)	
Radiology On-Call	134			**<0.001**
None		11 (37%)	7 (7%)	
Weekdays - Daytime Only		5 (17%)	11 (11%)	
Weekdays - 24 h		1 (3%)	0 (0%)	
Every Day - Daytime Only		3 (10%)	4 (4%)	
Every Day - 24 h		10 (33%)	82 (79%)	
ERAS Protocol	134	8 (27%)	59 (57%)	**0.006**
ERAS Nurse	134	4 (13%)	28 (27%)	0.2
Dedicated Physiotherapy Input	134			0.1
Nil dedicated		9 (30%)	11 (11%)	
Weekdays - Daily		11 (37%)	35 (34%)	
Weekdays - Twice Daily		3 (10%)	11 (11%)	
Every Day - Daily		6 (20%)	35 (34%)	
Every Day - Twice Daily		1 (3%)	12 (12%)	

Data are reported as N (%), with p-values from Fisher's exact tests, or as median (interquartile range), with p-values from Mann-Whitney U tests, as applicable. Bold p-values are significant at $p < 0.05$. *The number of patients contributed to the study by each center during the 9 months study period. **The estimated number of patients per year, extrapolated from the 9-month totals. Abbreviations: ERAS - enhanced recovery after surgery, HIC - high income countries, ICU - intensive care unit, LMIC - low-middle income countries.

centers being classified as being from high-income (HIC) or low- or middle-income countries (LMIC), according to the World Bank Data [18]. A range of center-, patient-, tumor- and treatment-related factors were assessed, and considered for inclusion in the multivariable analysis. Data for a range of center-specific variables were also collected, but only the center volume was considered as a confounding factor in the multivariable analysis, as this have been demonstrated to be an important marker of perioperative outcomes [19,20]. The center volume was based on the number of cases treated by each center during the study period (nine months), from which the number of cases per year was then estimated. The resulting variable was then categorized for analysis, based on tertiles, such that there were approximately equal numbers of patients in each category. The resulting categories were <28 (n = 94 centers; HIC - 68, LMIC - 26), 28–50 (n = 28 centers; HIC - 25, LMIC - 3) and >50 cases (n = 15 centers, HIC - 13, LMIC - 2) per year. The TNM staging was based on pathology and used the 8th edition definitions [21].

Data collection

Individual patient data were entered into case report forms (CRFs), which were for data recording only, and designed not to deviate from safe patient care or instigate patient intervention. Case report forms (CRFs) were trialed in a two-month pilot, to ensure full key data acquisition; pilot data was not used in the analysis and reporting of the OGAA. Data input was via a dedicated encrypted server through the Research Electronic Data Capture (REDCap) web application. No patient identifiable information was entered into the database. The Birmingham Surgical Trials Consortium, University of Birmingham, hosted the REDCap system.

Statistical analyses

The study was conducted according to STROBE guidelines for observational studies [22]. Initially, center-level data were compared between those centers from LMIC and HIC. Continuous variables that were normally distributed were reported as mean ± standard deviation (SD), with p-values from independent sample t-tests, with medians and interquartile ranges (IQRs) and Mann-Whitney U tests used otherwise. Ordinal variables were also assessed using Mann-Whitney U tests, whilst nominal variables were analysed using Fisher's exact tests or Chi [2] tests, for variables with two or more than two categories, respectively. Patient-level data was then compared between the two groups using the same approach.

Multivariable analyses were then performed, to assess whether any differences between LMIC and HIC were independent of other prognostic or potentially confounding factors. This analysis used a generalized estimating equation (GEE) approach, to account for the multi-level structure of the data, by adjusting for within-center correlations of outcomes. As such, the center was set as the subject effect, and the patient ID as the within-subject effect, with an exchangeable correlation structure assumed. The country income group was entered into the model at the first step, with a backwards stepwise approach, using $p > 0.1$ as the criteria for exclusion, employed to identify which of the other factors were independent predictors of outcome. Prior to the analysis, the goodness of fit of continuous factors were assessed graphically, with variables being divided into categories where poor fit was detected. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p < 0.05$ deemed to be indicative of statistical significance throughout.

