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Impact of liver cirrhosis, severity of cirrhosis and portal hypertension on the difficulty of laparoscopic and robotic minor liver resections for primary liver malignancies in the anterolateral segments

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ABSTRACT

Introduction: We performed this study in order to investigate the impact of liver cirrhosis (LC) on the difficulty of minimally invasive liver resection (MILR), focusing on minor resections in anterolateral (AL) segments for primary liver malignancies.

Methods: This was an international multicenter retrospective study of 3675 patients who underwent MILR across 60 centers from 2004 to 2021.

Results: 1312 (35.7%) patients had no cirrhosis, 2118 (57.9%) had Child A cirrhosis and 245 (6.7%) had Child B cirrhosis. After propensity score matching (PSM), patients in Child A cirrhosis group had higher rates of open conversion ($p = 0.024$), blood loss >500 mls ($p = 0.001$), blood transfusion ($p < 0.001$), postoperative morbidity ($p = 0.004$), and in-hospital mortality ($p = 0.041$). After coarsened exact matching (CEM), Child A cirrhotic patients had higher open conversion rate ($p = 0.05$), greater median blood loss ($p = 0.014$) and increased postoperative morbidity ($p = 0.001$). Compared to Child A cirrhosis, Child B cirrhosis group had longer postoperative stay ($p = 0.001$) and greater major morbidity ($p = 0.012$) after PSM, and higher blood transfusion rates ($p = 0.002$), longer postoperative stay ($p < 0.001$), and greater major morbidity ($p = 0.006$) after CEM. After PSM, patients with portal hypertension experienced higher rates of blood loss >500 mls ($p = 0.003$) and intraoperative blood transfusion ($p = 0.025$).

Conclusion: The presence and severity of LC affect and compound the difficulty of MILR for minor resections in the AL segments. These factors should be considered for inclusion into future difficulty scoring systems for MILR.

1. Introduction

Minimally invasive liver resection (MILR) has been increasingly adopted worldwide due to its widely reported short-term benefits such as lower blood loss, reduced post-operative morbidity and shorter hospitalization stay, with no compromise in oncologic outcomes compared to the traditional approach [1,2]. Despite its many purported advantages, it remains a technically challenging undertaking requiring expertise in both liver resection as well as minimally invasive surgery. As such, consensus guidelines emphasize the need for stepwise progression along the learning curve in order to ensure patient safety [3,4]. To this end, several Difficulty Scoring Systems (DSS) [5] have been developed to facilitate preoperative objective stratification of surgical complexity, so as to enable appropriate case selections for surgeons according to their expertise level, proper risk counselling of patients, as well as fair audit of surgical outcomes [5–9].

Primary liver malignancies often arise on a background of liver cirrhosis (LC), which compounds the difficulty of resection [10]. The cirrhotic liver parenchyma is often stiff and less amenable to transection, and bleeding tendency is increased especially when there is concomitant portal hypertension, thrombocytopenia and coagulopathy [11]. Patients are also at greater risk of post-operative complications such as post-hepatectomy liver failure and death [12]. A recent multicentre study demonstrated that LC was associated with adverse outcomes in laparoscopic liver resections (LLR) [13]. Not surprisingly, a recent survey of surgeons also revealed that most surgeons considered LC has a major factor impacting the outcomes of LLR [14]. Nonetheless to date, none of the DSS have considered the presence of cirrhosis in the calculation of the final difficulty score [5]. In the Iwate score only 1 difficulty point is accorded for the presence Child-Pugh B cirrhosis, but no points are given for Child-Pugh A cirrhosis. To date, the presence of portal hypertension is not included in any DSS, likely because it was traditionally considered a contraindication for LR.

Although, previous studies had demonstrated the detrimental impact of LC on the outcomes of LLR, these studies were associated with several limitations such as including all types/extents of LLR including difficult and simple resections and including various pathologies such as liver metastases and benign tumors which could potentially confound the study result [15]. Some authors had also reported that the impact of LC on the outcomes of LLR correlated with the extent and difficulty of LLR [16]. LC resulted in poorer outcomes in patients undergoing more complex [Institut Mutualiste Montsouris (IMM) II/III] but not simpler IMM I LLR [16].

Hence, with these previous limitations in mind, we performed this matched-controlled study to analyze the impact of the presence and severity of LC as well as portal hypertension (PHT) on the difficulty of MILR focusing specifically on patients with primary liver malignancies undergoing minor resection in the anterolateral segments.

2. Methods

This was a retrospective review of 9064 patients who underwent minor MILR of the anterolateral segments (segment 2/3/4b/5/6) across 60 international centers between 2004 and 2021. Of these, 4363 MILR were performed for hepatocellular carcinoma, cholangiohepatoma or intrahepatic cholangiocarcinoma. All institutions obtained their respective approvals according to their local center's requirements. This study was approved by the Singapore General Hospital Institution Review Board and the need for patient consent was waived. The deidentified data were collected in the individual centers. These were collated and analyzed centrally at the Singapore General Hospital.

Only patients who underwent totally laparoscopic or robotic liver resections were included. Hand-assisted or laparoscopic-assisted cases were excluded. 428 patients who had previous liver surgery were excluded. Of the remaining 3935 patients, 177 with concomitant multiple liver resections were excluded and a further 83 patients who underwent concomitant major operations such as bilio-enteric anastomoses, colectomies, stoma reversal, gastrectomies, splenectomies and vascular resections were excluded. Finally, 3675 cases were included in this study. Of note, patients who underwent concomitant minor operations such as hernia repair, local ablation and hilar lymph node dissection were included.

2.1. Definitions

Liver resections were defined according to the 2000 Brisbane classification [17]. Anterolateral segments included segments 2/3/4b/5/6. Only minor resections were included and these were classified as segmentectomy or wedge/partial resections. Notably, left lateral sectionectomies were excluded. Traditional major resections classified as resection of 3 or more segments were excluded. Additionally, right anterior and right posterior sectionectomies were also considered as major resections in this study and excluded [18,19]. Diameter of the largest lesion was used in the cases of multiple tumors.

Difficulty of resections were graded according to the Iwate score [9]. Post-operative complications were classified according to the Clavien-Dindo classification and recorded for up to 30 days or during the same hospitalization [20]. Clinically significant portal hypertension (PHT) was defined as the presence of ascites, varices or splenomegaly with a platelet count of less than 100×10^9/L [15,21]. Information on the presence of splenomegaly was obtained from an individual center's preoperative radiologic reports.

