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Risk factors for failure to rescue after hepatectomy in a high-volume UK tertiary referral center

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ABSTRACT

Background: Mortality after severe complications after hepatectomy (failure to rescue) is strongly linked to center volume. The aim of this study was to evaluate the risk factors for failure to rescue after hepatectomy in a high-volume center.
Methods: Retrospective study of 1,826 consecutive patients who underwent hepatectomy from 2011 to 2018. The primary outcome was a 90-day failure to rescue, defined as death within 90 days post-hepatectomy after a severe (Clavien-Dindo grade 3+) complication. Risk factors for 90-day failure to rescue were evaluated using a multivariable binary logistic regression model.
Results: The cohort had a median age of 65.3 years, and 56.6% of patients were male. The commonest indication for hepatectomy was colorectal metastasis (58.9%), and 46.9% of patients underwent major or extra-major hepatectomy. Severe complications developed in 209 patients (11.4%), for whom the 30- and 90-day failure to rescue rates were 17.0% and 35.4%, respectively. On multivariable analysis, increasing age ($P = .006$) and modified Frailty Index ($P = .044$), complication type (medical or combined medical/surgical versus surgical; $P < .001$), and body mass index ($P = .018$) were found to be significant independent predictors of 90-day failure to rescue.
Conclusion: Older and frail patients who experience medical complications are particularly at risk of failure to rescue after hepatectomy. These results may inform preoperative counseling and may help to identify candidates for prehabilitation. Further study is needed to assess whether failure to rescue rates could be reduced by perioperative interventions.

Introduction

Hepatectomy is a complex surgical intervention that provides the potential for cure or long-term survival for patients with primary or secondary hepatic malignancy. Although short-term outcomes after hepatectomy have improved in recent decades, the complication (20%–40%) and mortality rates (1%–5%) are not insignificant.[1] Several factors have previously been found to contribute to outcomes, including patient factors such as fitness, nutrition, and prehabilitation and treatment-related factors such as operative strategy and perioperative care. Although morbidity and mortality rates are well-established quality indicators in surgical practice, patient survival after complication is an emerging postoperative outcome metric, and this concept has been defined as "failure to rescue" (FTR).[2,3]

Multicenter studies of FTR after hepatectomy have recognized the importance of hospital volume, reporting an inverse correlation between this and rates of FTR.[1,4–8] Possible explanations for this include higher-volume centers having greater experience and being more likely to have robust perioperative protocols and dedicated specialist teams, allowing for early recognition and effective intervention for postoperative complications. However, there are currently limited studies of patient-level data assessing the influence of patient and perioperative factors on FTR.[4,9,10] Understanding the risk factors for FTR after hepatectomy may

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provide further insight into potential causes for observed differences between high and low-volume centers and identify areas for future work in perioperative care after hepatectomy. As such, the aim of this study was to evaluate the risk factors for FTR after hepatectomy in a single high-volume UK specialist center.

Methods

Patient workup

Patients who are referred to our center for consideration for hepatectomy are initially assessed for technical resectability at a specialist hepatobiliary multidisciplinary team meeting, where potential surgical candidates are carefully evaluated by an experienced team of hepatobiliary surgeons and anesthetists. The surgical approach (laparoscopic or open) and type of resection are proposed by the multidisciplinary team, with the final decision made by the operating surgeon. During the study period, there has been a gradual increase in the proportion of resections performed by laparoscopy, particularly for minor hepatectomy, whereas there has been a shift away from major hepatectomy and toward an increased use of parenchyma-sparing hepatectomy for patients with colorectal liver metastases. Computed tomography volumetric analysis was performed selectively in patients with suspected inadequate future liver remnant volume, followed by preoperative portal vein embolization, if required.

Postoperative management

Patients are routinely extubated immediately after surgery and undergo invasive hemodynamic monitoring (radial artery and central venous catheters) in a high-dependency unit or acute surgical ward, depending on their comorbidity and extent/complexity of hepatectomy. Since 2013, posthepatectomy care in our center has followed an Enhanced Recovery After Surgery (ERAS) pathway.[11] Any deviation from an expected postoperative recovery is promptly investigated, and complications are actively treated.

