Prospective Cohort Study

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Outcomes of elective liver surgery worldwide: a global, prospective, multicenter, cross-sectional study

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Background: The outcomes of liver surgery worldwide remain unknown. The true population-based outcomes are likely different to those vastly reported that reflect the activity of highly specialized academic centers. The aim of this study was to measure the true worldwide practice of liver surgery and associated outcomes by recruiting from centers across the globe. The geographic distribution of liver surgery activity and complexity was also evaluated to further understand variations in outcomes.

Methods: LiverGroup.org was an international, prospective, multicenter, cross-sectional study following the Global Surgery Collaborative Snapshot Research approach with a 3-month prospective, consecutive patient enrollment within January–December 2019. Each patient was followed up for 90 days postoperatively. All patients undergoing liver surgery at their respective centers were eligible for study inclusion. Basic demographics, patient and operation characteristics were collected. Morbidity was recorded according to the Clavien–Dindo Classification of Surgical Complications. Country-based and hospital-based data were collected, including the Human Development Index (HDI). (NCT03768141).

Results: A total of 2159 patients were included from six continents. Surgery was performed for cancer in 1785 (83%) patients. Of all patients, 912 (42%) experienced a postoperative complication of any severity, while the major complication rate was 16% (341/2159). The overall 90-day mortality rate after liver surgery was 3.8% (82/2,159). The overall failure to rescue rate was 11% (82/ 722) ranging from 5 to 35% among the higher and lower HDI groups, respectively.

Conclusions: This is the first to our knowledge global surgery study specifically designed and conducted for specialized liver surgery. The authors identified failure to rescue as a significant potentially modifiable factor for mortality after liver surgery, mostly related to lower Human Development Index countries. Members of the LiverGroup.org network could now work together to develop quality improvement collaboratives.

Keywords: failure to rescue, global surgery, human development index, liver surgery, morbidity, mortality, outcomes

Introduction

The most common indications for liver surgery include primary cancer, such as hepatocellular and cholangiocarcinoma, liver metastases, mostly colorectal, and benign liver lesions, including hydatid liver disease. Asia and the Western Pacific have the highest liver malignancy mortality rates nearing 20%, especially in upper-middle-income areas, while the lowest rates are observed in South America, Europe, South-East Asia, as well as in low-middle-income regions[1]. Liver cancer deaths were over 800 000 in 2020, with the highest rates observed in Eastern Asia and Northern Africa[2]. Furthermore, it has was shown that socioeconomic factors have a significant impact on liver cancer

HIGHLIGHTS

- International snapshot study following the global surgery collaborative approach.
- Over 2000 patients were included from all continents.
- The 90-day mortality rate after liver surgery was 4%.
- The failure to rescue rate ranged from 5 to 35% among higher and lower Human Development Index (HDI) groups.
- There is a great need to develop quality improvement collaboratives worldwide.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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outcomes[3]. The Human Development Index (HDI) is a metric of life expectancy, education, and standard of living, developed to assess social and economic differences among countries[4]. This metric is therefore useful to compare outcomes after liver surgery in different regions across the world.

Apart from being the only potentially curative approach for many liver malignancies[5], hepatobiliary surgery is often a vital intervention in managing benign liver diseases, such as large symptomatic liver cysts, hepatic adenomas, and hydatid liver disease, among others[6]. Liver surgery ranges vastly in degrees of complexity and relies on strong cohesive multidisciplinary care. However, access to safe surgery of the liver worldwide is yet to be addressed. It is in this context that identifying the gaps in global surgery of the liver can help pinpoint modifiable domains in healthcare provision and perioperative care to improve the accessibility and safety of surgery worldwide. A light was shed on the gross inequality in surgery and anesthesia care in the world by the former President of the World Bank, Jim Yong Kim, in his statement to promote the inclusion of surgical care in the global health agenda that 'surgical care is an indivisible, indispensable part of healthcare'[7]. As the need to upscale healthcare systems, infrastructure, and education in underserved countries is increasingly evident, global surgery, a field of research and advocacy to improve surgical care outcomes not restricted to specific diseases, populations, or geographical regions, is of mounting significance today[8,9]. Thus, global surgery research should not only focus on 'essential', cost-effective general surgical procedures[10] but also on highly specialized surgery, such as hepatobiliary.

Ultimately, the true demographics worldwide in terms of activity and outcomes of hepatobiliary surgery remain unknown and surgery of the liver as we know it reflects the activity of highly specialized academic centers. In addition, the true population-based outcomes are likely different to those vastly reported from high-volume academic centers[11–13]. A comprehensive understanding of the global necessity for surgical interventions is paramount to address the significant health challenges faced by populations worldwide. However, it is equally crucial to acknowledge and analyze the barriers to accessing surgical care, including workforce shortages and quality concerns, to effectively enhance global surgical standards. The importance of this endeavor lies in its potential to mitigate disparities and optimize hepatobiliary surgical outcomes across diverse healthcare settings[14].

In this International Liver Surgery Outcomes Study, the primary objective was to measure the true worldwide practice of liver surgery and associated outcomes by recruiting from centers across the globe, committing to consecutive case registration and rigorous data validation. The geographic distribution of liver surgery activity and complexity was also evaluated to further understand variations in outcomes.