2.2. Statistical analyses

Propensity score matching (PSM) [22] and Coarsened Exact Matching (CEM) [23] were used to estimate the effect of varying degrees of liver cirrhosis on minimally invasive minor anterolateral hepatectomy. For propensity score matching, the propensity score was estimated with logistic regression. The factors used in calculating the propensity score are the baseline variables stated in Table 1 – age at operation, gender, robotic or laparoscopic approach, previous abdominal operations, year of operation, ASA status, tumor type, tumor size, multifocality of tumor, concomitant minor operations or hilar lymph node dissection, type of resection, Iwate score and Iwate difficulty grade. For comparison in patients with or without portal hypertension, an additional variable of Child Pugh (CP) level was used in the matching. A random-effects parameter was also included in the model to account for between center variations.

For PSM of comparison of CP A cirrhotic against non-cirrhotic liver in Tables 1 and 2, patients of one strata were matched 1:1, using nearest neighbour matching, utilizing logit link, to patients of the other strata. To improve matching, a small caliper was used to achieve good balance of <0.1 across all variables after matching. During matching, any patient with missing data in any of the variables used for matching would be discarded. Similar methodology was employed for PSM comparison in Tables 3–6, comparing CP A to CP B, and cirrhosis with portal hypertension to cirrhosis without portal hypertension.

For CEM, continuous variables were coarsened using an automatic binning algorithm based on Sturge's rule into bins. Patients were 1:1 matched using with nearest neighbour matching without replacement within each stratum, any unmatched units in the stratum would be dropped. This methodology was applied to all 3 CEM models.

After matching, balance was checked via standardized mean difference across the covariates, with a threshold of 0.1 being indicative of tight match. Love plot of each match's covariate balance was plotted and presented below (**Supplementary data S1–S6**).

For unpaired comparisons of frequencies of categorical variables, Chi squared was used. For the unpaired comparisons of median values and interquartile ranges, Mann-Whitney *U* test was used, and for the comparisons of mean values and standard deviations, one-way test was used. For paired sample tests, McNemar's test was used for categorical

Table 1
Comparison between baseline characteristics of MILR if the anterolateral segments in Childs Pugh A cirrhosis v non-cirrhosis.

	All (N = 3430)	Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
		Child PughA Cirrhosis (N = 2118)	Non-cirrhosis (N = 1312)	P-value	Child Pugh A Cirrhosis (N = 991)	Non-cirrhosis (N = 991)	P-value (paired)	Child Pugh A Cirrhosis (N = 518)	Non-cirrhosis (N = 518)	P-value (paired)
Median age (IQR), yrs	64.00 [55.00, 72.00]	63.00 [55.00, 71.00]	64.00 [55.00, 73.00]	0.122	63.00 [55.00, 70.79]	64.00 [55.00, 72.00]	0.445	64.00 [56.00, 71.00]	64.00 [56.00, 71.00]	0.878
Male sex, n (%)	2468 (72.0)	1567 (74.0)	901 (68.7)	**0.001**	721 (72.8)	717 (72.4)	0.880	424 (81.9)	424 (81.9)	NA
Median BMI (IQR)	24.60 [22.21, 27.44]	24.70 [22.24, 27.52]	24.41 [22.20, 27.25]	0.076	24.60 [22.32, 27.62]	24.30 [22.03, 26.99]	0.072	24.60 [22.21, 27.00]	24.20 [22.10, 26.82]	0.338
Robotic, n (%)	400 (11.7)	221 (10.4)	179 (13.6)	0.005	138 (13.9)	128 (12.9)	0.555	24 (4.6)	24 (4.6)	NA
Laparoscopic, n (%)	3030 (88.3)	1897 (89.6)	1133 (86.4)		853 (86.1)	863 (87.1)		494 (95.4)	494 (95.4)	
Previous abdominal surgery, n (%)	670 (20.2)	399 (19.8)	271 (20.8)	0.508	194 (19.6)	202 (20.4)	0.694	63 (12.2)	63 (12.2)	NA
Year of surgery, n (%)										
2004–2009	193 (5.6)	132 (6.2)	61 (4.6)	**0.028**	61 (6.2)	53 (5.3)	0.325	19 (3.7)	19 (3.7)	NA
2010–2015	968 (28.2	617 (29.1)	351 (26.8)		279 (28.2)	279 (28.2)		127 (24.5)	127 (24.5)	
2016–2021	2269 (66.2)	1369 (64.6)	900 (68.6)		651 (65.7)	659 (66.5)		372 (71.8)	372 (71.8)	
ASA score, n (%)										
1/2	2356 (68.7)	1454 (68.7)	902 (68.8)	**0.987**	688 (69.4)	682 (68.8)	0.807	391 (75.5)	391 (75.5)	NA
3/4	1071 (31.3)	662 (31.3)	409 (31.2)		303 (30.6)	309 (31.2)		127 (24.5)	127 (24.5)	
Tumor type, n (%)										
HCC	3026 (88.4)	1989 (94.0)	1037 (79.5)	**<0.001**	926 (93.4)	923 (93.1)	0.815	514 (99.2)	514 (99.2)	NA
ICC/cholangiohepatoma	396 (11.6)	128 (6.0)	268 (20.5)		65 (6.6)	68 (6.9)		4 (0.8)	4 (0.8)	
Median tumor size, mm (IQR)	29.00 [20.00, 40.00]	26.00 [20.00, 37.00]	30.00 [21.00, 45.00]	**<0.001**	30.00 [20.00, 40.00]	30.00 [20.00, 40.00]	0.564	25.00 [20.00, 33.00]	25.00 [19.00, 35.00]	0.417
Multiple tumors, n (%)	302 (8.8)	206 (9.7)	96 (7.3)	**0.019**	68 (6.9)	75 (7.6)	0.597	9 (1.7)	9 (1.7)	NA
Wedge/partial, n (%)	2004 (58.4)	1319 (62.3)	685 (52.2)	**<0.001**	554 (55.9)	558 (56.3)	0.888	314 (60.6)	314 (60.6)	NA
Segmentectomy, n (%)	1426 (41.6)	799 (37.7)	627 (47.8)		437 (44.1)	433 (43.7)		204 (39.4)	204 (39.4)	
Concomitant minor surgery excluding cholecystectomy, n (%)	113 (3.3)	86 (4.1)	27 (2.1)	**0.002**	22 (2.2)	21 (2.1)	1.000	2 (0.4)	2 (0.4)	NA
Hilar lymph node dissection, n (%)	112 (3.3)	9 (0.4)	103 (7.9)	**<0.001**	9 (0.9)	13 (1.3)	0.453	1 (0.2)	1 (0.2)	NA
Median Iwate difficulty score, [IQR](range)	4.00 [3.00, 6.00] (1, 9)	4.00 [2.00, 6.00] (1, 9)	4.00 [3.00, 7.00] (1, 9)	**<0.001**	4.00 [3.00, 6.00] (1, 9)	4.00 [3.00, 6.00] (1, 9)	0.870	4.00 [3.00, 6.00] (1, 8)	4.00 [3.00, 6.00] (1, 8)	NA
Iwate difficulty, n (%)										
Low	1533 (44.7)	1053 (49.7)	480 (36.6)	**<0.001**	418 (42.2)	406 (41.0)	0.856	249 (48.1)	249 (48.1)	NA
Intermediate	1253 (36.6)	758 (35.8)	495 (37.8)		364 (36.7)	383 (38.6)		182 (35.1)	182 (35.1)	
High	642 (18.7)	306 (14.5)	336 (25.6)		209 (21.1)	202 (20.4)		87 (16.8)	87 (16.8)	