Data collection

Data were retrospectively extracted from a prospectively maintained departmental database. This included all consecutive patients undergoing either laparoscopic or open hepatectomy between January 1, 2011, and December 31, 2018 (inclusive) at a single UK tertiary hepatobiliary center (Queen Elizabeth Hospital, Birmingham, UK). Due to the retrospective design of this study, Institutional Review Board approval was not required. Patient comorbidity burden was quantified using the Charlson Comorbidity Index,[12] and physical status by the American Society of Anesthesiologists Physical Status Classification System[13] and the Modified Frailty Index (mFI).[14] The mFI consists of 11 variables and has been shown to be significantly associated with poor surgical outcomes.[14] The extent of hepatectomy was classified as minor, major, or extra-major in accordance with the Tokyo 2020 terminology of liver anatomy and resections.[15]

Any complications that occurred during the postoperative inpatient stay of the index admission were identified and graded using the Clavien–Dindo Classification System.[16] Patients who died within 90 days of surgery were classified as having a grade 5 complication, even if this occurred after discharge. Patients were then categorized based on the highest Clavien–Dindo grade, with those grade 3 to 5 deemed to have developed a "major" complication. The primary outcome of the study was 90-day FTR, which was defined as death within 90 days of surgery after a major postoperative complication. As such, analysis of this outcome included only those patients who developed major complications during the index admission.

Statistical methods

Initially, patients with severe complications were compared to the remainder of the cohort, using Mann–Whitney *U* tests for ordinal or continuous variables and Fisher exact tests for categorical variables. The subgroup of patients with severe complications was then assessed to identify factors that were associated with FTR. Initially, separate univariable binary logistic regression models were produced for each factor, with goodness-of-fit assessed using the Hosmer-Lemeshow test. A multivariable analysis was then produced, with variable selection using a backward-stepwise approach (removal at $P > .1$). The analysis was then repeated for the cohort as a whole to identify predictors of 90-day mortality. The multivariable model of 90-day FTR was then converted into a risk score. For categorical variables, the coefficients from the model (ie, log-odds ratios) were rounded to the nearest integer after multiplying by 2 to minimize the impact of rounding errors to assign a point score to each category. Continuous variables were divided into 5 categories, with intervals defined based on values that would give regression coefficients of approximately integer values, after multiplying by 2. The performance of the resulting model was then assessed using a receiver operating characteristic (ROC) curve, and the association with 90-day FTR was visualized by producing a binary logistic regression model with the risk score as a continuous covariate.

Continuous variables were not found to be normally distributed, so they are summarized as median (IQR) throughout. Cases with missing data were excluded from the analysis of the affected variable for univariable analyses, with multivariable analysis using a complete-cases approach. All analyses were performed using SPSS version 24 (IBM SPSS, Inc, Armonk, NY).

Results

Cohort characteristics

Data were available for a total of $N = 1826$ patients, with a median age of 65.3 years (IQR: 56.0–73.1), with the majority having a diagnosis of colorectal liver metastases (58.9%); further details of the cohort are reported in Table I.

Postoperative complications

A total of $N = 540$ (29.6%) patients developed at least 1 postoperative complication (Table II), with the most common surgical complications being bile leak (4.5%), wound infection (3.5%), and intra-abdominal collection requiring radiologic drainage (3.5%), and the most common medical complications were pneumonia (6.1%) and cardiac-related (3.6%). The 30- and 90-day mortality rates were 1.9% and 4.2%, respectively. Major postoperative complications, defined as those with Clavien-Dindo grades 3 to 5, developed in 11.4% ($N = 209$) of the cohort. Patients who developed major complications were significantly older (median: 67.0 vs 65.0 years, $P = .006$), more likely to be male (64.1% vs 55.7%, $P = .021$), had significantly higher mFI scores ($P = .015$), and were more likely to have been diagnosed with biliary tract malignancy (18.2% vs. 8.6%, $P < .001$) than those that did not develop major complications (Table I). Of the operative factors considered, major complications were associated with significantly higher rates of open surgery ($P = .008$), greater extent of resection ($P < .001$), and longer operating time ($P < .001$), with greater perioperative blood transfusion ($P < .001$) and resulting in a significantly longer length of stay ($P < .001$).