Methods

Study design

LiverGroup.org was an international, prospective, multicenter, cross-sectional study following the Global Surgery Collaborative Snapshot Research approach which was introduced in the UK in 2013[15]. Such research methodology provides a worldwide population-based overview of the current clinical practice and allows for hypothesis generating comparative analyses. The study protocol was registered in advanced at ClinicalTrials.gov (NCT03768141) and audit approval was obtained by the Royal Free Hospital London, UK. This work is reported in line with the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria[16] (Supplemental Digital Content 3, http://links.lww.com/JS9/B128).

Study interval

The project and study design were initiated in May 2017, center recruitment in September 2018, with a 3-month of prospective, consecutive patient enrollment within January to December 2019. Each patient was followed up for up to 90 days post-operatively. None of the participating centers were affected by the first peak of COVID-19 during the study period[17].

Center inclusion and recruitment

Any surgeon performing liver surgery was eligible to participate and there were no exclusion criteria for center participation, to reflect the nature of this global surgery study. Centers were recruited through various methods, including: collaborative networks and partnerships with healthcare institutions, through national societies of surgical trainees, through different associations and societies by promoting our study to their members, through research collaborations with centers that had prior projects with the study investigators, through preselected country and regional leaders dedicated to recruit centers within their region, through dissemination of study information at conferences, through multiple emails and newsletters, social media, instant messaging groups, by utilizing personal contacts, and referrals within the global surgery community.

Participants and procedures

All patients undergoing liver surgery at their respective centers were eligible for study inclusion. The inclusion criteria were patients of 18 years of age or older, any indication for surgery, including surgery for both benign and malignant disease, and all minimally invasive approaches. The exclusion criteria were patients undergoing liver transplantation, liver biopsies, or image-guided liver ablation alone. For this manuscript, only single-stage liver resections were included, two-stage liver resection[18] for the purposes of liver parenchyma augmentation were excluded. It was predetermined at the beginning of the study design that data on two-stage liver resections would warrant separate examination and documentation. The purpose of the present study was to report the true morbidity and mortality associated with liver surgery. Only reason I would delete this is because it sounds like a bias introduced rather than a measure to minimise it (which I believe was the intention).

Data

Basic demographics, patient and operation characteristics were collected. The complexity of liver surgery was defined according to certain criteria and each criterion was given a single point (maximum 13) to create the Liver Surgery Complexity Score. Morbidity was recorded according to the Clavien–Dindo Classification of Surgical Complications[19], the FABIB Liver Surgery-Specific Classification[20] and the novel Comprehensive

Complication Index (CCI)[21] up to 90 days postoperatively. Major complications were defined as Clavien–Dindo grade ≥ 3a (any complication requiring an intervention or organ failure). High-volume centers were defined as those having submitted at least 30 cases over the 3-month recruitment period (extrapolating it to 120 cases annually). The failure-to-rescue rate was calculated by dividing the number of patients that died after surgery over the total number of patients with complications[22]. All data were collected using the LiverGroup.org specially designed electronic Case Report Form (eCRF). Furthermore, country-based and hospital-based data were collected, including the Human Development Index (HDI)[4], Gross National Income (GNI)[23], Education Index[23], Life Expectancy Index (LEI)[23], and the Total Health Expenditure[24]. These parameters were used to compare the outcomes of liver surgery worldwide. Cost analysis was conducted using the validated AssesSurgery GmbH calculator[25] only for European countries, including Switzerland and the United States of America. All values in Euro or Swiss Francs were converted to US Dollars for comparisons and uniform reporting purposes.

Power considerations

This study aimed for the maximum number of patients able to recruit. Assuming a 90-day mortality rate of 5 and 50% reduction to 2.5%, an alpha error of 0.05, power of 80%, the sample size calculation revealed the need for 1828 patients to be recruited. When adjusting for 10% drop-out or missing data rate, the final sample size calculation was set at 2011 cases in total.

Statistical methods

Continuous variables were compared with the Student *t*-test, the Mann–Whitney *U* test and the Kruskal–Wallis *H* test or one-way ANOVA where appropriate. Differences among proportions derived from categorical data were compared using the Fisher and the Pearson χ^2-tests, where appropriate. The Complexity of Liver Surgery Score (maximum score 13) was internally validated using the intraclass collection coefficient and the Cronbach's alpha test. ROC curve analysis was used to assess its predictive value and the Yuden's index to identify the optimal score cut-off point. A multivariable, binary regression analysis was performed to identify independent factors of 90-day mortality. The nature of missingness and proportions of missing data per variable were assessed. Variables containing data *missing completely at random* and missing in fewer than 10% of observations were handled as complete case analysis[26]. Cases with missing outcome only (morbidity and mortality) data were excluded and there were no attempts to perform multiple imputation calculations to replace them. All *P*-values were 2-sided and considered statistically significant if $P < 0.05$. Statistical analysis was performed using R version 3.3.2 (R Core Team, GNU GPL v2 License), R Studio version 1.0.44 (RStudio, Inc. GNU Affero General Public License v3, 2016) with the graphical user interface (GUI) rBiostatistics.com (rBiostatistics. com, 2017).

Results

Participants

A total of 2159 patients were included (Fig. 1) from six continents, 36 countries (Fig. 2), and 136 institutions. Demographics, disease, and operation characteristics are reported in Tables 1 and 2.