variables and Wilcoxon Signed-Rank test was used for continuous. The statistical analyses were performed with RStudio version 1.4.1717, R version 4.1.0.

3. Results

A total of 3675 patients were included for final analysis (Fig. 1). Of these, 1312 had no cirrhosis, 2118 had CP A cirrhosis and 245 patients had CP B cirrhosis.

3.1. Non-cirrhotic vs. CP A cirrhosis patients

A total of 3430 patients were enrolled in this cohort, including 2118 patients with CP A cirrhosis and 1312 patients without cirrhosis. The baseline characteristics are shown in Table 1. We conducted PSM and CEM to offset potential confounding factors. Before matching, gender ($p = 0.001$), year of surgery ($p = 0.028$), tumor type ($p < 0.001$), median tumor size ($p < 0.001$), multiple tumors ($p = 0.019$), surgical type ($p < 0.001$), concomitant minor surgery ($p = 0.002$), hilar lymph node dissection ($p < 0.001$), median difficulty score ($p < 0.001$), and IWATE difficulty score ($p < 0.001$) were statistically different between two groups. After 1:1 PSM, 991 matched pairs were included for further analysis. All the baseline characteristics of the two groups reached statistical equilibrium. Similarly, after 1:1 CEM matching, 518 matched pairs were included for further analysis and all baseline indicators reached equilibrium.

The perioperative outcomes are summarized in Table 2. In the entire unmatched cohort, the CP A cirrhosis group had a higher rate of open conversion (6.0% VS 4.3%, $p = 0.035$), blood loss >500 mls (11.4% VS 8.8%, $p = 0.018$), intraoperative blood transfusion (7.4% VS 4.5%, $p = 0.001$), rate of pringle maneuver application ($p < 0.001$), median postoperative stay ($p = 0.001$), postoperative morbidity ($p = 0.004$), in-

Table 2
Comparison between perioperative outcomes of MILR in Child's Pugh A cirrhosis vs non-cirrhosis.

	All (N = 3430)	Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:1 CEM		
		CP A Cirrhosis (N = 2118)	Non-cirrhosis (N = 1312)	P-value	CP A Cirrhosis (N = 991)	Non-cirrhosis (N = 991)	P-value (paired)	CP A Cirrhosis (N = 518)	Non-cirrhosis (N = 518)	P-value (paired)
Open conversion, n (%)	183 (5.3)	127 (6.0)	56 (4.3)	**0.035**	62 (6.3)	39 (3.9)	**0.024**	32 (6.2)	18 (3.5)	**0.050**
Median operating time (IQR), min	190.00 [135.00, 253.75]	190.00 [134.00, 250.00]	195.00 [140.00, 260.00]	0.062	192.00 [130.00, 260.00]	190.00 [135.00, 252.00]	0.479	190.00 [135.00, 250.00]	185.00 [130.00, 245.50]	0.532
Median blood loss (IQR), ml	150.00 [50.00, 300.00]	150.00 [50.00, 300.00]	150.00 [50.00, 300.00]	0.538	170.00 [50.00, 350.00]	150.00 [50.00, 300.00]	**<0.001**	150.00 [50.00, 300.00]	100.00 [50.00, 255.00]	**0.014**
Blood loss >500 mls, n (%)	343 (10.4)	232 (11.4)	111 (8.8)	**0.018**	132 (13.9)	81 (8.5)	**0.001**	51 (10.3)	44 (8.7)	0.380
Intraoperative blood transfusion, n (%)	216 (6.3)	157 (7.4)	59 (4.5)	**0.001**	77 (7.8)	39 (3.9)	**<0.001**	33 (6.4)	22 (4.2)	0.178
Pringle maneuver applied, n (%)	1626 (48.0)	942 (45.1)	684 (52.8)	**<0.001**	474 (48.5)	495 (50.6)	0.295	258 (50.2)	257 (50.1)	1.000
Median postoperative stay, d (IQR), mean (SD)	5.00 [4.00, 7.00], 6.56 (6.80)	5.00 [4.00, 7.00], 6.74 (7.47)	5.00 [4.00, 7.00], 6.28 (5.53)	**0.001**	5.00 [4.00, 7.00], 6.87 (9.51)	5.00 [4.00, 7.00], 6.31 (4.81)	0.114	6.00 [4.00, 8.00], 6.84 (5.68)	5.00 [4.00, 7.00], 6.55 (5.10)	0.104
Postoperative morbidity, n (%)	517 (15.1)	349 (16.5)	168 (12.8)	**0.004**	162 (16.4)	116 (11.7)	**0.004**	84 (16.3)	48 (9.3)	**0.001**
Major morbidity (Clavien-Dindo grade> 2), n (%)	120 (3.5)	75 (3.6)	45 (3.4)	0.940	36 (3.6)	30 (3.0)	0.525	17 (3.3)	15 (2.9)	0.855
Reoperation, n (%)	12 (0.3)	10 (0.5)	2 (0.2)	0.147	7 (0.7)	1 (0.1)	0.077	3 (0.6)	1 (0.2)	0.617
30-day readmission, n (%)	65 (1.9)	45 (2.1)	20 (1.5)	0.260	24 (2.4)	17 (1.7)	0.349	9 (1.7)	6 (1.2)	0.606
30-day mortality, n (%)	6 (0.2)	6 (0.3)	0 (0.0)	0.089	2 (0.2)	0 (0.0)	0.480	1 (0.2)	0 (0.0)	1.000
In-hospital mortality, n (%)	12 (0.3)	12 (0.6)	0 (0.0)	**0.005**	6 (0.6)	0 (0.0)	**0.041**	1 (0.2)	0 (0.0)	1.000
90-day mortality, n (%)	11 (0.3)	11 (0.5)	0 (0.0)	**0.009**	4 (0.4)	0 (0.0)	0.134	1 (0.2)	0 (0.0)	1.000

hospital mortality (p = 0.005), and 90-day mortality (p = 0.009) compared to non-cirrhotics. After 1:1 PSM, rate of open conversion (p = 0.024), median blood loss (p < 0.001), blood loss >500 mls (p = 0.001), intraoperative blood transfusion (p < 0.001), postoperative morbidity (p = 0.004), and in-hospital mortality (p = 0.041) were higher in the CP A cirrhosis group. In the 1:1 CEM cohort, the CP A cirrhosis group had higher rate of open conversion (p = 0.05), greater median blood loss (p = 0.014) and increased postoperative morbidity (p = 0.001).