Table I
Cohort characteristics by Clavien–Dindo grade

	Overall (N = 1,826)	Highest Clavien–Dindo grade		P value
		Grade: 0–2 (N = 1,617)	Grade: 3–5 (N = 209)	
Age (y)	65.3 (56.0–73.1)	65.0 (55.5–73.0)	67.0 (60.2–74.1)	.006
Sex (% male)	1,034 (56.6%)	900 (55.7%)	134 (64.1%)	.021
BMI (kg/m^2)	27.2 (24.4–30.7)	27.1 (24.4–30.7)	27.5 (24.1–30.6)	.642
Charlson Comorbidity Index	8 (5–9)	8 (5–9)	8 (5–9)	.505
ASA classification				.808
2	1,302 (71.3%)	1,151 (71.2%)	151 (72.2%)	
3+	524 (28.7%)	466 (28.8%)	58 (27.8%)	
Modified Frailty Index				.015*
0	1,192 (65.3%)	1,073 (66.4%)	119 (56.9%)	
1	473 (25.9%)	402 (24.9%)	71 (34.0%)	
2+	161 (8.8%)	142 (8.8%)	19 (9.1%)	
Diagnosis				< .001
Colorectal liver metastases	1,075 (58.9%)	966 (59.7%)	109 (52.2%)	
Hepatocellular carcinoma	165 (9.0%)	147 (9.1%)	18 (8.6%)	
Gallbladder/cholangiocarcinoma	177 (9.7%)	139 (8.6%)	38 (18.2%)	
Other malignant	163 (8.9%)	142 (8.8%)	21 (10.0%)	
Benign	246 (13.5%)	223 (13.8%)	23 (11.0%)	
Extent of resection				< .001*
Minor	969 (53.1%)	901 (55.7%)	68 (32.5%)	
Major	608 (33.3%)	529 (32.7%)	79 (37.8%)	
Extra-major	249 (13.6%)	187 (11.6%)	62 (29.7%)	
Operative approach				.008
Open	1571 (86.0%)	1379 (85.3%)	192 (91.9%)	
Laparoscopic	255 (14.0%)	238 (14.7%)	17 (8.1%)	
Operating time (min)	269 (212–339)	262 (207–333)	324 (251–433)	< .001
Perioperative blood transfusion				< .001*
None	1,585 (86.8%)	1,436 (88.8%)	149 (71.3%)	
1–2 units	148 (8.1%)	113 (7.0%)	35 (16.7%)	
>2 units	93 (5.1%)	68 (4.2%)	25 (12.0%)	
Length of stay (d)	6 (5–8)	6 (5–7)	12 (7–23)	< .001

Data are reported as median (IQR), with P values from Mann–Whitney U tests, or as N (column %), with P values from Fisher's exact tests, unless stated otherwise. Analyses are based on N = 1,826, with the exception of those concerning BMI (N = 1,825) and operating time (N = 1,790).
ASA, American Society of Anesthesiologists Physical Status Classification System; *BMI*, body mass index.
* P value from Mann–Whitney U test, as the factor is ordinal.

FTR

Analysis of FTR included only those patients who developed severe complications in the postoperative period. Of the N = 209 patients with Clavien-Dindo grade 3 to 5 complications, N = 3 had uneventful surgery, with no complications noted in the postoperative period, but they were classified as Clavien–Dindo grade 5 as they died after discharge but within 90 days of surgery. As such, these were excluded from the analysis of FTR because they did not fit the definition of this outcome, leaving N = 206 for analysis. Of these, 1 patient died 118 days after surgery but before discharge; as such, they were classified as having Clavien–Dindo grade 5 complications, but not as having 90-day mortality. For the N = 206 patients included in the analysis, the 30-day and 90-day FTR rates were 17.0% (N = 35) and 35.4% (N = 73), respectively.

Predictors of 90-day FTR

Associations between a range of factors and 90-day FTR were then assessed to identify predictors of this outcome (Tables III and IV). This found that the type of complication (medical vs surgical) was the strongest predictor of 90-day FTR (P < .001). Specifically, rates of 90-day FTR increased from 22.7% in those who developed surgical complications only to 53.8% in those with medical complications only and 68.2% in those with both surgical and medical complications. Increasing age (P < .001), Charlson Comorbidity Index (P < .001), and mFI (P = .004) were also found to be significantly associated with higher rates of 90-day FTR on univariable analysis. In addition, the 90-day FTR rate was found to decrease significantly over the study period, from 42.9% in surgeries performed between 2011 and 2013 to 32.8% in 2017–2018 (odds ratio: 0.88 per year, 95% CI: 0.77–1.00, P = .043). A multivariable analysis was then performed to identify independent predictors of 90-day FTR. The complication type persisted as the strongest predictor of 90-day FTR on this analysis (P < .001), with increasing age (P = .006) and mFI (P = .044) also found to be significant independent predictors of 90-day FTR. The analysis additionally identified increasing body mass index (BMI) to be significantly independently associated with lower rates of 90-day FTR (odds ratio: 0.67 per 5 kg/m^2; 95% CI: 0.48–0.93, P = .018). Further investigation of this effect found a significant association between BMI and the complication type (Jonckheere-Terpstra test, P = .022), with a median BMI of 26.6 kg/m^2 (IQR: 23.8–29.4) in those with only surgical complications, which increased to 28.2 kg/m^2 (25.7–32.2) in those with only medical complications and 27.5 kg/m^2 (25.0–31.8) in those with both surgical and medical complications. As such, after adjustment for the complication type, the effect of BMI became significant on multivariable analysis. This relationship is visualized in Figure 1.