Surgery was performed for cancer in 1785 (82.7%) patients, of whom 296 (13.7%) had received a liver resection previously. In 914 (42.3%) patients the indication for resection was colorectal liver metastases (CRLM), while in 386 (17.9%) it was hepatocellular carcinoma (HCC) (Table 1). Minimally invasive surgery was performed in 512 patients (23.7%) patients (Table 2). A total of 781 (36.3%) underwent liver wedge (nonanatomical) resections. Additional to surgery, intraoperative ablations of liver lesions were performed in 136 (6.3%) of patients. The overall mean Complexity of Liver Surgery Score was 0.6 (SD 0.8), ranging from 0 to 6. This score could discriminate morbidity and mortality in a relatively linear manner; higher the score, higher the morbidity (ranging from 11% to 75%) and mortality (3% to 29%, respectively, $P < 0.001$) rates were at 90 days postoperatively (Supplementary Figure 14, Supplemental Digital Content 1, http://links.lww.com/JS9/B126). Similarly, on multivariable analysis, the complexity of the liver sugary score, with a cut-off of 2 points (Supplementary Figure 15 Supplemental Digital Content 1, http://links.lww.com/JS9/B126), was identified as an independent predictor of mortality (OR 3.83, 95% CI: 2.27–6.37, $P < 0.001$) (Supplementary Figure 16 Supplemental Digital Content 1, http://links.lww.com/JS9/B126). Figure 4.

In 211 (9.8%) patients, liver resection was performed together with a form of biliary and/or venous reconstruction. The median intraoperative and first 24 h postoperatively packed red blood cell (RBC) transfusion was 0 (10th–90th percentile: 0–1). Finally, a total of 1434 (80.1%) patients were successfully extubated in the operation room (Table 2).

Outcomes

Outcomes were measured from the completion of surgery up until 90 days postoperatively. Of all patients, 912 (42.2%) experienced a postoperative complication of any severity, while the major complication rate was 15.8% (341/2,159) (Tables 3 and 4). Organ failure occurred in 88 (4.1%), ascites (Grade 2 or higher) in 130 (6.0%), bile leak in 182 (8.4%), infection in 344 (15.9%), and bleeding in 140 (6.5%) of the patients (Tables 3 and 4). The median ICU and hospital stay was 1 (IQR 0–2) and 8 (5–11) days, respectively. The median hospital readmission rate was 11.1%

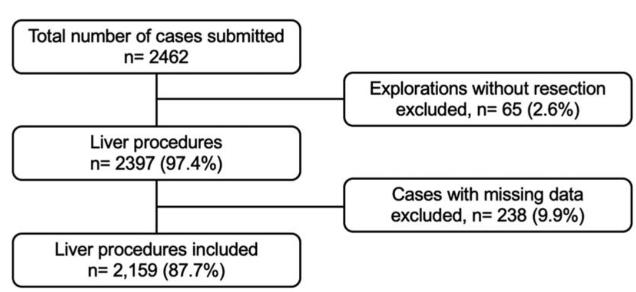

Figure 1. Flow diagram of included cases in the study. Cases with outcome data (morbidity and mortality) were excluded from the analysis.