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

Table 2
Patient-, tumor- and treatment-level factors associated with low/middle income and high-income countries of patients undergoing esophagectomy for esophageal cancers.

	Number of Cases	LMIC	HIC	p-Value
Patient factors				
Age (Years)	2247	55.7 ± 12.0	65.2 ± 9.7	**<0.001**
Gender (% Male)	2247	204 (66.2%)	1563 (80.6%)	**<0.001**
Body Mass Index, kg/m^2	2240	22.6 ± 4.5	26.8 ± 5.1	**<0.001**
ASA Grade	2246			**<0.001***
1		75 (24.4%)	223 (11.5%)	
2		188 (61.0%)	1072 (55.3%)	
3		41 (13.3%)	625 (32.2%)	
4		4 (1.3%)	18 (0.9%)	
ECOG Status	2241			**<0.001***
0		128 (41.6%)	1236 (63.9%)	
1		141 (45.8%)	594 (30.7%)	
2		32 (10.4%)	91 (4.7%)	
3		7 (2.3%)	9 (0.5%)	
4		0 (0.0%)	3 (0.2%)	
Charlson Comorbidity Index	2247	5 (4–6)	6 (5–7)	**<0.001**
COPD	2247	48 (15.6%)	259 (13.4%)	0.3
Diabetes	2247	26 (8.4%)	245 (12.6%)	**0.038**
Cardiovascular Disease	2247	15 (4.9%)	327 (16.9%)	**<0.001**
Smoking Status	2183			**<0.001**
Never		155 (50.8%)	687 (36.6%)	
Ex-smoker		105 (34.4%)	896 (47.7%)	
Current		45 (14.8%)	295 (15.7%)	
Tumor factors				
Histology	2246			**<0.001**
Adenocarcinoma		93 (30.2%)	1560 (80.5%)	
Squamous Cell Carcinoma		203 (65.9%)	331 (17.1%)	
Other		12 (3.9%)	47 (2.4%)	
Tumor Location	2246			**<0.001**
Proximal		15 (4.9%)	42 (2.2%)	
Middle		62 (20.1%)	179 (9.2%)	
Distal/Siewert 1-2		222 (72.1%)	1661 (85.7%)	
Siewert 3		9 (2.9%)	56 (2.9%)	
TNM Stage (on Pathology)	2223			**0.005***
Stage 0		62 (20.3%)	262 (13.7%)	
Stage I		34 (11.1%)	309 (16.1%)	
Stage II		75 (24.5%)	275 (14.3%)	
Stage III		78 (25.5%)	659 (34.4%)	
Stage IV		57 (18.6%)	412 (21.5%)	
Treatment factors				
Preoperative Nutrition	2245			**<0.001**
None		132 (42.9%)	993 (51.3%)	
Oral Supplements		94 (30.5%)	742 (38.3%)	
Enteral Tube Nutrition		75 (24.4%)	173 (8.9%)	
Parenteral Nutrition		7 (2.3%)	29 (1.5%)	
Neoadjuvant Therapy	2247			**<0.001**
None		131 (42.5%)	429 (22.1%)	
Chemoradiotherapy		153 (49.7%)	648 (33.4%)	
Chemotherapy alone		21 (6.8%)	858 (44.2%)	
Radiotherapy alone		3 (1.0%)	4 (0.2%)	
Postoperative Nutrition	2246			**<0.001**
None		56 (18.2%)	804 (41.5%)	
Feeding Jejunostomy		113 (36.7%)	990 (51.1%)	
Nasojejunal tube		139 (45.1%)	144 (7.4%)	
Technical factors				
Anastomosis Technique**	2243			**<0.001**
Circular Stapled		52 (16.9%)	1112 (57.5%)	
Handsewn		182 (59.1%)	427 (22.1%)	
Linear Stapled		74 (24.0%)	396 (20.5%)	
Anastomosis Site**	2238			**<0.001**
Chest		90 (29.3%)	1636 (84.7%)	
Neck		217 (70.7%)	295 (15.3%)	
Abdominal Phase	2234			**0.002**
Minimally Invasive		138 (45.4%)	1059 (54.9%)	
Open		166 (54.6%)	871 (45.1%)	
Thoracic Phase	2241			**<0.001**
Minimally Invasive		151 (49.5%)	588 (30.4%)	
Open		107 (35.1%)	1269 (65.5%)	
Transhiatal		47 (15.4%)	79 (4.1%)	
Positive Margins	2247	39 (12.7%)	369 (19.0%)	**0.007**