The multivariable model was then used to produce a risk score. For the mFI and complication type, the regression coefficients were multiplied by 2 and rounded to the nearest integer. For age, the regression coefficient indicated that the risk score should increase by approximately 1 point per decade; hence, intervals were defined based on decades of age, starting from 50 years. For BMI, the regression coefficient indicated that an increase of approximately 5 kg/m^2 should reduce the risk score by 1 point; hence, points were assigned based on the commonly used BMI intervals. The resulting risk score is reported in Supplementary Table S1, with the cohort

Table II
Postoperative complications

Outcome	Rate
Any surgical complication	276 (15.1%)
Bile leak	82 (4.5%)
Wound infection	63 (3.5%)
Radiologic drainage of collection	63 (3.5%)
Post-hepatectomy liver failure	
Grade A	29 (1.6%)
Grade B	10 (0.5%)
Grade C	17 (0.9%)
Postoperative hemorrhage	34 (1.9%)
Reoperation for bleeding	16 (0.9%)
Other surgical complication	72 (3.9%)
Any medical complication	290 (15.9%)
Pneumonia	111 (6.1%)
Cardiac complication	66 (3.6%)
Respiratory failure (requiring vent.)	25 (1.4%)
AKI (requiring RRT)	17 (0.9%)
Other medical complication	106 (5.8%)
Highest Clavien–Dindo grade	
Grade 0 (no complication)	1,286 (70.4%)
Grade 1	110 (6.0%)
Grade 2	221 (12.1%)
Grade 3	118 (6.5%)
Grade 4	14 (0.8%)
Grade 5 (death)	77 (4.2%)
30-d mortality	35 (1.9%)
30-d failure to rescue ($N = 206$)*	35 (17.0%)
90-d mortality	76 (4.2%)
90-d failure to rescue ($N = 206$)*	73 (35.4%)

Rates are based on $N = 1{,}826$, unless stated otherwise.
AKI, acute kidney injury; *RRT*, renal replacement therapy; *Vent.*, ventilation.
* Only includes the subgroup of patients with Clavien–Dindo Grade 3–5 complications occurring during the index admission.

having a median score of 6 points (range: 1–13). The risk score was found to be significantly predictive of 90-day FTR, yielding an area under the ROC curve of 0.775 (95% CI: 0.705–0.846, $P < .001$), with 90-day FTR rates of 18% (6/34), 34% (20/58), and 83% (15/18) in those scoring <4, 6–7, and 10+ points, respectively (Figure 2). However, the performance of the risk score was assessed using the same cohort that was used to derive the score; hence, it likely represents an overestimate of performance due to the impact of overfitting. As such, further validation would be required before the risk score could be considered for use in clinical practice.

Predictors of 90-day mortality

The multivariable analysis was then repeated for the cohort as a whole to identify predictors of 90-day mortality (Supplementary Table S2). The type of complication was not considered in this model because this analysis additionally included those patients without postoperative complications. Of the demographic factors considered, increasing age ($P < .001$) and male sex ($P = .030$) were found to be significant independent predictors of 90-day mortality. The other predictors of this outcome were surgical factors, namely increasing extent of resection ($P < .001$), longer operating time ($P = .038$), and greater requirement of perioperative blood transfusion ($P = .035$). Unlike the analysis of 90-day FTR, mFI was not found to be a significant independent predictor of 90-day mortality on multivariable analysis ($P = .103$; hence, excluded by the stepwise procedure), despite being significantly associated with 90-day mortality on univariable analysis ($P < .001$).

Further analysis found that this was largely due to the correlation between mFI and age (Spearman's rho: 0.30, $P < .001$). Consequently, after adjustment for the effect of age, the residual effect of mFI was not sufficient to reach statistical significance. Comparisons of the interplay between age and mFI with respect to the outcomes of 90-day mortality and FTR are visualized in Figure 3.

Discussion

This study has identified several independent risk factors that predict FTR after hepatectomy, which primarily relates to patient fitness: age, frailty, low BMI, and the presence of medical (versus surgical) complications. FTR is a surgical outcome metric that is increasingly reported in the literature,[1–10,17–23] but few studies have focused on identifying risk factors for FTR. In this study, we found that the FTR rate at 90 days was twofold higher than the 30-day FTR rate (35.4% vs 17.0%), which illustrates the importance of presenting 90-day outcome data after hepatectomy.[9,18] By contrast, other studies on FTR after hepatectomy have reported 30-day FTR only.[4,5,24] With the exception of age, the risk factors for FTR were different from the risk factors for mortality (Tables III and IV; Supplementary Table S2). As one might expect, mortality risk was related to the extent/complexity of hepatectomy, as reflected by the operating time and perioperative blood transfusion, whereas FTR risk was influenced by patient fitness rather than the extent of surgery. This finding contrasts with the results of 1 study of perihilar cholangiocarcinoma and 2 registry studies, which found significant associations between the extent of resection and FTR.[4,10,17]