3.2. CP A vs. CP B cirrhosis patients

In the entire unmatched cohort (2118 CP A group versus 245 CP B), there were some differences in median age, proportion of robotic versus laparoscopic approach, extent of surgery and median Iwate difficulty score excluding CP score (Table 3). After 1:1 PSM and 1:1 CEM, 215 and 191 pairs of patients were included for further comparison, respectively. All baseline differences disappeared in the matched patient cohorts.

Table 4 summarizes the perioperative outcomes. After 1:1PSM, the CP B cirrhosis group had a longer postoperative stay (p = 0.001) and a higher rate of major morbidity (p = 0.012). In the 1:1 CEM cohort, CP B patients had higher rates of blood transfusion (p = 0.002), longer postoperative stay (p < 0.001), and greater major morbidity (p = 0.006).

Cirrhotic patients (all CP grades) without vs. with PHT.

The entire unmatched cohort contained 626 patients with cirrhosis and PHT, and 1701 patients with cirrhosis but without PHT (Table 5). After 1:1 PSM and 1:1 CEM, 450 and 290 matched pair were included in each group, respectively, and all baseline characteristics were balanced (Table 5).

Perioperative outcomes are summarized in Table 6. In the 1:1PSM cohort, patients with PHT experienced higher rates of blood loss >500 mls (p = 0.003) and intraoperative blood transfusion (p = 0.025). There were no differences in other outcomes. After 1:1 CEM, the two groups had no significant differences in outcomes.

4. Discussion

Minor resections (wedge and segmentectomy) in AL segments are often considered the 'easiest' technical resections in MILR by almost all existing DSS. Both the Ban DSS [6] and its later modification, the Iwate criteria [9], allocate fewer difficulty points to lesions in superficial, anterolateral segments. In the Hasegawa score, lesions in anterolateral segments 2/3/4 are accorded lower scores (0 points) versus lesions in S5/6 (1 point) and S7/8 (2 points) [24]. The Southampton score assigns 0 difficulty points for minor resections, versus 2 points for technically major and 4 points for anatomically major resections respectively [7]. Finally, in the IMM score, wedge resection and left lateral sectionectomies are considered to be the simplest resections, while anterolateral segmentectomies are intermediate level [8]. As such, these cases are thought to be suitable for novice surgeons in the early stages of their learning curve for LLR.

In this large multicentre study, we found that patient with CP A cirrhosis who underwent minor LLR in the AL segments experienced higher rates of open conversion, blood loss and greater post-operative morbidity compared to patients with no cirrhosis. Although patient cohorts were matched to ensure there were no differences in preoperative baseline characteristics, the group with CP A cirrhosis had inferior perioperative outcomes. This implies that the presence of underlying LC does in fact, increase the complexity of LLR, even for technically 'easy' LLRs.

Previous studies had suggested that LC increased the complexity of LLR. Hobeika et al. analyzed 282 matched pairs of patients with and without cirrhosis who underwent LLR across 27 centers [13]. The LC group experienced higher rates of severe complications (odds ratio (OR) 1·74, 95% confidence interval (CI) 0·92 to 3·41; p = 0·096), PHLF (OR

Table 3
Comparison between baseline characteristics of MILR in 2118 Childs Pugh A vs 245 Childs Pugh B cirrhosis.