Categorical data are reported as N (%), with p-values from Fisher's exact test or Chi [2] test for factors with two or more than two factors, respectively, unless stated otherwise. Continuous data are reported as mean ± SD, with p-values from independent samples t-tests, or as median (interquartile range), with p-values from Mann-Whitney U tests, as applicable. Bold p-values are significant at $p < 0.05$. *p-Value from Mann-Whitney U test, as the factor is ordinal. **Excludes N = 4 patients were no anastomosis was performed. Abbreviations: ASA - American Society of Anaesthesiology, COPD - Chronic Obstructive Pulmonary Disease, ECOG - Eastern Cooperative Oncology Group, HIC - high income countries, LMIC - low-middle income countries.

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

Table 3
Postoperative outcomes associated with low/middle income and high-income countries in patients undergoing esophagectomy for esophageal cancer.

	Number of Cases	LMIC	HIC	p-Value
Primary Outcome				
90-Day Mortality	2247	29 (9.4%)	71 (3.7%)	**<0.001**
Secondary Outcomes				
Anastomotic Leak/Conduit Necrosis	2247	51 (16.6%)	278 (14.3%)	0.3
Anastomotic Leak/Conduit Necrosis Grade	2247			0.3*
None		257 (83.4%)	1661 (85.7%)	
Grade 1		29 (9.4%)	133 (6.9%)	
Grade 2		6 (1.9%)	73 (3.8%)	
Grade 3		16 (5.2%)	72 (3.7%)	
Any Complication	2247	168 (54.5%)	1261 (65.0%)	**<0.001**
Clavien-Dindo Grade III-V Complication	2247	72 (23.4%)	500 (25.8%)	0.4
ICU Length of Stay (Days)	2234	3 (1–6)	3 (2–7)	**0.031**
Total Length of Stay (Days)	2234	12 (9–19)	12 (9–18)	0.4
Return to Theatre	2247	32 (10.4%)	237 (12.2%)	0.4
30 Day Mortality	2247	26 (8.4%)	45 (2.3%)	**<0.001**

Categorical data are reported as N (%), with p-values from Fisher's exact test or Chi [2] test for factors with two, or more than two factors, respectively, unless stated otherwise. Continuous data are reported as median (interquartile range), with p-values from Mann-Whitney U tests. Bold p-values are significant at $p < 0.05$. *p-Value from Mann-Whitney U test, as the factor is ordinal. Abbreviations: HIC - high income countries, LMIC - low-middle income countries, ICU - intensive care unit.

Results

Center-level factors

This study included 2247 patients undergoing esophagectomy across 137 centers (106 HIC, 31 LMIC) (Fig. 1). HIC centers contributed a significantly higher volume of cases to the study (median: 13 vs 4 per center, $p < 0.001$) and had a higher number of total hospital beds (median: 800 vs 330 beds, $p < 0.001$). The HIC group were also significantly more likely to have an on-call radiology service accessible 24 h every day (79%, vs. 33%, $p < 0.001$) and to employ an enhanced recovery after surgery (ERAS) protocol (57% vs. 27%, $p = 0.006$). Associations between other center-level factors and country income are presented in Table 1.