In our study, patients who developed complications were particularly at risk of FTR if they had severe frailty (mFI of 2+) or combined medical and surgical complications, with odds ratios of 3.86 and 9.24, respectively. Given the observed differences between FTR and mortality, we would recommend that 90-day FTR rates should be presented along with mortality rates in future studies. The presence of a medical complication was the strongest independent risk factor for FTR in this study, with the FTR rising from 22.7% in surgical-only complications to 53.8% and 68.2%, respectively, in patients with medical-only or combined surgical and medical complications. The exact reasons why medical complications, in particular, increased the risk of FTR in this cohort of patients operated on in a high-volume center are unclear, but it is recognized that elderly or frail patients who develop surgical complications after major surgery are at high risk of acquiring secondary medical complications.[4,6–9,17] Indeed, frailty was found to be an independent risk factor for FTR in our study. The effects of frailty on outcomes after major surgery are well established,[25–28] and efforts to objectively assess frailty before major surgery may aid preoperative counseling and risk stratification. Patients at high risk of FTR after hepatectomy may also benefit from prehabilitation before surgery or could be offered lower-risk interventions than major hepatectomy, such as parenchyma-sparing hepatectomy or nonsurgical treatment.

The 4 factors identified as being significant independent predictors of 90-day FTR on multivariable analysis were used to produce a simple risk score, which was found to have acceptable performance, with an area under the ROC curve of 0.775. However, the decision to produce this score was made post hoc, on the recommendation of a reviewer. As such, the study was not designed with this aim in mind, so it was not optimized to produce a risk score. Specifically, no validation cohort was available to assess the real-world performance of the risk score, with the reported predictive accuracy based on an analysis of the cohort from which the score was derived, which likely represents an overestimate of performance due to the impact of overfitting. Consequently, although the risk score provides an interesting proof of concept, indicating that prediction of 90-day FTR risk after hepatectomy is likely possible, further validation of the score would be required before it could be considered for use in clinical practice.

Table III
Predictors of 90-day failure to rescue (part 1)

Factor	90-d FTR	Univariable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (per decade)*		2.02 (1.45–2.82)	< .001	1.65 (1.16–2.35)	.006
<65 y	17.6% (15/85)	-	-	-	-
65–74 y	44.3% (35/79)	-	-	-	-
75+ y	54.8% (23/42)	-	-	-	-
Sex			.060		NS
Female	27.0% (20/74)	1	-	-	-
Male	40.2% (53/132)	1.81 (0.97–3.37)	.060	-	-
Body mass index (per 5 kg/m^2)*		0.86 (0.65–1.13)	.269	0.67 (0.48–0.93)	.018
<25	37.7% (26/69)	-	-	-	-
25–29	38.8% (31/80)	-	-	-	-
30+	28.1% (16/57)	-	-	-	-
CCI (per point)*		1.23 (1.10–1.39)	< .001		NS
0–5	20.6% (13/63)	-	-	-	-
6–8	32.4% (23/71)	-	-	-	-
9+	51.4% (37/72)	-	-	-	-
ASA classification			.959		NS
2	35.3% (53/150)	1	-	-	-
3+	35.7% (20/56)	1.02 (0.54–1.93)	.959	-	-
Modified Frailty Index			.004		.044
0	26.7% (31/116)	1	-		
1	42.3% (30/71)	2.01 (1.07–3.75)	.029	1.87 (0.89–3.92)	.096
2+	63.2% (12/19)	4.70 (1.70–13.0)	.003	3.86 (1.19–12.5)	.024
Diagnosis			.324		NS
Colorectal liver metastases	39.6% (42/106)	1	-	-	-
Hepatocellular carcinoma	44.4% (8/18)	1.22 (0.44–3.34)	.700	-	-
Gallbladder/cholangiocarcinoma	26.3% (10/38)	0.54 (0.24–1.24)	.146	-	-
Other malignant	38.1% (8/21)	0.94 (0.36–2.46)	.896	-	-
Benign	21.7% (5/23)	0.42 (0.15–1.23)	.113	-	-

Univariable analyses are based on the $N = 206$ patients who developed Clavien–Dindo grade 3–5 complications during the index admission. Rates of 90-day FTR rates are reported for each subgroup as n/N (%). Separate univariable binary logistic regression models were then produced for each factor. All factors were then considered for inclusion in a multivariable binary logistic regression model using the backward-stepwise approach to variable selection; the final model was based on $N = 200$ ($N = 71$ events) after excluding cases with missing data for any of the factors considered.
CCI, Charlson comorbidity index; *FTR*, failure to rescue; *NS*, not selected for inclusion by the stepwise procedure; *OR*, odds ratio.
* For ordinal or continuous variables, FTR rates are reported within subgroups; the variables were then treated as continuous covariates in the logistic regression models, with odds ratios reported per the stated number of units increase.