	All (N = 2363)	Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
		Childs Pugh A (N = 2118)	Childs Pugh B (N = 245)	P-value	Childs Pugh A (N = 215)	Childs Pugh B (N = 215)	P-value (paried)	Childs Pugh A (N = 191)	Childs Pugh B (N = 191)	P-value (paired)
Median age (IQR), yrs	63.00 [55.00, 71.00]	63.00 [55.00, 71.00]	61.00 [51.00, 69.00]	**0.002**	59.00 [52.10, 68.00]	61.00 [51.00, 70.00]	0.791	61.00 [53.00, 69.00]	60.00 [51.00, 68.95]	0.068
Male sex, n (%)	1760 (74.5)	1567 (74.0)	193 (78.8)	0.121	172 (80.0)	171 (79.5)	1.000	156 (81.7)	156 (81.7)	NA
BMI	24.70 [22.28, 27.50]	24.70 [22.24, 27.52]	24.94 [22.48, 27.33]	0.873	24.16 [22.05, 26.65]	24.77 [22.43, 27.12]	0.275	24.72 [23.01, 27.19]	24.40 [22.15, 26.97]	0.113
Robotic, n (%)	260 (11.0)	221 (10.4)	39 (15.9)	**0.013**	36 (16.7)	33 (15.3)	0.787	23 (12.0)	23 (12.0)	NA
Laparoscopic, n (%)	2103 (89.0)	1897 (89.6)	206 (84.1)		179 (83.3)	182 (84.7)		168 (88.0)	168 (88.0)	
Previous abdominal surgery, n (%)	440 (19.5)	399 (19.8)	41 (17.2)	0.385	33 (15.3)	38 (17.7)	0.603	27 (14.1)	27 (14.1)	NA
Year of surgery, n (%)										
2004–2009	148 (6.3)	132 (6.2)	16 (6.5)	0.174	14 (6.5)	14 (6.5)	0.873	11 (5.8)	11 (5.8)	NA
2010–2015	702 (29.7)	617 (29.1)	85 (34.7)		71 (33.0)	70 (32.6)		65 (34.0)	65 (34.0)	
2016–2021	1513 (64.0)	1369 (64.6)	144 (58.8)		130 (60.5)	131 (60.9)		115 (60.2)	115 (60.2)	
ASA score, n (%)										
1/2	1621 (68.7)	1454 (68.7)	167 (68.2)	0.918	138 (64.2)	147 (68.4)	0.342	135 (70.7)	135 (70.7)	NA
3/4	740 (31.3)	662 (31.3)	78 (31.8)		77 (35.8)	68 (31.6)		56 (29.3)	56 (29.3)	
Tumor type, n (%)										
HCC	2225 (94.2)	1989 (94.0)	236 (96.3)	0.174	213 (99.1)	213 (99.1)	1.000	191 (100.0)	191 (100.0)	NA
ICC/cholangiohepatoma	137 (5.8)	128 (6.0)	9 (3.7)		2 (0.9)	2 (0.9)		0 (0.0)	0 (0.0)	
Median tumor size, mm (IQR)	26.00 [20.00, 38.00]	26.00 [20.00, 37.00]	30.00 [20.00, 45.00]	0.026	28.00 [20.00, 45.00]	30.00 [20.00, 45.00]	0.839	30.00 [20.00, 43.50]	30.00 [20.00, 45.00]	0.259
Multiple tumors, n (%)	230 (9.7)	206 (9.7)	24 (9.8)	1.000	15 (7.0)	17 (7.9)	0.855	5 (2.6)	5 (2.6)	NA
Wedge/partial liver resection, n (%)	1444 (61.1)	1319 (62.3)	125 (51.0)	**0.001**	99 (46.0)	116 (54.0)	0.068	97 (50.8)	97 (50.8)	NA
Segmentectomy, n (%)	919 (38.9)	799 (37.7)	120 (49.0)		116 (54.0)	99 (46.0)		94 (49.2)	94 (49.2)	
Concomitant minor surgery excluding cholecystectomy, n (%)	100 (4.2)	86 (4.1)	14 (5.7)	0.289	10 (4.7)	12 (5.6)	0.823	6 (3.1)	6 (3.1)	NA
Hilar lymph node dissection, n (%)	10 (0.4)	9 (0.4)	1 (0.4)	1.000	2 (0.9)	1 (0.5)	1.000	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score excluding Child score, [IQR] (range)	4.00 [2.00, 6.00] (1, 9)	4.00 [2.00, 6.00] (1, 9)	4.00 [2.00, 6.00] (1, 8)	**0.046**	4.00 [3.00, 6.00] (1, 8)	4.00 [2.00, 6.00] (1, 8)	0.293	4.00 [3.00, 6.00] (1, 8)	4.00 [3.00, 6.00] (1, 8)	NA
Iwate difficulty exclude Child score, n (%)										
Low	1157 (49.0)	1055 (49.8)	102 (41.6)	0.043	87 (40.5)	94 (43.7)	0.507	80 (41.9)	80 (41.9)	NA
Intermediate	859 (36.4)	760 (35.9)	99 (40.4)		79 (36.7)	81 (37.7)		71 (37.2)	71 (37.2)	
High	346 (14.6)	302 (14.3)	44 (18.0)		49 (22.8)	40 (18.6)		40 (20.9)	40 (20.9)	

7·13, 0·91 to 323·10; p = 0·068), and a higher risk of death (OR 5·13, 1·08 to 48·61; p = 0·039) versus non-cirrhotics. Similarly, Goh et al. reported a single-center matched study compared MILR in patients with LC versus without, and found that the LC group had greater blood loss, higher blood transfusion rates, increased conversion and postoperative morbidity, as well as longer operation times and postoperative hospital stay [16]. In the aforementioned study, 41% of lesions were located in 'difficult segments (I, IVa, VII, VIII). Hence, a major difference from our study was that both the Hobeika et al. and Goh et al. studies contained a mixture of major and minor LLRs. Interestingly, Goh et al. found that upon subset analyses, LC only significantly impacted outcomes of more complex resection [Institut Mutualiste Montsouris (IMM) II/III] and not simpler IMM I resections [16].

Hence, in contrast to these previous studies; the present study focused exclusively on "technically simple" minor resections in the AL segments, so as to minimise the confounding effect of tumour location and extent of resection on perioperative outcomes. Furthermore, only patients with primary malignancies were included unlike previous studies [13,16], as a major confounding factor in these studies was the inclusion of patients with other pathologies including benign lesions and colorectal liver metastases which occurred more frequently in the non-cirrhotic cohort. In the present analysis, despite controlling for various factors the LC cohort was associated with significantly poorer outcomes compared to the non-cirrhotic arm. These results suggest that there is room to further refine existing DSS for MILR by incorporating the presence of cirrhosis as a variable into the computation of scores. This will facilitate a more accurate preoperative estimation of technical difficulty, so as to allow appropriate case selection according to the expertise level of individual surgeons.

In the second part of this study, we compared outcomes following LLR for patients with CP B versus CP A. Major morbidity rates were higher in CP B cirrhosis, and this ultimately resulted in longer LOS as well. It is worthwhile to note, however, that intra-operative outcomes (operating time, blood loss, transfusion, conversion rates) were similar. These results were similar to Watanabe's study [25], where 357 LLR patients were divided into three cohorts as follows: CP A (n = 280), CP B7 (n = 42) and CP B8/9 (n = 35) (22). 14% of patients in the CP A cohort underwent anatomic resection while all patients in the advanced cirrhosis group had non-anatomical resections. Patients with CP B cirrhosis had significantly more post-operative complications versus CP A (P = 0.033), with no differences in operative time and blood loss. Furthermore, the CP B8/9 group had significantly higher complication rate than other two groups (CP A vs. B7 vs. B8/9: 8.2% vs. 9.6% vs. 26%, respectively; p = 0.010). Troisi et al. performed a multicenter PSM study for patients with CP B cirrhosis who underwent open versus LLR for hepatocellular carcinoma [26]. Amongst the LLR cohort, patients with CP B9 developed more complications compared to those with B8 and B7 cirrhosis. From this, we can infer that although the severity of cirrhosis might not directly impact the conduct of surgery, patients with severe liver disease are more systemically unwell and hence they are at greater

Table 4
Comparison between perioperative outcomes of MILR in Child's Pugh A vs B cirrhosis.