Patient and tumor characteristics

Patient undergoing esophagectomy from HIC were significantly older (mean: 65.2 vs 55.7 years, $p < 0.001$), more likely to be male (80.6% vs 66.2%, $p < 0.001$), and had higher Charlson Comorbidity Index scores (median: 6 vs 5, $p < 0.001$), compared to those from LMIC (Table 2). The distribution of smoking status also differed significantly between groups ($p < 0.001$), with higher rates of ex- (47.7% vs. 34.4%) and current- (15.7% vs. 14.8%) smokers at HIC, compared to LMIC. Differences in tumor histology and location were also evident between the two groups, with rates of esophageal adenocarcinoma (80.5% vs 30.2%, $p < 0.001$) and distal/Siewert 1–2 (85.7% vs 72.1%, $p < 0.001$) cancers were significantly higher in HIC, compared to LMIC. Patients in HIC also had a significantly higher rate of pathological Stage III/IV cancers, compared to LMIC (55.9% vs 44.1%, $p = 0.005$).

Treatment characteristics

There were significantly higher rates of pre-operative oral supplementation (38.3% vs 30.5%, $p < 0.001$) and postoperative feeding jejunostomy (51.1% vs 36.7%, $p < 0.001$) in HIC compared to LMIC (Table 2). Rates of neoadjuvant therapy were significantly higher in HIC compared to LMIC (78.9% vs 57.5%, $p < 0.001$). However, in HIC, this was predominantly by chemotherapy alone, with rates of chemoradiotherapy being higher in LMIC than HIC (49.7% vs 33.4%). Subgroup analysis found that this observation was largely a consequence of the difference in the distribution of tumor histologies between the groups, specifically the higher rates of SCCs in LMIC (65.9% vs. 17.1%). For the cohort as a whole, 65.0% of SCCs were treated with chemoradiotherapy, compared to 26.9% of adenocarcinomas. As such, subgroup analyses by the tumor histology found the rates of chemoradiotherapy to be similar in LMIC and HIC for both adenocarcinomas (29.0% vs. 26.7%) and SCCs (61.6% vs. 67.1%), with the remaining cases more likely to be treated with chemotherapy alone in HIC (Supplementary Table 1).

Technical factors

There were significantly higher rates of circular stapled anastomosis (57.5% vs 16.9%, $p < 0.001$) and chest anastomosis (84.7% vs 29.3%, $p < 0.001$) in HIC compared to LMIC (Table 2). LMIC were significantly more likely to use an open approach on the abdominal phase (54.6% vs. 45.1%, $p = 0.002$), but less likely to use an open approach to the thoracic phase (31.5% vs. 65.5%, $p < 0.001$) than HIC. There were significantly lower rates of margin positive resections in LMIC compared to HIC (12.7% vs 19.0%, $p = 0.007$).

Postoperative outcomes

Postoperative mortality

There were significantly higher 30-day (8.4% vs 2.3%, $p < 0.001$) and 90-day (9.4% vs 3.7%, $p < 0.001$) mortality rates in LMIC compared to HIC (Table 3). Multivariable analysis identified increasing age and ECOG status, tumor location (i.e. middle or proximal tumors), linear stapled anastomoses, and neck anastomoses as independent predictors of 90-day mortality (Table 4). After accounting for these factors, LMIC were associated with a significantly higher rates of 90-day mortality (OR: 2.31, $CI_{95\%}$: 1.17–4.55, $p = 0.015$) (Table 4).

Anastomotic leak and conduit necrosis

Rates of the composite outcome of anastomotic leaks/conduit necrosis were similar in the LMIC and HIC groups (16.6% vs. 14.3%, $p = 0.3$). Further, rates of Grade 1 (9.4% vs 6.9%), Grade 2 (1.9% vs 3.8%) and Grade 3 (5.2% vs 3.7%) anastomotic leaks/conduit necrosis were also similar between LMIC and HIC. On multivariable analysis, accounting for potentially confounding factors, there were no significant differences on anastomotic leaks/conduit necrosis between LMIC and HIC (OR: 1.06, $CI_{95\%}$: 0.57–1.99, $p = 0.9$) (Supplementary Table 2).

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

Table 4
Multivariable analysis of 90-day mortality in patients undergoing esophagectomy for esophageal cancer.