The relationship between hospital volume and outcome after major surgery has been widely documented,[1,4–6,8,17–19,24] and several studies have demonstrated that the difference in outcomes between high- and low-volume centers is due to differences in rates of FTR.[7,17–19,23] It is a widely held belief that earlier diagnosis and more effective treatment of postoperative complications leads to lower FTR rates, which may be more achievable in high-volume centers. It is likely that multiple factors contribute to lower FTR rates in high-volume centers, including patient selection, perioperative management, and surgical technique. Earlier diagnosis and treatment of severe complications may be possible due to the greater experience of all members of the multidisciplinary team, including surgeons, anesthetists, intensivists, radiologists, gastroenterologists, and allied health professionals. The effect of team experience on FTR may be deduced from the significant reduction in 90-day FTR observed over the study period, from 42.9% in 2011 to 2013 to 32.8% from 2017 to 2018. High-volume centers frequently employ postoperative care pathways that allow rapid detection of any deviation from expected recovery. The observed reduction in FTR during the study period also coincided with the introduction of an ERAS pathway in our center in 2013. It is noteworthy that the incidence of severe complications did not change between 2011 and 2013 and between 2017 and 2018 (11.5% vs 11.9%; $P = .854$) and that the year of surgery was not significantly associated with 90-day FTR on multivariable analysis. This would suggest that the observed reduction in FTR over time was probably not related to any specific interventions such as ERAS but rather due to a stepwise accumulation of team and center experience. The results of this study demonstrate that FTR remains an important issue after hepatectomy, even in a high-volume center, perhaps due to a greater propensity to accept high-risk patients for major surgery compared to low-volume centers. It would be interesting to evaluate risk factors for FTR after hepatectomy in low-volume centers, although this would likely require multi-institutional studies.

Given that the risk factors for FTR in this study are predominantly related to preoperative fitness, it is logical that high-risk patients should be targeted for preoperative interventions designed to improve fitness for major surgery, with the potential for improved outcomes and lower FTR rates. Prehabilitation before major surgery has been adopted in several centers[11,29–32] and involves systematic assessment of a patient's physical fitness, nutritional status, and cardiopulmonary status, followed by targeted interventions, such as nutritional supplementation and exercise programs, with the aim of improving outcomes. In view of limited resources in many health care systems, focusing prehabilitation on patients at high risk of FTR is likely to yield the greatest benefit.

Study limitations

The main limitation of this study is its retrospective design, although this factor was minimized by the use of a prospectively maintained departmental database. Preoperative laboratory parameters were not routinely collected in the database, and it was therefore not possible to evaluate the potential role of serum albumin or other biochemical indices in predicting FTR. Although the presence and severity of specific postoperative complications are

Table IV
Predictors of 90-day failure to rescue (part 2)

Factor	90-d FTR	Univariable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Year of surgery (per year)*		0.88 (0.77–1.00)	.043		NS
2011–2013	42.9% (30/70)	-	-	-	-
2014–2016	30.7% (23/75)	-	-	-	-
2017–2018	32.8% (20/61)	-	-	-	-
Extent of resection			.300		NS
Minor	28.8% (19/66)	1	-	-	-
Major	35.9% (28/78)	1.39 (0.68–2.81)	.365	-	-
Extra-major	41.9% (26/62)	1.79 (0.86–3.72)	.121	-	-
Operative approach			.589		NS
Laparoscopic	29.4% (5/17)	1	-	-	-
Open	36.0% (68/189)	1.35 (0.46–3.99)	.589	-	-
Operating time (per hour)*		0.96 (0.84–1.10)	.572		NS
<5 h	36.7% (29/79)	-	-	-	-
5–6 h	35.8% (24/67)	-	-	-	-
7+ h	33.3% (18/54)	-	-	-	-
Perioperative blood transfusion			.789		NS
None	34.0% (50/147)	1	-	-	-
1–2 units	38.2% (13/34)	1.20 (0.56–2.60)	.642	-	-
>2 units	40.0% (10/25)	1.29 (0.54–3.09)	.562	-	-
Complication type			< .001		< .001
Surgical only	22.7% (30/132)	1	-	1	-
Medical only	53.8% (28/52)	3.97 (2.01–7.83)	< .001	4.00 (1.87–8.52)	< .001
Surgical and Medical	68.2% (15/22)	7.29 (2.72–19.5)	< .001	9.24 (2.89–29.6)	< .001

