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Impact of liver cirrhosis, the severity of cirrhosis, and portal hypertension on the outcomes of minimally invasive left lateral sectionectomies for primary liver malignancies

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Background: The impact of cirrhosis and portal hypertension on perioperative outcomes of minimally invasive left lateral sectionectomies remains unclear. We aimed to compare the perioperative outcomes between patients with preserved and compromised liver function (noncirrhotics versus Child-Pugh A) when undergoing minimally invasive left lateral sectionectomies. In addition, we aimed to determine if the extent of cirrhosis (Child-Pugh A versus B) and the presence of portal hypertension had a significant impact on perioperative outcomes.

Methods: This was an international multicenter retrospective analysis of 1,526 patients who underwent minimally invasive left lateral sectionectomies for primary liver malignancies at 60 centers worldwide between 2004 and 2021. In the study, 1,370 patients met the inclusion criteria and formed the final study group. Baseline clinicopathological characteristics and perioperative outcomes of these patients were compared. To minimize confounding factors, 1:1 propensity score matching and coarsened exact matching were performed.

Results: The study group comprised 559, 753, and 58 patients who did not have cirrhosis, Child-Pugh A, and Child-Pugh B cirrhosis, respectively. Six-hundred and thirty patients with cirrhosis had portal hypertension, and 170 did not. After propensity score matching and coarsened exact matching, Child-Pugh A patients with cirrhosis undergoing minimally invasive left lateral sectionectomies had longer operative time, higher intraoperative blood loss, higher transfusion rate, and longer hospital stay than patients without cirrhosis. The extent of cirrhosis did not significantly impact perioperative outcomes except for a longer duration of hospital stay.

Conclusion: Liver cirrhosis adversely affected the intraoperative technical difficulty and perioperative outcomes of minimally invasive left lateral sectionectomies.

Introduction

Minimally invasive liver resections (MILRs) have been increasingly performed during the past 2 decades.[1–3] With the advent of surgical technology, improved anesthetic knowledge of the physiological effects of MILR, and accumulating laparoscopic expertise among hepatobiliary surgeons, several robust studies have shown improved perioperative outcomes in MILR compared with open liver resections with regards to the peri- and early postoperative periods (decreased blood loss, shorter operative time, lower complication rates, and shorter hospital stay).[4–9] Some of these advantages of MILR are also seen in patients with cirrhosis.[10]

Left lateral sectionectomy (LLS) has been proposed as the ideal procedure for MILR due to its unique anatomical characteristics, such as its midline position in the abdominal cavity, small parenchymal volume, predictable vascular anatomy, and straight transection line.[11,12] These contribute to a shorter learning curve and amenability to standardization of surgical technique for minimally-invasive LLS (MI-LLS).[13,14] This was supported in the 2014 Morioka consensus, where the laparoscopic approach was deemed to be the standard of care for LLS.[15] Today, MI-LLS is accepted to be the gold standard for the treatment of primary hepatic tumors in patients treated at tertiary institutions with a specialized hepatobiliary service.[12,16,17] This procedure has, over time, become so commonplace in the armamentarium of hepatobiliary surgeons; however, the impact of cirrhosis and portal hypertension (PHT) on the difficulty and perioperative outcomes of MI-LLS remains unclear and poorly studied.[18]

Several difficulty scoring systems have been formulated over the years in an attempt to grade the complexity of MILR.[19] None of

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these have, however, taken into account the presence of cirrhosis or PHT.[9,19–22] Although the Iwate scoring system recognized and took into account the impact of Child-Turcotte-Pugh (CTP) B cirrhosis on the difficulty of MILR, the presence of CTP A cirrhosis or portal hypertension was not included in the system.[9] Contrary to these scoring systems, a recent survey of expert MILR surgeons revealed that most surgeons regarded the presence of cirrhosis as having a major impact on the difficulty of MILR.[23] Furthermore, studies have suggested that the impact of cirrhosis would differ according to the extent and complexity of the liver resection.[18]

With this controversy in mind, we performed this study to determine the impact and severity of cirrhosis on the difficulty and postoperative outcomes of MI-LLS. To reduce the effect of potential confounding factors, we used 2 matching techniques. Furthermore, the study population was only limited to patients who underwent MI-LLS for primary liver malignancies and excluded resections for other pathologies.

Methods

This was a retrospective review comprising 3,426 patients from 60 centers worldwide who underwent MI-LLS (laparoscopic and robotic) between 2004 and 2021. Thirty-nine were Western, and 21 were Eastern centers. All centers performed a minimum annual volume of over 10 MLR per annum, and 55 had a volume of over 20 MILR per annum. The centers provided unselected consecutive data of patients over a fixed period. Of these, 1,526 MI-LLS were performed for primary liver malignancies (hepatocellular carcinoma, cholangiohepatoma, 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 de-identified 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. Patients who underwent concomitant major operations such as bilio-enteric anastomoses, colectomies, stoma reversal, gastrectomies, splenectomies, and vascular resections were excluded. Notably, patients who underwent concomitant minor operations such as hernia repair, local ablation, and hilar lymph node dissection were included. Patients with a history of previous liver resections or who underwent MILR with concomitant other liver resections were also excluded. Consequently, 1,370 cases were included in the final study group.

A list of preoperative clinicopathological data for which patients were matched can be found in Tables I to V. Of note, the baseline difficulty of MI-LLS was matched across study groups based on the Iwate scoring system. Important peri- and postoperative parameters compared include operative time, estimated blood loss, transfusion requirement, use of Pringle maneuver, conversion rate, duration of hospital stay, Clavien-Dindo complications, reoperation rate, and perioperative mortality.