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio ($CI_{95\%}$)	p-value	Odds Ratio ($CI_{95\%}$)	p-value
Hospital factors				
Country Type, LMIC	2.73 (1.74–4.29)	**<0.001**	2.31 (1.17–4.55)	**0.015**
Center Volume (per year)*		0.2		0.1
<28	REF	–	REF	–
28-50	1.12 (0.70–1.79)	0.6	1.39 (0.79–2.45)	0.3
>50	0.72 (0.43–1.21)	0.2	0.61 (0.30–1.22)	0.2
Patient factors				
Age (per Decade)	1.29 (1.05–1.58)	**0.017**	1.61 (1.21–2.14)	**<0.001**
Gender, Male	0.91 (0.56–1.46)	0.7	–	NS
Body Mass Index, kg/m^2		0.3		NS
<18.5	1.50 (0.66–3.43)	0.3	–	–
18.5-24.9	REF	–	–	–
25.0-29.9	0.77 (0.48–1.23)	0.3	–	–
30.0+	0.68 (0.38–1.21)	0.2	–	–
ASA Grade		0.1		NS
1	REF	–	–	–
2	0.77 (0.42–1.42)	0.4	–	–
3-4	1.25 (0.67–2.34)	0.5	–	–
ECOG Status		**<0.001**		**<0.001**
0	REF	–	REF	–
1	1.55 (1.00–2.42)	0.050	1.26 (0.73–2.19)	0.4
2	3.76 (2.00–7.07)	**<0.001**	2.77 (1.36–5.63)	**0.005**
3-4	7.82 (2.49–24.49)	**<0.001**	12.41 (3.24–47.51)	**<0.001**
Charlson Comorbidity Index (per Point)	1.20 (1.07–1.34)	**0.001**	–	NS
Smoking Status		0.3		0.1
Never	REF	–	REF	–
Ex-smoker	1.09 (0.69–1.73)	0.7	1.02 (0.64–1.64)	0.9
Current	1.56 (0.89–2.74)	0.1	1.85 (0.98–3.48)	0.1
Tumor factors				
Histology		**0.004**		NS
Adenocarcinoma	REF	–	–	–
Squamous Cell Carcinoma	2.01 (1.32–3.07)	**0.001**	–	–
Other	1.96 (0.69–5.60)	0.2	–	–
Tumor Location		**0.003**		**0.045**
Distal/Siewert 1-2	REF	–	REF	–
Middle	2.44 (1.47–4.04)	**<0.001**	1.97 (1.11–3.49)	**0.020**
Proximal	2.45 (0.95–6.33)	0.1	1.87 (0.87–4.01)	0.1
Siewert 3	1.23 (0.38–4.03)	0.7	0.53 (0.12–2.35)	0.4
TNM Stage (on Pathology)		0.5		0.1
Stage 0	REF	–	REF	–
Stage I	0.72 (0.31–1.66)	0.4	0.52 (0.21–1.32)	0.2
Stage II	1.22 (0.58–2.56)	0.6	0.99 (0.48–2.04)	1.0
Stage III	1.19 (0.62–2.29)	0.6	1.32 (0.65–2.65)	0.4
Stage IV	1.35 (0.68–2.67)	0.4	1.60 (0.78–3.30)	0.2
Preoperative Nutrition		0.4		NS
None	REF	–	–	–
Oral Supplements	0.72 (0.46–1.14)	0.2	–	–
Enteral Tube Nutrition	0.99 (0.52–1.88)	0.9	–	–
Parenteral Nutrition	1.77 (0.53–5.95)	0.4	–	–
Neoadjuvant Therapy		**0.004**		NS
None	REF	–	–	–
Chemoradiotherapy	0.86 (0.54–1.36)	0.5	–	–
Chemotherapy alone	0.42 (0.24–0.71)	**0.001**	–	–
Radiotherapy alone**	NA**	NA**	–	–
Technical factors				
Anastomosis Technique		**<0.001**		**0.018**
Circular Stapled	REF	–	REF	–
Handsewn	1.72 (1.04–2.84)	**0.034**	0.78 (0.39–1.54)	0.5
Linear Stapled	2.59 (1.59–4.22)	**<0.001**	1.66 (0.88–3.14)	0.1
Anastomosis Site		**<0.001**		**<0.001**
Chest	REF	–	REF	–
Neck	3.04 (2.02–4.58)	**<0.001**	2.83 (1.53–5.25)	**<0.001**
Abdominal Phase		0.2		NS
Minimally Invasive	REF	–	–	–
Open	1.32 (0.88–1.97)	0.2	–	–
Thoracic Phase		0.6		NS
Minimally Invasive	REF	–	–	–
Open	0.82 (0.54–1.25)	0.4	–	–
Transhiatal	0.95 (0.39–2.30)	0.9	–	–
Postoperative Nutrition		0.1		NS
None	REF	–	–	–
Feeding Jejunostomy	1.68 (1.05–2.68)	**0.029**	–	–
Nasojejunal tube	1.73 (0.91–3.29)	0.1	–	–