Univariable analyses are based on the $N = 206$ patients who developed Clavien–Dindo grade 3–5 complications during the index admission. Rates of 90-day FTR rates are reported for each subgroup as n/N (%). Separate univariable binary logistic regression models were then produced for each factor. All factors were then considered for inclusion in a multivariable binary logistic regression model using the backward-stepwise approach to variable selection; the final model was based on $N = 200$ ($N = 71$ events) after excluding cases with missing data for any of the factors considered.
CCI, Charlson comorbidity index; *FTR*, failure to rescue; *NS*, not selected for inclusion by the stepwise procedure; *OR*, odds ratio.
* For ordinal or continuous variables, FTR rates are reported within subgroups; the variables were then treated as continuous covariates in the logistic regression models, with odds ratios reported per the stated number of units increase.

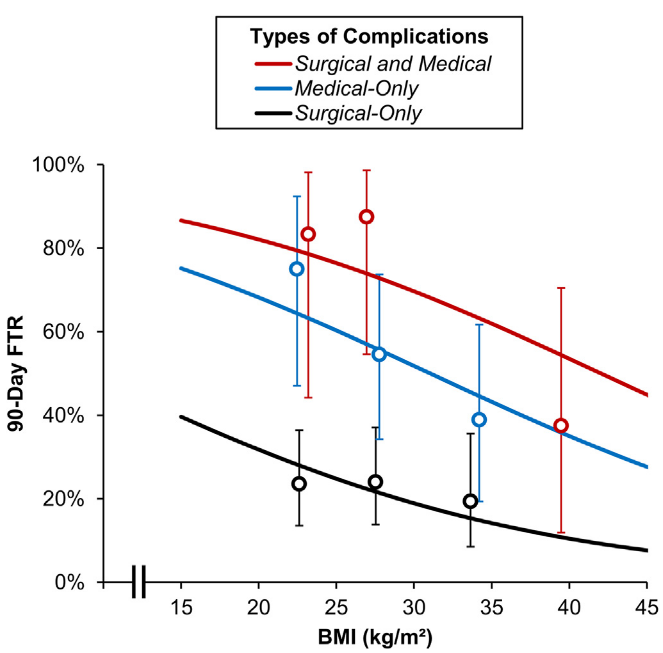

Figure 1. 90-day failure to rescue rates by body mass index (BMI) and types of complications Trend lines are from a binary logistic regression model, with 90-day failure to rescue as the dependent variable, BMI as a continuous covariate, and types of complications as a categorical covariate. Points represent the observed 90-day failure to rescue rate for patients in the BMI subgroups of <25, 25 to 29, and 30+ kg/m^2 and are plotted at the mean BMI within each subgroup, with whiskers representing 95% CIs. *BMI*, body mass index; *FTR*, failure to rescue.

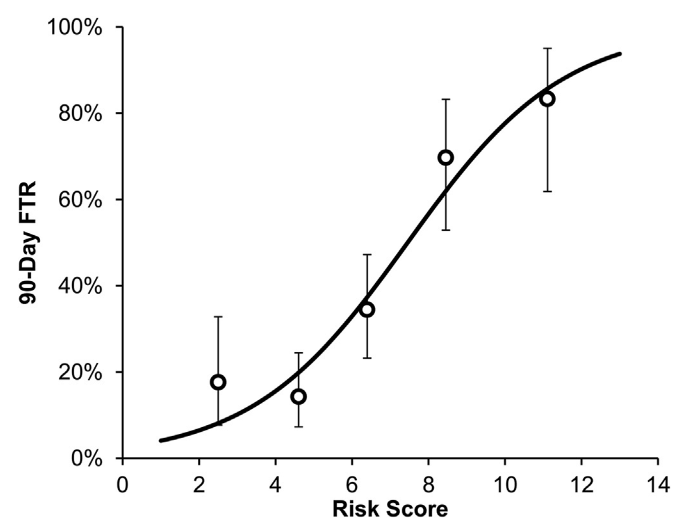

Figure 2. Association between risk score and 90-day failure to rescue The trend line is from a binary logistic regression model, treating the risk score from Supplementary Table S1 as a continuous covariate. Points represent the rates of 90-day FTR in patients with scores of <4, 4 to 5, 6 to 7, 8 to 9, and 10+ points and are plotted at the mean score in each interval, with whiskers representing 95% CIs. *FTR*, failure to rescue.