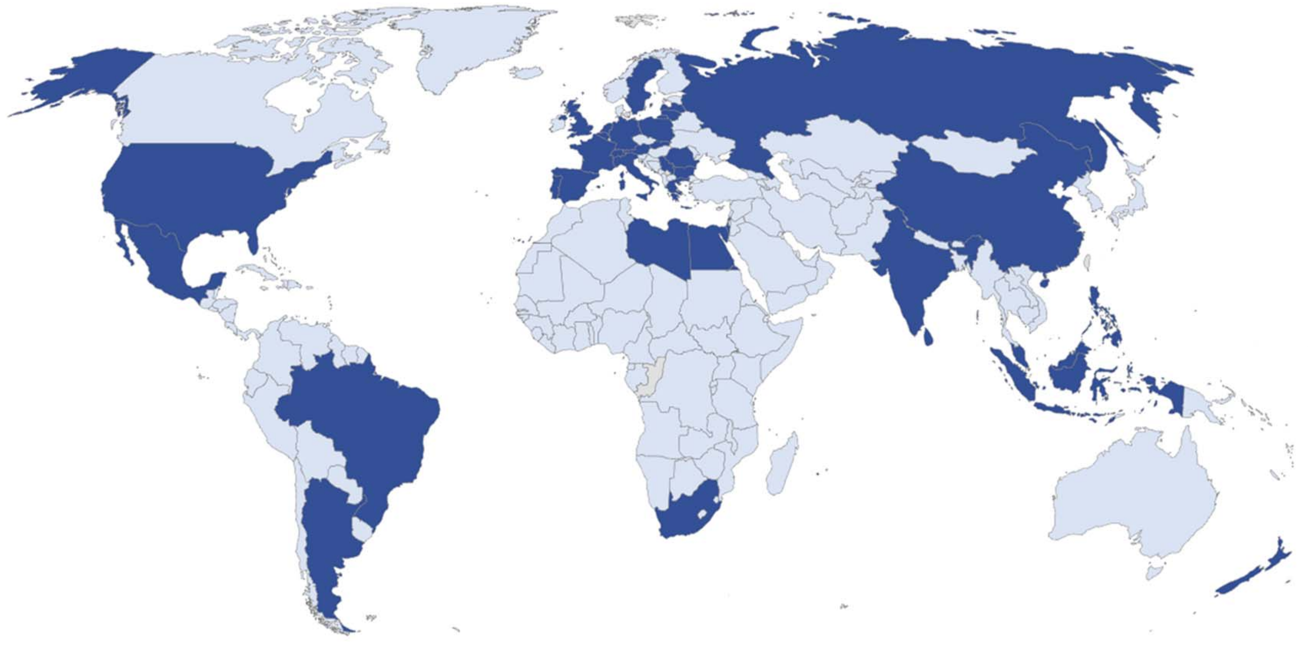

Figure 2. Map of participating centers worldwide. Dark blue indicates participation.

(240/2159) up until 90 days postoperatively. The overall 90-day mortality rate after liver surgery was 3.8% (82/2159). The mortality rate among high-volume participating centers ranged from 0 to 9% (Supplementary figure 1 Supplemental Digital Content 1, http://links.lww.com/JS9/B126). Morbidity and mortality rates according to the different indications and types of operations are reported in Table 3. Of note, the 90-day postoperative mortality varied significantly among indications for surgery, with colorectal cancer metastases being 2% while for hilar cholangiocarcinoma as high as 19%. Furthermore, although there were significant differences in baseline characteristics and overall complication rates, major morbidity (14 vs. 16%, OR 1.14 (95% CI: 0.82–1.59, $P=0.483$) and mortality (3 vs. 4%, OR 1.52 (95% CI: 0.77–3.33, $P=0.295$) did not differ between benign and malignant indications for liver surgery (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/B127).

The overall failure to rescue rate was 11.4% (82/ 722) (dead/ complications). The overall mean estimated cost of liver surgery in Europe and the USA was 14 034 (SD 7279) US Dollars. Supplementary figure 2 Supplemental Digital Content 1, http://links.lww.com/JS9/B126 illustrates the increasing estimated cost per different grades of postoperative complications. Briefly, the cost of complications approximately double with organ failure requiring ITU admission and triple when complications lead to death.

Hospital characteristics

The mortality rate in relatively small (<850 beds) *versus* large (≥ 850 beds) hospitals was not significantly different in this cohort (4.4 vs. 3.4%, OR 1.31, 95% CI: 0.82–2.10, $P=0.261$). Teaching or university affiliated hospitals; however, were associated with lower mortality rates when compared to nonteaching hospitals (3.5 vs. 7.4%, OR 0.45, 95% CI: 0.25–0.87, $P=0.011$). There was a trend to higher mortality rate associated with private when compared to public hospitals 3.7 vs. 7.9%, OR 2.23, 95% CI: 0.84–5.03, $P=0.081$).

Patient, operative characteristics, and outcomes across the human development index groups

The Human Development Index (HDI) (Supplementary figure 3 Supplemental Digital Content 1, http://links.lww.com/JS9/B126) is a summary measure of achievement in key dimensions of human development: Life Expectancy (LEI), Education (EI) and the Gross National Income (GNI) Indices[23]. All participating centers fell into three groups, the low- to medium- (0.550–0.699), high- (0.700–0.799) and very high- (≥ 0.800) HDI groups. Although sex and comorbidities did not differ significantly among the three HDI groups, patients from low- to middle HDI countries were younger, were more likely to suffer from a benign disease, had similar postoperative morbidity rates but despite that, a significantly higher mortality rate when compared to high- and very high-HDI groups (13, 7, and 4%), respectively ($P=0.004$). Figure 3 illustrates the different complexity of liver surgery scores, morbidity, failure to rescue, and mortality rates among the three HDI groups. Of note, complexity increased while failure to rescue and mortality rates decreased per higher HDI group. Similar trends arose when analyzing LEI, EI, and GNI, and other indices separately (Table 5, Supplementary Figures 4–13 Supplemental Digital Content 1, http://links.lww.com/JS9/B126).

Discussion

The 'true' picture of liver surgery that this snapshot study allows us to depict, reflects the current demographic distribution of activity and outcomes worldwide. Namely, regions of higher

Table 1

Patient and disease characteristics.

Parameters	Values
Patient Characteristics	
Age, median (IQR)	64 (54–71)
Female sex, *n* (%)	1016 (43)
Race, *n* (%)	
African	38 (2)
Asian	159 (7)
Caucasian	1887 (87)
Other	75 (4)
BMI kg/m^2, median (IQR)	26 (23–29)
Comorbidities, *n* (%)	
Coronary artery disease	237 (10)
Heart failure	85 (4)
Diabetes mellitus	383 (16)
Metastatic cancer	664 (27)
Hepatitis B or C	194 (9)
Liver cirrhosis	164 (7)
Stroke	45 (2)
COPD/Asthma	170 (7)
Other	747 (34)
Disease Characteristics, *n* (%)	
Malignancy	2050 (84)
Cholangiocarcinoma - hilar	113 (5)
Cholangiocarcinoma - intrahepatic	161 (7)
Colorectal liver metastases	1070 (43)
Hemangioma	60 (2)
Hepatic adenoma	48 (2)
Hepatocellular carcinoma	410 (17)
Nodular regenerative hyperplasia	1 (0)
Noncolorectal liver metastases	174 (7)
Sarcoma	9 (0)
Other	409 (16)
Sequence of surgery, *n* (%)	
Metachronous	398 (48)
Synchronous - combined	90 (11)
Synchronous - liver first	85 (10)
Synchronous - primary first	244 (30)
Previous therapy, *n* (%)	
Preoperative chemotherapy	753 (35)
Biological agents used	301 (14)
Previous abdominal surgery	1215 (56)
Previous liver resection	341 (14)
Liver specific characteristics	
Diameter of the largest lesion, median (IQR)	27 (16–43)
Liver parenchyma, *n* (%)	
Normal	802 (37)
Fibrosis	187 (9)
Cirrhosis	183 (9)
Steatosis	267 (12)
Chemotherapy induced injury	252 (12)
PVE prior to resection, *n* (%)	92 (4)
sFLR prior to resection, median %, (IQR)	42 (34–60)
sFLR prior to resection, mean %, (SD)	49 (21)