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

The univariable analysis was performed using a separate binary logistic regression model for each factor. All factors were then entered into a multivariable generalized estimating equations model, with variable selection using a backwards stepwise approach, as described in the methods. The final multivariable model was based on N = 2119 cases (N = 96 events). Bold p-values are significant at $p < 0.05$. NS = not selected for inclusion in the model by the stepwise procedure. *Quantified by the estimated number of cases treated per year, extrapolated from the numbers treated during the study period. **Due to the small number of cases treated with radiotherapy alone (N = 7), these were excluded from the model, in order to achieve convergence. Abbreviations: ASA - American Society of Anaesthesiology, CI - confidence interval, COPD - Chronic Obstructive Pulmonary Disease, ECOG - Eastern Cooperative Oncology Group, HIC - high income countries, LMIC - low-middle income countries, NS - not selected for inclusion by the stepwise procedure, REF – reference category.

Complication rates

The overall complication rate was found to be significantly higher in HIC than LMIC (65.0% vs. 54.5%, $p < 0.001$). However, rates of major complications (Clavien-Dindo grade III-V) were found to be similar in the LMIC and HIC groups (23.4% vs. 25.8%, $p = 0.4$). On multivariable analysis (Supplementary Table 3), the difference in the major complication rate between LMIC and HIC remained non-significant, with an adjusted odds ratio of 0.85, ($CI_{95\%}$: 0.54–1.32, $p = 0.5$).

Other outcomes

Of the other postoperative outcomes considered (Table 3), the rate of return to theatre was not found to differ significantly between LMIC and HIC (10.4% vs. 12.2%, $p = 0.4$). The overall length of stay was also similar in the two groups (both median: 12 days, $p = 0.4$), although there was a tendency for shorter ICU length of stay in LMIC (median: 3, interquartile range: 1–6 days), compared to HIC (3, 2–7 days, $p = 0.031$).

Discussion

To date, no contemporary global data exists to assess the impact of esophagectomy in LMIC compared to HIC. Therefore, this study is timely in assessing the impact of esophagectomy practices in LMIC compared to HIC. This international study across 137 centers across 41 countries demonstrated LMIC centers were associated with significantly higher 90-day mortality compared to HIC, despite no significant differences in the rates of anastomotic leaks or major complications. These findings were consistent in adjusted models for center volume, as well as patient-, tumor- and technical-related factors. Since postoperative mortality is a good quality indicator with respect to outcomes after major cancer surgery, these data are relevant to ensure ongoing appraisal of safe cancer surgery practices worldwide.

An explanation for the findings of the study demonstrating higher mortality rates in LMIC with no discerning difference in anastomotic leak and major complication rates may relate to failure to rescue (FTR). FTR has been increasingly recognised and adopted as an important metric to assess quality of care [23]. Early data on FTR from open cholecystectomy and transurethral prostatectomy demonstrated a significant association between FTR and variations in mortality, and that FTR was independently associated with hospital-level characteristics over patient-level factors. Recently, using data from complex high-risk surgical procedures, Ghaferi et al. [24] demonstrated that the worst hospitals had a 2.5-fold increase in mortality compared to the best hospitals (8.0% vs. 3.0%), despite similar complication rates at the worst and best hospitals (36.4% vs. 32.7%). However, FTR rates were considerably higher at the worst, compared with the best hospitals (16.7% vs. 6.8%). In esophageal cancer surgery, European data have previously demonstrated FTR were associated with center volume and patient-level factors [25,26], but none have assessed impact by country income.