	All (N = 2363)	Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:1 CEM		
		Childs Pugh A (N = 2118)	Childs Pugh B (N = 245)	P-value	Childs Pugh A (N = 215)	Childs Pugh B (N = 215)	P-value (paried)	Childs Pugh A (N = 191)	Childs Pugh B (N = 191)	P-value (paired)
Open conversion, n (%)	138 (5.8)	127 (6.0)	11 (4.5)	0.419	10 (4.7)	8 (3.7)	0.803	10 (5.2)	9 (4.7)	1.000
Median operating time (IQR), min	190.00 [135.00, 250.00]	190.00 [134.00, 250.00]	201.50 [144.00, 260.00]	0.164	200.00 [143.00, 269.50]	194.00 [143.00, 260.00]	0.469	200.00 [145.00, 258.00]	200.50 [149.25, 260.00]	0.737
Median blood loss (IQR), ml	150.00 [50.00, 300.00]	150.00 [50.00, 300.00]	150.00 [50.00, 350.00]	0.078	200.00 [52.50, 400.00]	150.00 [60.00, 350.00]	0.738	150.00 [100.00, 350.00]	180.00 [84.50, 400.00]	0.482
Blood loss >500 mls, n (%)	270 (11.9)	232 (11.4)	38 (15.9)	0.056	26 (12.4)	32 (15.2)	0.568	26 (13.9)	32 (17.2)	0.451
Intraoperative blood transfusion, n (%)	200 (8.5)	157 (7.4)	43 (17.6)	**<0.001**	29 (13.5)	37 (17.2)	0.332	15 (7.9)	37 (19.4)	**0.002**
Pringle maneuver applied, n (%)	1045 (44.8)	942 (45.1)	103 (42.9)	0.571	93 (44.3)	97 (46.2)	0.766	94 (50.3)	82 (43.6)	0.213
Median postoperative stay, d (IQR), mean (SD)	6.00 [4.00, 8.00], 7.05 (7.60)	5.00 [4.00, 7.00], 6.74 (7.47)	7.00 [5.00, 13.00], 9.66 (8.21)	**<0.001**	6.00 [4.00, 10.00], 9.07 (18.02)	7.00 [5.00, 13.00], 9.53 (7.11)	**0.001**	6.00 [4.00, 8.00], 7.09 (6.42)	8.00 [5.00, 13.00], 9.70 (7.67)	**<0.001**
Postoperative morbidity, n (%)	408 (17.3)	349 (16.5)	59 (24.1)	**0.004**	40 (18.6)	50 (23.3)	0.282	37 (19.4)	45 (23.6)	0.374
Major morbidity (Clavien-Dindo grade> 2), n (%)	100 (4.2)	75 (3.6)	25 (10.2)	**<0.001**	7 (3.3)	20 (9.3)	**0.012**	4 (2.1)	18 (9.4)	**0.006**
Reoperation, n (%)	12 (0.5)	10 (0.5)	2 (0.8)	0.358	0 (0.0)	2 (0.9)	0.480	0 (0.0)	0 (0.0)	NA
30-day readmission, n (%)	50 (2.1)	45 (2.1)	5 (2.0)	1.000	4 (1.9)	4 (1.9)	1.000	7 (3.7)	3 (1.6)	0.343
30-day mortality, n (%)	10 (0.4)	6 (0.3)	4 (1.6)	**0.014**	1 (0.5)	3 (1.4)	0.617	0 (0.0)	2 (1.0)	0.480
In-hospital mortality, n (%)	14 (0.6)	12 (0.6)	2 (0.8)	0.650	1 (0.5)	1 (0.5)	1.000	0 (0.0)	2 (1.0)	0.480
90-day mortality, n (%)	16 (0.7)	11 (0.5)	5 (2.0)	0.019	2 (0.9)	3 (1.4)	1.000	0 (0.0)	2 (1.0)	0.480

risk of post-operative complications. One important application of DSS for MILR is to enable appropriate preoperative risk counselling for patients. To this end, the inclusion of the presence of cirrhosis as well as its severity into future DSS would enhance its effectiveness.

Finally, we found that patients with cirrhosis as well as PHT had slightly higher rates of blood loss ($P < 0.001$) and blood transfusion ($P = 0.025$) on PSM compared to their counterparts with no PHT, although the differences did not persist on CEM. This suggests that the MIS approach may partially mitigate the risks of LR in this group of patients, particularly that of bleeding. The magnified laparoscopic view in MILR allows precise dissection of vasculobiliary structures, which may be ligated by surgical clips and energy devices [26], while continuous pneumoperitoneum pressure tamponades venous ooze from the liver surface.

A key strength of this study is that it contains one of the largest multicentre patient cohorts to date, from both Eastern and Western units and focussed on a specific subset of patients undergoing MILR. However, there are several limitations that must be highlighted. The retrospective nature of this study, as well as the inclusion of patients over a relatively long period meant that information and selection biases are inherent despite the utilization of two robust statistical matching techniques. Most cases were performed in high-volume centers and the results may not be readily generalizable. However, the recent move to centralise complex surgical procedures to specialty units may mean that this is a realistic portrayal of surgical practises in the near future. Almost 40% of resections in this study were segmentectomies. As such, the median Iwate score was 4, places them in the 'intermediate' difficulty category, hence cases were slightly more complex despite being in the 'easy' anterolateral segments. The proportion of patients with CP B cirrhosis and PHT were also relatively small. Furthermore, although the measurement of hepatic venous-portal gradient is the gold standard for the diagnosis of portal hypertension, this invasive method is not routinely used in most centers prior to liver resection. Hence, a simple definition was used for the presence of clinically-significant PHT due to the limitations of this study. Finally, as an international multicenter study, there would be heterogeneity in each individual center's surgical technique, selection process and postoperative management.

5. Conclusion

This study demonstrated that the presence and severity of LC affected and compounded the difficulty of LLR even for 'simple' minor resections in AL segments, resulting in higher rates of open conversion, blood loss and greater post-operative morbidity. Inclusion of cirrhosis into future DSS would be important for case selection and would allow more accurate benchmarking of cases for surgical audits.

Ethical approval for research

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Name of principal investigator

Peter Kingham.

Table 5
Comparison between baseline characteristics of MILR in 2361 cirrhosis patients with and without portal hypertension.