Table 2

Operation characteristics.

Parameters	Values
Mode of resection, *n* (%)	
Open	1777 (75)
Laparoscopic	513 (22)
Robotic	42 (2)
Hybrid / converted to open	42 (2)
Operation duration in min., median (IQR)	220 (150–300)
Operation performed, *n* (%)	
Ablation only	23 (1)
Bisegmentectomy	116 (5)
Left hepatectomy	228 (10)
Left lateral sectionectomy	190 (8)
Left trisectionectomy	30 (1)
Nonanatomical resection	873 (37)
Right hepatectomy	372 (16)
Right posterior sectionectomy	126 (5)
Right trisectionectomy	81 (3)
Segmentectomy	309 (13)
Trisegmentectomy	25 (1)
Complexity of liver surgery, *n* (%)	
Hilar lymphadenectomy	285 (13)
More than one liver resection	410 (19)
Resection and ablation	94 (4)
Portal vein resection and reconstruction	41 (2)
Hepatic vein resection and reconstruction	24 (1)
Hepatic artery resection and reconstruction	12 (1)
Vena vava resection and reconstruction	19 (1)
Bile duct resection and extrahepatic reconstruction	81 (4)
Bile duct resection and intrahepatic reconstruction	50 (2)
Enteric resection and reconstruction	132 (6)
Extrahepatic nongastrointestinal resection	62 (3)
Ante situ perfusion and resection	2 (0)
Ex situ perfusion and resection	*0 (0)*
Complexity of liver surgery score, mean (SD)	0.6 (0.8)
Vascular exclusion, *n* (%)	
On-demand pringle	433 (20)
Intermittent pringle	502 (24)
Pringle and inferior vena cava clamping	13 (1)
Total vascular exclusion	19 (1)
Total clamp time in min., median, (IQR)	25 (12–40)
Transection technique, *n* (%)	
Crush clamp	294 (14)
CUSA / Dissectron	*1348 (62)*
Bipolar	822 (38)
Stapler	300 (14)
Other	592 (27)
Transection time in min., median (IQR)	60 (35–100)
Other information	
Blood transfusions, mean (SD)	0.4 (1.3)
Extubated in the operation room, n (%)	1434 (80)

Human Development Index (HDI, a composite metric of life expectancy, education, and per capita income) perform an increasing number of liver resections, while Sub-Saharan Africa is grossly underrepresented. Liver surgery today bears important morbidity overall, with as many as 4 in 10 patients experiencing at least one postoperative complication of any severity with an overall 90-day mortality rate of 4%.

Across the represented HDI groups, there was an inverse relationship between increasing HDI and 90-day mortality rates with a four-fold higher mortality in the medium HDI group than in the very high-HDI group. Major morbidity, however, while also highest in the medium HDI group, was lowest in the high-HDI countries rather than in the very high-HDI countries. Interestingly, despite the very high-HDI countries owning the lowest mortality, the major morbidity was substantial. When evaluating the surgical complexity scores, it becomes apparent that the high morbidity is associated with higher complexity. The

Table 3

Morbidity and mortality rates according to the different indications and types of operations.