Although FTR is an interesting concept, underlying factors associated with FTR are complex and relate to broader hospital-level resources available to detect and manage postoperative complications following major surgery. Although surgeon and hospital experience are also associated with outcomes [19,27], the mechanism by which these factors work in conjunction with hospital resources to potentiate FTR are not well understood [28]. Data from Sheetz et al. [29] suggests that hospital size, occupancy, ICU availability, teaching status, and technology offer a survival advantage to patients undergoing major surgery, and are associated with FTR. However, these factors are not reversible in the immediate setting, and likely serve as proxies for an overall pedigree of hospital with sufficient resources to manage the complexity of high-risk surgical patients and their complications. Although nurse staffing may be more readily augmented, the exact mechanism by which lower nurse-to-patient ratios reduce FTR events is unknown. It is plausible that this characteristic also serves as a surrogate for a hospital's preparedness to perform high-risk operations. Despite these associations, hospital characteristics, patient factors, and operative volume explain a small proportion of the variation in FTR rates that exist across hospitals. These factors may potentially act more as threshold barriers to safety when performing complex surgeries. There is emerging evidence to suggest that caregiver attitudes, safety culture, and care process adherence may be more actionable means of improving surgical care [30,31]. Data from our survey also demonstrated HIC were associated with high volume centers, improved on-call esophageal services, 24-h on-call radiology services, and ERAS protocols and nurses, which are likely to attribute to improved outcomes in HIC and LMIC [18].

This study has important limitations to acknowledge. Firstly, this study was not able to capture all relevant data, which may have resulted in residual confounding by unmeasured or unmeasurable factors, possibly accounting for differences in outcome for 90-day mortality, anastomotic leaks and major complications. Secondly, the causes of death of patients experiencing postoperative mortality following discharge, especially in LMIC, remains unclear, as these data were not captured. However, these data provide us impetus for future qualitative research that may help explain such differences. Thirdly, there may be inherent differences between tumor biology between LMIC and HIC, which may not be measured and adjusted for. For instance, rates of SCC in LMIC are significantly higher than HIC, which may lead to variable oncological therapy, such as definitive chemoradiotherapy and surgical approach. Finally, staging information, such as access to positron emission tomography (PET), staging laparoscopy and endoscopic ultrasonography (EUS) were not captured in this study. As such, better access in HIC of these staging strategies may have led to better patient selection and, hence, improved outcomes. However, given the ongoing limitations to current staging of esophageal cancer, this may be an inherent bias regardless of access to these.

Conclusion

LMIC resections were independently associated with higher 90-day postoperative mortality, likely reflecting a failure to rescue of these patients following esophagectomy, despite similar composite anastomotic leaks and major complication rates. These findings warrant further research to identify potential issues and solutions to improve global outcomes following esophagectomy for cancer.

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

Declaration of competing interest

None declared.

Acknowledgements

We are grateful to the Birmingham Surgical Trials Consortium at the University of Birmingham for the use of their servers for secure online data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.12.006.

References

[1] Collaborators GBDOC. The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(6):582–97. https://doi.org/10.1016/S2468-1253(20)30007-8.

[2] Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3(4):524–48. https://doi.org/10.1001/jamaoncol.2016.5688.

[3] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.

[4] Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 2019. https://doi.org/10.1001/jamaoncol.2019.2996.

[5] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA A Cancer J Clin 2015;65(2):87–108. https://doi.org/10.3322/caac.21262.

[6] Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2019;269(2):291–8. https://doi.org/10.1097/SLA.0000000000002611.

[7] Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2017. https://doi.org/10.1097/SLA.0000000000002611.

[8] 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(4):696–702. https://doi.org/10.1016/j.ejso.2016.11.013.

[9] Markar S, Gronnier C, Duhamel A, et al. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg 2015;262(6):972–80. https://doi.org/10.1097/SLA.0000000000001011.

[10] Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). Ann Surg 2015;262(2):286–94. https://doi.org/10.1097/SLA.0000000000001098.