recorded in the database, it is not possible to determine the exact timing of complications or the temporal sequence in patients with multiple complications. This degree of granularity may give additional insights into the timing of diagnosis and treatment of complications and their impact on outcomes but would require a

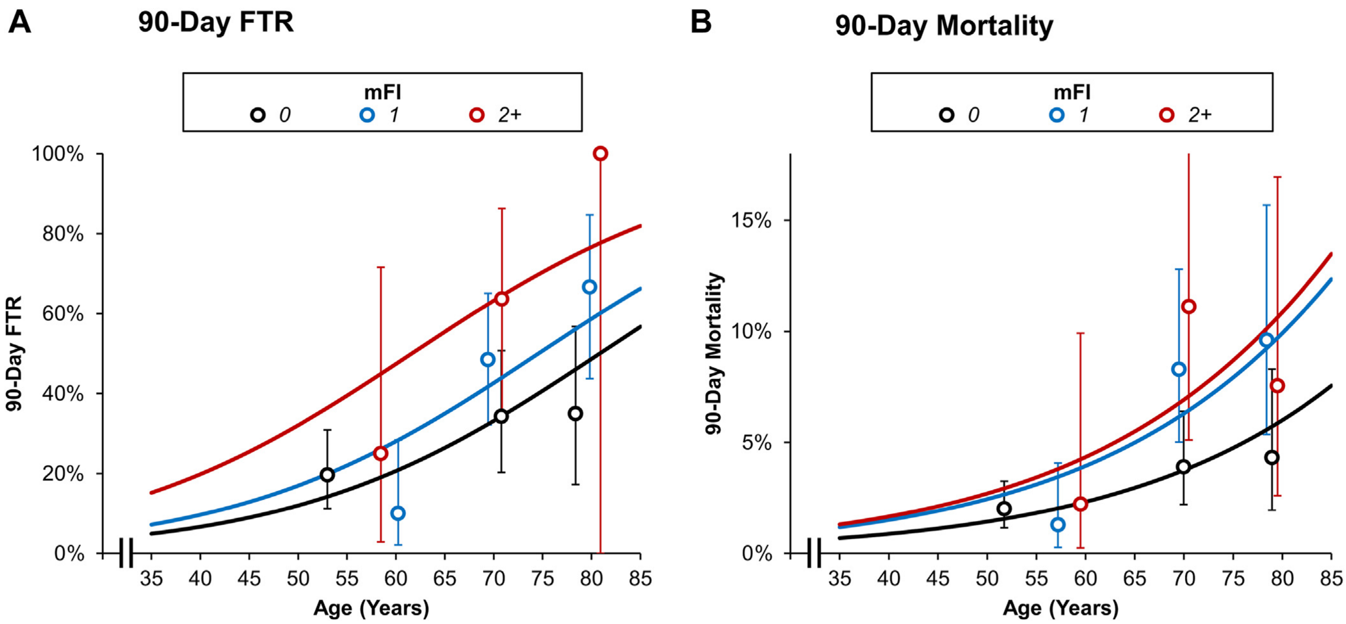

Figure 3. 90-day failure to rescue and mortality rates by age and modified frailty index trend lines are from binary logistic regression models, with 90-day FTR/mortality as the dependent variable, age as a continuous covariate, and modified frailty index as a categorical covariate. Points represent the observed 90-day failure to rescue/mortality rates for patients in the age subgroups of <65, 65 to 74, and 75+ years and are plotted at the mean age within each subgroup, with whiskers representing 95% CIs. *FTR*, failure to rescue; *mFI*, modified frailty index.

prospective study. It is also possible that some elderly and/or frail patients in this cohort may not have received maximal treatment escalation (eg, intensive care management for multiorgan failure) due to their premorbid status and perceived futility (eg, invasive treatment withheld or withdrawn). This is an important consideration that cannot be addressed by these data. Given that this study cohort was derived from a Western hepatobiliary center, as expected, the most common indication for hepatectomy was colorectal liver metastases. Therefore, the results of this study may not be generalizable to patients undergoing hepatectomy for hepatocellular carcinoma with or without cirrhosis, and further work in this patient population is required.

In conclusion, risk factors for FTR after hepatectomy in a high-volume center include age, frailty, low body mass index, and postoperative medical complications. Patients at risk of FTR should be appropriately counseled before major surgery and should be considered for less invasive treatments if possible. Prospective studies are needed to determine whether FTR rates in high-risk patients can be reduced by perioperative interventions, including prehabilitation.

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CRediT authorship contribution statement

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Supplementary materials

Supplementary materials associated with this article can be found in the online version, at [https://doi.org/10.1016/j.surg.2024.01.025].

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