Parameters	Complexity score, mean (SD)	Grade >2, n, (%)	Mortality, n, (%)
Indication			
Hilar cholangiocarcinoma	2.0 (1.0)	38/88 (43)	16/85 (19)
Intrahepatic cholangiocarcinoma	0.8 (1.0)	39/151 (26)	7/147 (5)
Colorectal liver metastases	0.6 (0.7)	116/914 (13)	22/898 (2)
Focal nodular hyperplasia	0.1 (0.3)	6/32 (19)	1/32 (3)
Hemangioma	0.1 (0.3)	3/58 (5)	3/55 (6)
Hepatic adenoma	0.1 (0.3)	1/44 (2)	1/45 (2)
Hepatocellular carcinoma	0.3 (0.5)	58/386 (15)	16/382 (4)
Noncolorectal liver metastases	0.7 (0.9)	20/141 (14)	1/147 (1)
Gallbladder cancer	0.9 (0.7)	12/64 (19)	7/62 (11)
Surgical approach			
Open	0.7 (0.9)	303/1647 (18)	70/1625 (4)
Hybrid/converted to open	0.5 (0.9)	10/42 (24)	2/41 (5)
Laparoscopic	0.3 (0.5)	26/428 (6)	10/413 (2)
Robotic	0.1 (0.3)	2/42 (5)	0/42 (0)
Type of operation			
Ablation only	0.0 (0.0)	0/11 (0)	0/11 (0)
Bisegmentectomy	0.6 (0.7)	15/116 (13)	7/113 (6)
Left hepatectomy	0.8 (1.0)	43/215 (20)	11/208 (5)
Left lateral sectionectomy	0.4 (0.7)	15/190 (8)	5/187 (3)
Left trisectionectomy	1.0 (1.0)	11/28 (39)	3/28 (11)
Nonanatomical resection	0.5 (0.7)	91/781 (12)	16/765 (2)
Right hepatectomy	0.5 (0.7)	69/349 (20)	15/348 (4)
Right posterior sectionectomy	0.7 (1.0)	32/126 (25)	9/123 (7)
Right trisectionectomy	1.0 (1.0)	32/71 (45)	5/71 (7)
Segmentectomy	0.3 (0.6)	26/241 (11)	10/238 (4)
Trisegmentectomy	1.0 (1.0)	7/25 (28)	1/25 (4)
Complexity of liver surgery			
No complexity features	–	173/1411 (12)	43/1385 (3)
Hilar lymphadenectomy	–	92/285 (32)	24/277 (9)
More than one liver resection	–	68/410 (17)	22/406 (5)
Resection and ablation	–	12/94 (13)	4/93 (4)
Portal vein resection and reconstruction	–	20/41 (49)	8/40 (20)
Hepatic vein resection and reconstruction	–	12/24 (50)	2/24 (8)
Hepatic artery resection and reconstruction	–	6/12 (50)	2/12 (17)
Vena cava resection and reconstruction	–	9/19 (47)	3/19 (16)
Bile duct resection and extrahepatic reconstruction	–	41/81 (51)	14/78 (18)
Bile duct resection and intrahepatic reconstruction	–	23/50 (46)	4/49 (8)
Associated enteric resection and reconstruction	–	39/132 (30)	8/130 (6)
Extrahepatic non gastrointestinal resection	–	18/62 (29)	1/62 (2)

Table 4

Postoperative outcomes.

Parameters	Values
Clavien–Dindo highest grade, *n* (%)	
No complications	1394 (58)
Grade 1 – no treatment	214 (9)
Grade 2 – pharmacological treatment	420 (18)
Grade 3a – intervention under LA	185 (8)
Grade 3b – intervention under LA	86 (4)
Grade 4a – single organ failure	42 (2)
Grade 4b – multi-organ failure	10 (1)
Grade 5– death	46 (2)
Clavien–Dindo grades grouped, *n* (%)	
Any complication	912 (42)
Grade >1	722 (33)
Grade >2	341 (16)
Grade >3a	170 (8)
FABIB Classification, *n* (%)	
Failure	
None	2308 (96)
A	42 (2)
B	25 (1)
C	22 (1)
Overall	89 (4)
Ascites	
None	2265 (94)
A	100 (4)
B	27 (1)
C	5 (0)
Overall	132 (6)
Bile leak	
None	2209 (92)
A	71 (3)
B	87 (4)
C	30 (1)
Overall	187 (8)
Infection	
None	2045 (85)
A	226 (9)
B	93 (4)
C	33 (1)
Overall	370 (15)
Bleeding	
None	2253 (94)
A	84 (4)
B	30 (1)
C	30 (1)
Overall	144 (6)
Other postoperative outcomes	
Intensive care unit stay, median (IQR)	1 (0–2)
Hospital stay in days, median (IQR)	8 (5–11)
Hospital readmission rate, *n* (%)	240 (10)
Mortality rate, *n* (%)	87 (3.7)
Centre adjusted mortality rate, median (IQR)	2.1 (0–3.8)

resulting relationship of these outcome metrics, particularly in the medium and very high-HDI group, rises further themes for discussion and research.

Failure-to-rescue, defined as death after a treatable complication, was described as an effective measure of preventable postoperative mortality[22,27]. This global snapshot study reveals a failure-to-rescue rate of over 10% in liver surgery worldwide. The stark contrast between the mortality rates between medium and very high-HDI groups, considering the relatively similar morbidity rates, is highly suggestive of higher preventable mortality in lower HDI groups. Similarly, in the African Surgical Outcomes Study (ASOS), a high incidence of preventable deaths in low-risk patients following surgery was identified and attributed to inadequate identification and treatment of life-threatening complications during the perioperative period[28]. Furthermore, several Global Surgery studies have emphasized the importance of failure to rescue as one of the few factors that are

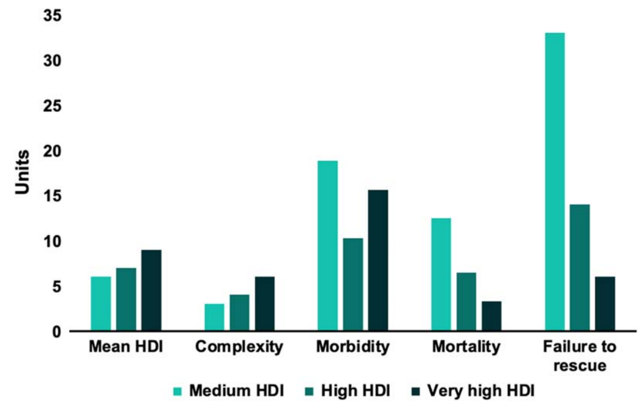

Figure 3. Complexity of liver surgery, morbidity, mortality, and failure to rescue among the 3 HDI groups (medium, high, and very high). Mean HDI and complexity scores were multiplied by 10 for visualization purposes. Morbidity, mortality, and failure to rescue rates represent percentages.