[11] GlobalSurg C. Mortality of emergency abdominal surgery in high-, middle- and low-income countries. Br J Surg 2016;103(8):971–88. https://doi.org/10.1002/bjs.10151.

[12] van der Werf LR, Busweiler LAD, van Sandick JW, van Berge Henegouwen MI, Wijnhoven BPL. Dutch upper GICAg. Reporting national outcomes after esophagectomy and gastrectomy according to the esophageal complications consensus group (ECCG). Ann Surg 2019. https://doi.org/10.1097/SLA.0000000000003210.

[13] Nepogodiev D, Martin J, Biccard B, Makupe A, Bhangu A, National Institute for Health Research Global Health Research Unit on Global S. Global burden of postoperative death. Lancet 2019;393(10170):401. https://doi.org/10.1016/S0140-6736(18)33139-8.

[14] Evans RPT, Singh P, Nepogodiev D, et al. Study protocol for a multicenter prospective cohort study on esophagogastric anastomoses and anastomotic leak (the Oesophago-Gastric Anastomosis Audit/OGAA). Dis Esophagus 2020;33(1). https://doi.org/10.1093/dote/doz007.

[15] Collaborative ST. Writing/Steering C, Data Management G, External Advisory G. REspiratory COmplications after abdomiNal surgery (RECON): study protocol for a multi-centre, observational, prospective, international audit of postoperative pulmonary complications after major abdominal surgery. Br J Anaesth. Jan 2020;124(1):e13–6. https://doi.org/10.1016/j.bja.2019.10.005.

[16] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(2):187–96. https://doi.org/10.1097/SLA.0b013e3181b13ca2.

[17] Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. Lancet 2003;361(9374):2032–5. https://doi.org/10.1016/s0140-6736(03)13640-9.

[18] Oesophago-Gastric Anastomosis Study Group on behalf of the West Midlands Research C. International variation in surgical practices in units performing oesophagectomy for oesophageal cancer: a unit survey from the oesophago-gastric anastomosis audit (OGAA). World J Surg 2019;43(11):2874–84. https://doi.org/10.1007/s00268-019-05080-1.

[19] Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346(15):1128–37. https://doi.org/10.1056/NEJMsa012337.

[20] Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349(22):2117–27. https://doi.org/10.1056/NEJMsa035205.

[21] Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA A Cancer J Clin 2017;67:7. https://doi.org/10.3322/caac.21388.

[22] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.

[23] Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. Med Care 1992;30(7):615–29. https://doi.org/10.1097/00005650-199207000-00004.

[24] Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg 2009;250(6):1029–34. https://doi.org/10.1097/sla.0b013e3181bef697.

[25] Almoudaris AM, Mamidanna R, Bottle A, et al. Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England. JAMA Surg 2013;148(3):272–6. https://doi.org/10.1001/jamasurg.2013.791.

[26] Liou DZ, Serna-Gallegos D, Mirocha J, Bairamian V, Alban RF, Soukiasian HJ. Predictors of failure to rescue after esophagectomy. Ann Thorac Surg 2018;105(3):871–8. https://doi.org/10.1016/j.athoracsur.2017.10.022.

[27] Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011;364(22):2128–37. https://doi.org/10.1056/NEJMsa1010705.

[28] Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. Med Care 2011;49(12):1076–81. https://doi.org/10.1097/MLR.0b013e3182329b97.

[29] Sheetz KH, Dimick JB, Ghaferi AA. Impact of hospital characteristics on failure to rescue following major surgery. Ann Surg 2016;263(4):692–7. https://doi.org/10.1097/SLA.0000000000001414.

[30] Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 2009;360(5):491–9. https://doi.org/10.1056/NEJMsa0810119.

[31] Birkmeyer NJ, Finks JF, Greenberg CK, et al. Safety culture and complications after bariatric surgery. Ann Surg 2013;257(2):260–5. https://doi.org/10.1097/SLA.0b013e31826c0085.

Downloaded for Vicki McDonagh (vicki.mcdonagh@burtonh-tr.wmids.nhs.uk) at Derby Teaching Hospitals NHS Foundation Trust from ClinicalKey.com by Elsevier on January 27, 2021.
For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.