	All (N = 2327)	Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
		Cirrhosis PHT (N = 626)	Cirrhosis NPHT (N = 1701)	P-value	Cirrhosis PHT (N = 450)	Cirrhosis NPHT (N = 450)	P-value	Cirrhosis PHT (N = 290)	Cirrhosis NPHT (N = 290)	P-value (paired)
Median age (IQR), yrs	63.00 [55.00, 71.00]	63.00 [55.00, 71.00]	63.00 [55.00, 71.00]	0.734	62.00 [54.00, 70.00]	64.00 [55.00, 70.00]	0.217	61.00 [54.00, 69.00]	62.00 [55.00, 69.00]	0.607
Male sex, n (%)	1731 (74.4)	468 (74.8)	1263 (74.3)	0.844	339 (75.3)	335 (74.4)	0.822	230 (79.3)	230 (79.3)	NA
Median BMI (IQR)	24.68 [22.22, 27.45]	25.08 [22.84, 28.00]	24.50 [22.10, 27.25]	**<0.001**	24.93 [22.50, 27.70]	25.00 [22.49, 27.68]	0.826	24.80 [22.70, 27.40]	24.34 [22.16, 27.24]	0.426
Robotic, n (%)	260 (11.2)	56 (8.9)	204 (12.0)	**0.046**	43 (9.6)	41 (9.1)	0.907	12 (4.1)	12 (4.1)	NA
Laparoscopic, n (%)	2067 (88.8)	570 (91.1)	1497 (88.0)		407 (90.4)	409 (90.9)		278 (95.9)	278 (95.9)	
Previous abdominal surgery, n (%)	436 (19.7)	142 (22.7)	294 (18.5)	**0.028**	98 (21.8)	97 (21.6)	1.000	36 (12.4)	36 (12.4)	NA
Childs Pugh A, n (%)	2082 (89.5)	1581 (92.9)	501 (80.0)	**0.028**	392 (87.1)	398 (88.4)	0.561	280 (96.6)	280 (96.6)	NA
Childs Pugh B, n (%)	245 (10.5)	120 (7.1)	125 (20.0)		58 (12.9)	52 (11.6)		10 (3.4)	10 (3.4)	
Year of surgery, n (%)										
2004–2009	144 (6.2)	48 (7.7)	96 (5.6)	0.113	33 (7.3)	37 (8.2)	0.939	10 (3.4)	10 (3.4)	NA
2010–2015	692 (29.7)	173 (27.6)	519 (30.5)		121 (26.9)	118 (26.2)		92 (31.7)	92 (31.7)	
2016–2021	1491 (64.1)	405 (64.7)	1086 (63.8)		296 (65.8)	295 (65.6)		188 (64.8)	188 (64.8)	
ASA score, n (%)										
1/2	1604 (69.0)	393 (62.8)	1211 (71.3)	**<0.001**	298 (66.2)	297 (66.0)	1.000	205 (70.7)	205 (70.7)	NA
3/4	721 (31.0)	233 (37.2)	488 (28.7)		152 (33.8)	153 (34.0)		85 (29.3)	85 (29.3)	
Tumor type, n (%)										
HCC	2194 (94.3)	613 (97.9)	1581 (93.0)	**<0.001**	441 (98.0)	440 (97.8)	1.000	288 (99.3)	288 (99.3)	NA
ICC/cholangiohepatoma	132 (5.7)	13 (2.1)	119 (7.0)		9 (2.0)	10 (2.2)		2 (0.7)	2 (0.7)	
Median tumor size, mm (IQR)	26.00 [20.00, 38.00]	25.00 [18.00, 35.00]	27.00 [20.00, 40.00]	**<0.001**	25.00 [18.00, 35.00]	25.00 [20.00, 35.00]	0.620	23.50 [18.00, 32.00]	25.00 [19.25, 30.00]	0.748
Multiple tumors, n (%)	228 (9.8)	50 (8.0)	178 (10.5)	0.088	35 (7.8)	32 (7.1)	0.807	4 (1.4)	4 (1.4)	NA
Wedge/partial liver resection, n (%)	1420 (61.0)	410 (65.5)	1010 (59.4)	**0.008**	291 (64.7)	293 (65.1)	0.942	199 (68.6)	199 (68.6)	NA
Segmentectomy, n (%)	907 (39.0)	216 (34.5)	691 (40.6)		159 (35.3)	157 (34.9)		91 (31.4)	91 (31.4)	
Concomitant minor surgery excluding cholecystectomy, n (%)	95 (4.1)	31 (5.0)	64 (3.8)	0.242	22 (4.9)	21 (4.7)	1.000	5 (1.7)	5 (1.7)	NA
Hilar lymph node dissection, n (%)	9 (0.4)	5 (0.8)	4 (0.2)	0.065	0 (0.0)	1 (0.2)	1.000	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score, [IQR] (range)	4.00 [3.00, 6.00] (1, 9)	4.00 [2.00, 6.00] (1, 9)	4.00 [3.00, 6.00] (1, 9)	0.008	3.00 [2.00, 6.00] (1, 8)	3.00 [2.00, 5.00] (1, 9)	0.704	3.00 [2.00, 5.00] (1, 9)	3.00 [2.00, 5.00] (1, 9)	NA
Iwate difficulty, n (%)										
Low	1097 (47.2)	309 (49.4)	788 (46.4)	0.013	232 (51.6)	233 (51.8)	0.533	169 (58.3)	169 (58.3)	NA
Intermediate	841 (36.2)	236 (37.7)	605 (35.6)		152 (33.8)	164 (36.4)		97 (33.4)	97 (33.4)	
High	388 (16.7)	81 (12.9)	307 (18.1)		66 (14.7)	53 (11.8)		24 (8.3)	24 (8.3)	

Possible conflict of interest

Yes.

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Table 6
Comparison between perioperative outcomes of MILR in cirrhosis patients with and without PHT.