modifiable[29,30]. This has led to its use as a new quality indicator of surgical services[31]. Although the key modifiable domains that impact mortality following major complications in liver surgery remain hypothesis driven, the timely recognition and management of complications together with optimal infrastructure can hardly be disputed. Nationwide studies, albeit all from very high-HDI countries, have attributed interhospital differences in failure to rescue rates after liver surgery, at least in part, to hospital volume[32,33]. However, at an international level, there appears to be no significant association between the two, with hospital size and volume not being associated with postoperative outcomes.

The burden of postoperative mortality after surgery, of any kind, is estimated to account for nearly 10% of all deaths each year worldwide, which makes it the third leading cause of deaths, preceded only by ischemic heart disease and stroke[34]. Improving surgical care must embrace initiatives to reduce postoperative deaths as much as to address the disparities in surgical activity in underserved areas. While the present study reveals gaps in the field of liver surgery, failure to rescue encompasses the wider surgical ecosystem, including workforce and infrastructure factors. Identifying what drove the improved standards in the very high-HDI countries that have also allowed for resections of higher complexity will help address the high failure to rescue rates observed in the medium HDI group. In establishing an international collaborative group, LiverGroup.org members could now work together to develop quality improvement collaboratives.

This study also revealed other important findings. Liver surgery is currently performed bloodless, with only about 1 out of 10 patients requiring a blood transfusion. This is in contrast with historic reports that associated liver surgery with significant blood loses[35]. This may be attributed to improved surgical techniques and precision instruments, preoperative planning and advanced imaging technologies, inflow occlusion[36], hemostatic agents and devices for effective bleeding control, optimized transfusion strategies and blood management protocols, as well as enhanced perioperative care practices. However, mortality rates reaching nearly 20% in patients that suffer from hilar cholangiocarcinoma, requiring complex liver surgery, biliary and/or venous reconstruction are unacceptable and twice as high when compared to the current literature[37]. Further research in this field is required to make surgery for cholangiocarcinoma safer, among others including risk stratification and patient selection scores, perioperative care optimization protocols, quality improvement initiatives, multicenter collaborations, and data registries.

Table 5

Characteristics of patients within the human development index (HDI) groups.

Parameters	Low to medium HDI $n=48$	High-HDI $n=126$	Very- high#HDI $n=1985$	*P*
Age, median (IQR)	48 (35–63)	54 (36–64)	65 (55–72)	< **0.001**
Female sex, *n* (%)	23 (48)	50 (40)	863 (44)	0.574
BMI kg/m^2, median (IQR)	23 (22–27)	25 (22–27)	26 (23–29)	0.113
Coronary artery disease, *n* (%)	3 (6)	15 (12)	211 (11)	0.553
Diabetes mellitus, *n* (%)	10 (21)	21 (17)	337 (17)	0.776
Metastatic cancer, *n* (%)	21 (44)	86 (68)	1678 (68)	< **0.001**
Hepatitis B or C, *n* (%)	4 (8)	28 (14)	162 (8)	< **0.001**
Liver cirrhosis, *n* (%)	5 (10)	9 (7)	145 (7)	0.714
COPD/Asthma, *n* (%)	2 (4)	6 (5)	144 (7)	0.418
Malignancy, *n* (%)	21 (44)	86 (68)	1678 (85)	< **0.001**
Complexity of liver surgery, mean (SD)	0.3 (0.7)	0.4 (0.7)	0.6 0.8	< **0.001**
Minimally invasive approach, *n* (%)	18 (38)	32 (25)	464 (23)	< **0.001**
Operation duration in min., median (IQR)	360 (251–492)	300 (205–360)	214 (150–300)	< **0.001**
Blood transfusion units, mean, (SD)	0.9 (2)	0.5 (1)	0.3 (1)	**0.007**
Extubated in the operation room, *n* (%)	39 (89)	78 (71)	1317 (81)	**0.018**
Complication of any severity, 90 days	28 (58)	51 (41)	833 (42)	0.070
Grade ≥ 3a complication, 90 days	48 (19)	126 (10)	1985 (16)	0.195
Grade ≥ 3b complication, 90 days	4 (8)	7 (6)	159 (8)	0.607
CCI until 90 days postoperatively, median (IQR)	9 (0–21)	0 (0–11)	0 (0–21)	0.074
Intensive care unit stay, median (IQR)	3 (2–4)	1 (0–2)	1 (0–2)	0.133
Hospital stay in days, median (IQR)	8 (5–9)	10 (6–15)	8 (5–11)	0.214
Mortality rate, 90 days, *n* (%)	6 (13)	8 (7)	68 (4)	**0.004**

Statistically significant values are in bold.

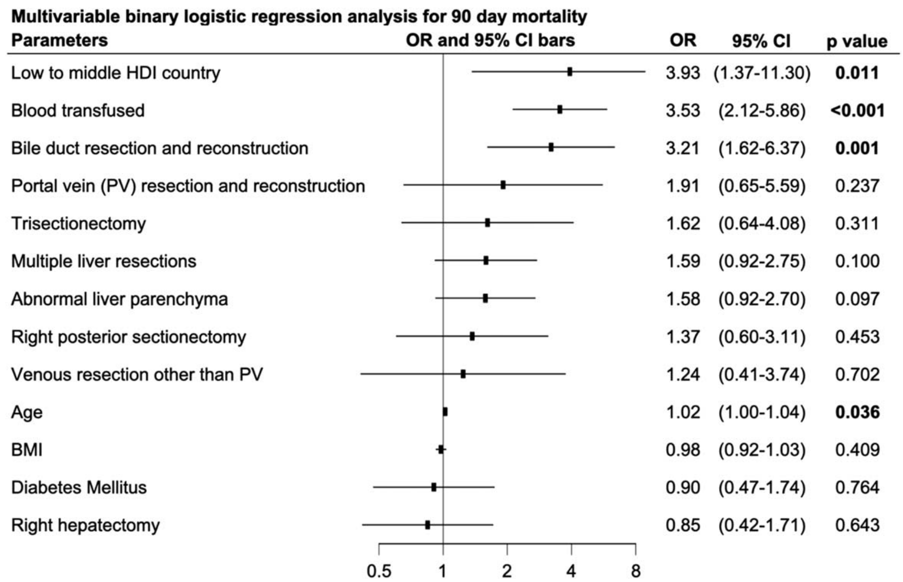

Figure 4. Multivariable analysis for independent factors of 90-day mortality, including the low- to middle HDI group.

A third of the patients underwent parenchymal preserving operations (i.e. nonanatomical resection, also known as wedges). This is in contrast to previous reports with anatomical, non-parenchymal preserving operations performed due to the perceived oncological benefit and simplicity of liver surgery[38]. Furthermore, minimally invasive surgery was attempted and/or performed in a quarter of the patients in this cohort, however the levels of surgical complexity in this group were lowest, which may explain superior outcomes. Interestingly, worse outcomes were associated with operations that were converted from minimally invasive to open surgery. This may reflect higher complexity as well as intraoperative complications affecting patient outcomes[39].

Apart from the patient and family burden, postoperative complications also affect cost and hospital resources[40]. In-hospital cost appear to double for reinterventions and quadruple with organ failure. The highest costs were related to patients in whom failure-to-rescue occurred. Prevention and early identification of postoperative complications may help increase patient turnover as well as save cost, allowing to offer surgery to more patients and reduce the waiting time for surgery.

The strengths of this study lie in the magnitude of the LiverGroup.org network, its geographic distribution, the prospective nature of this study, the duration of follow-up, and the liver surgery-specific details obtained. Nevertheless, a study of this scale has some inevitable limitations. *Firstly*, selective reporting is an issue with any type of global surgery studies[41] and there were no data monitors assigned to each center. However, with anonymous reporting and the high mortality rates associated with specific disease and operation characteristics, the writing committee members did not consider this as a significant issue. *Secondly*, the short time frame of three months for data capture by local investigators may risk selection bias, such as seasonal variation in local presentations. However, longer enrollment strategies, with a higher time burden, may have affected study participation. *Thirdly*, this study used several classifications and terminology that may not be familiar to local investigators, and this may have affected the correctness of data capture. However, the electronic Case Report Form (CRF) as well as the LiverGroup.org platform contained explanations for each classification and term used as well as online converters for laboratory values and other important calculators. *Fourthly*, the surgeon experience and learning curve was not assessed in this study, thus no associations could be made with regards to outcomes, especially among the different HDI country groups. *Lastly*, under-representation of certain regions in global surgery studies is a common phenomenon and this can be attributed to limited research infrastructure and funding opportunities in certain regions, lack of awareness and access to global surgery studies, language and cultural barriers that impact participation, variation in regulatory and ethical considerations across countries, as well as differences in surgical capacity and expertise among regions. Addressing these barriers requires initiatives to promote inclusivity and equity, such as capacity-building programs, targeted funding support, collaborations with regional partners, translation, and cultural adaptation of study materials, and active engagement with underrepresented regions to overcome specific challenges they may face[42].

In conclusion, to our knowledge, this is the first global surgery study specifically designed and conducted for specialized, liver surgery. We identified failure to rescue as a significant potentially modifiable factor for mortality after liver surgery, mostly related to lower Human Development Index (HDI) countries. Members of the LiverGroup.org network could now work together to develop quality improvement collaboratives, with the next obvious step being studying failure to rescue in lower HDI countries. We propose a strategy encompassing joint research on failure-to-rescue factors in lower HDI countries, skill-based training programs, technology transfer, infrastructure development, policy advocacy, and local capacity-building

Ethical approval

This project obtained audit approval from the Royal Free Hospital Audit and Compliance, Quality Governance department with the registration ID: RFH TASS40_2016/17.

Consent

This project, registered as an audit, did not require informed consent in the UK as it was truly observational with fully anonymised data.

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Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Data availability statement

The Scientific and Management Committees will decide about requests from LiverGroup.org Members regarding data sharing and will consider all such requests based on quality and the validity of the proposed project.

Provenance and peer review

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