	All (N = 2327)	Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:1 CEM		
		Cirrhosis PHT (N = 626)	Cirrhosis NPHT (N = 1701)	P-value	Cirrhosis PHT (N = 450)	Cirrhosis NPHT (N = 450)	P-value	Cirrhosis PHT (N = 290)	Cirrhosis NPHT (N = 290)	P-value (paired)
Open conversion, n (%)	137 (5.9)	49 (7.8)	88 (5.2)	**0.021**	38 (8.4)	25 (5.6)	0.118	25 (8.6)	13 (4.5)	0.067
Median operating time (IQR), min	190.00 [136.00, 252.00]	180.00 [124.00, 245.00]	195.00 [140.00, 255.00]	**0.010**	180.00 [124.50, 250.00]	185.00 [134.00, 240.00]	0.872	180.00 [124.25, 240.00]	180.00 [130.00, 243.00]	0.563
Median blood loss (IQR), ml	150.00 [50.00, 300.00]	200.00 [50.00, 350.00]	110.00 [50.00, 300.00]	**<0.001**	200.00 [100.00, 400.00]	120.00 [50.00, 300.00]	**<0.001**	200.00 [100.00, 327.50]	150.00 [50.00, 300.00]	0.046
Blood loss >500 mls, n (%)	262 (11.7)	89 (14.8)	173 (10.6)	**0.008**	70 (15.9)	39 (9.0)	**0.003**	36 (13.0)	34 (12.5)	0.787
Intraoperative blood transfusion, n (%)	198 (8.5)	65 (10.4)	133 (7.8)	0.061	51 (11.3)	31 (6.9)	**0.025**	24 (8.3)	17 (5.9)	0.296
Pringle maneuver applied, n (%)	1033 (45.0)	281 (45.4)	752 (44.8)	0.850	199 (44.5)	186 (41.6)	0.446	127 (43.9)	113 (39.6)	0.298
Median postoperative stay, d (IQR), mean (SD)	6.00 [4.00, 8.00], 7.09 (7.65)	5.00 [4.00, 8.00], 7.08 (6.96)	6.00 [4.00, 8.00], 7.09 (7.89)	0.231	5.77 [4.00, 8.00], 7.01 (6.21)	5.00 [4.00, 7.00], 6.98 (12.59)	0.141	5.00 [4.00, 7.00], 7.04 (7.23)	5.00 [4.00, 8.00], 6.82 (5.29)	0.887
Postoperative morbidity, n (%)	402 (17.3)	128 (20.5)	274 (16.2)	0.017	78 (17.4)	73 (16.3)	0.721	54 (18.6)	42 (14.5)	0.201
Major morbidity (Clavien-Dindo grade> 2), n (%)	98 (4.2)	33 (5.3)	65 (3.8)	0.155	23 (5.1)	15 (3.3)	0.243	11 (3.8)	10 (3.4)	1.000
Reoperation, n (%)	12 (0.5)	3 (0.5)	9 (0.5)	1.000	2 (0.4)	2 (0.4)	1.000	1 (0.3)	1 (0.3)	1.000
30-day readmission, n (%)	50 (2.2)	12 (1.9)	38 (2.2)	0.754	11 (2.4)	14 (3.1)	0.663	6 (2.1)	8 (2.8)	0.789
30-day mortality, n (%)	9 (0.4)	2 (0.3)	7 (0.4)	1.000	1 (0.2)	2 (0.4)	1.000	2 (0.7)	1 (0.3)	1.000
In-hospital mortality, n (%)	13 (0.6)	2 (0.3)	11 (0.6)	0.533	1 (0.2)	1 (0.2)	1.000	2 (0.7)	2 (0.7)	1.000
90-day mortality, n (%)	15 (0.6)	2 (0.3)	13 (0.8)	0.380	1 (0.2)	3 (0.7)	0.617	2 (0.7)	3 (1.0)	1.000

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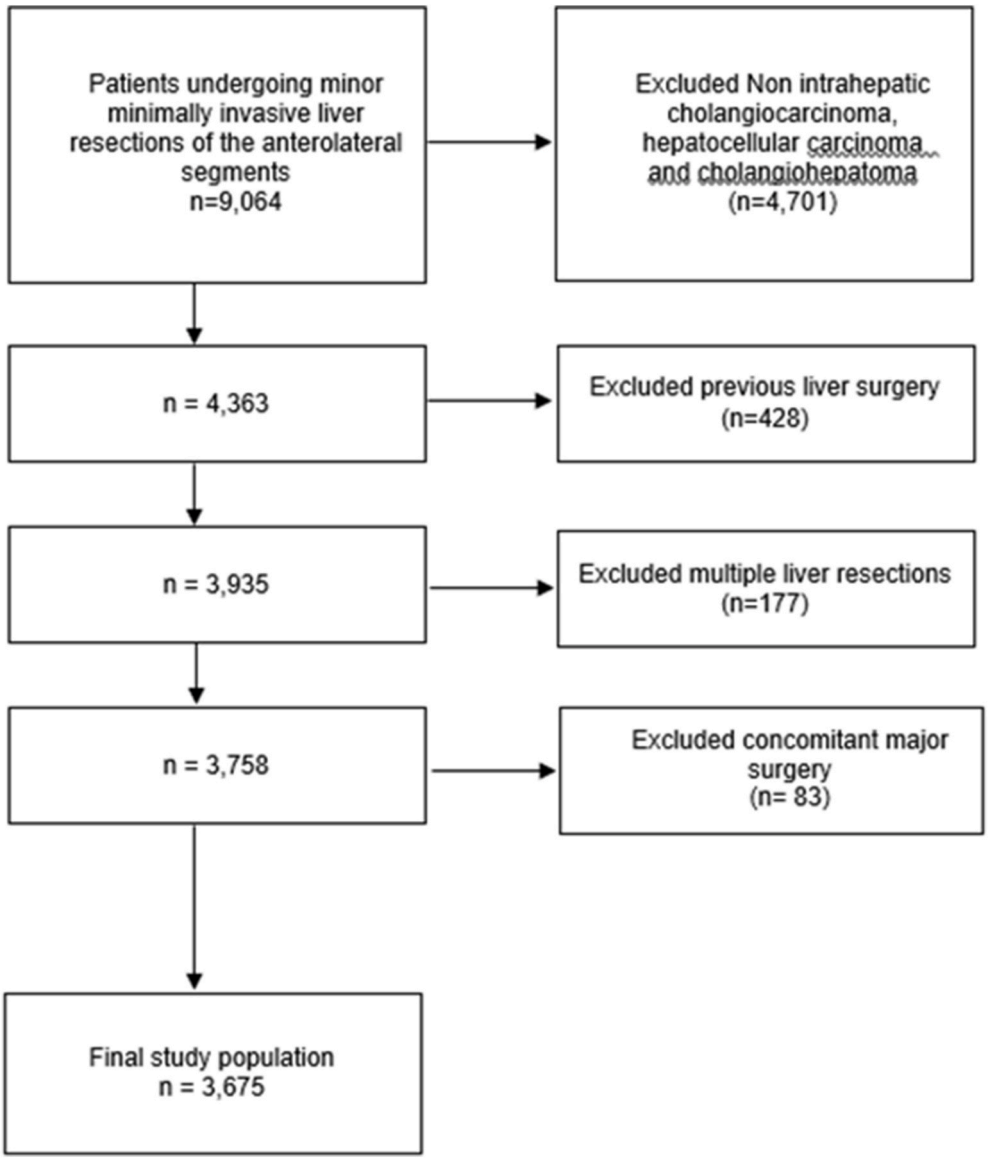

Fig. 1. Selection of patients meeting study inclusion criteria.

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i) Dr Goh BK has received travel grants, honorarium and research grants from Johnson and Johnson, Olympus and Intuitive Surgery.
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Appendix A. Supplementary data

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