Definitions

An LLS was defined according to the 2000 Brisbane classification as anatomic resection of segments 2 and 3.[24] Diameter of the largest lesion was used in the cases of multiple tumors. The difficulty of LLS resections was graded according to the Iwate score. Clinically significant PHT was defined based on radiological and clinical criteria such as the presence of ascites, esophageal varices, or splenomegaly with a platelet count of <100,000/μL (portal venous pressure/hepatic venous pressure gradient was not routinely measured in most centers). Postoperative complications were stratified according to the Clavien-Dindo classification and recorded for up to 30 days or during the same hospitalization, including 30-day readmissions.[25]

Statistical analysis

Propensity score matching (PSM) and Coarsened Exact Matching (CEM) were used to estimate the effect of varying degrees of liver cirrhosis on MI-LLS. For PSM, the propensity score was estimated with logistic regression with a mixed-effect model. The factors used in calculating the propensity score are the baseline variables in Tables I, III, and V, respectively. A random effects parameter was also included in the model to account for between-center variation. For PSM comparison of CTP A cirrhotic against noncirrhotic liver in Tables I and II, patients of one stratum were matched 1:1, using nearest neighbor matching without replacement or discard, using logit link, to patients of the other strata. To improve matching, a small caliper was used to achieve a 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 was discarded. A similar methodology was employed for PSM comparison in Tables III to VI, comparing CTP A to B and cirrhosis with and without PHT.

Continuous variables were coarsened for CEM using an automatic binning algorithm based on Sturge's rule into bins. Patients were 1:1 matched using nearest neighbor matching without replacement within each stratum; any unmatched units in the stratum were dropped. This methodology was applied to all 3 CEM models. After matching, the balance was checked via standardized mean difference across the covariates, with a threshold of 0.1 indicative of a tight match. The love plot of each match's covariate balance was plotted and presented below (Supplementary Materials S1–S6).

For unpaired comparisons of frequencies of categorical variables, χ^2 analysis was used. For the unpaired comparisons of median values and IQRs, the Mann-Whitney *U* test was used, and for the comparisons of mean values and SDs, one-way tests were used. For paired sample tests, McNemar's test was used for categorical variables and Wilcoxon signed-rank test for continuous variables. The statistical analyses were performed with RStudio version 1.4.1717 (Posit Software, PBC) and R version 4.1.0 (R Foundation for Statistical Computing).

Results

A total of 1,370 patients who underwent MI-LLS for primary liver malignancies were included in the study. Eight-hundred and fifty-two cases (62.2%) were performed in Eastern, and 518 (37.8%) were performed in Western centers. Of these, 559 (40.8%) patients had no cirrhosis, and 811 (59.2%) patients had cirrhosis (753 CTP A; 58 CTP B). There was no significant difference in the proportion of cirrhotics amongst patients in Eastern (511/852 [60.0%]) compared with Western centers (299/518 [57.7%]; $P = .410$). Of the cirrhotic patients, 800 were evaluated for PHT and divided into 2 subgroups: with PHT ($N = 630$) and without PHT ($N = 170$). Eleven patients had missing information on PHT. A total of 2.4% ($n = 33$) and 0.9% ($n = 12$) of patients presented with major postoperative morbidity and mortality, respectively. In addition, 3.3% ($n = 45$) of MI-LLS required conversion to open surgery, and the overall mortality rate was 0.7% ($n = 10$).

Noncirrhotic versus CTP A cirrhotic patients

This study group comprised a total of 1,312 patients, with 753 in the CTP A group and 559 in the noncirrhotic group. In the entire

Table I
Comparison between baseline characteristics of MI-LLS in Child-Pugh A cirrhosis versus noncirrhosis

	All ($N = 1,312$)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM		
		Child A cirrhosis ($n = 753$)	Noncirrhosis ($N = 559$)	*P* value	Child A cirrhosis ($n = 396$)	Noncirrhosis ($N = 396$)	*P* value (paired)	Child A cirrhosis ($n = 128$)	Noncirrhosis ($N = 128$)	*P* value (paired)
Median age, y (IQR)	63.76 (55.00, 71.91)	63.00 (55.00, 70.00)	65.00 (55.00, 73.00)	.033	62.95 (55.00, 70.00)	64.00 (54.00, 72.00)	.788	63.00 (55.75, 68.00)	61.65 (55.75, 68.00)	.294
Male sex, *n* (%)	984 (75.0)	577 (76.6)	407 (72.8)	.130	301 (76.0)	306 (77.3)	.731	116 (90.6)	116 (90.6)	NA
BMI (IQR)	24.32 (22.00, 27.20)	24.30 (21.98, 27.50)	24.39 (22.19, 26.90)	.619	24.30 (22.00, 27.69)	24.12 (22.12, 26.87)	.175	23.88 (21.72, 26.72)	24.01 (22.18, 27.02)	.415
Robotic, *n* (%)	177 (13.5)	96 (12.7)	81 (14.5)		54 (13.6)	57 (14.4)	.841	9 (7.0)	9 (7.0)	NA
Laparoscopic, *n* (%)	1135 (86.5)	657 (87.3)	478 (85.5)	.406	342 (86.4)	339 (85.6)		119 (93.0)	119 (93.0)	
Previous abdominal surgery, *n* (%)	204 (16.1)	105 (14.7)	99 (17.8)	.157	67 (16.9)	63 (15.9)	.775	6 (4.7)	6 (4.7)	NA
Year of surgery, *n* (%)				.036			.957			NA
2004–2009	86 (6.6)	49 (6.5)	37 (6.6)		28 (7.1)	26 (6.6)		3 (2.3)	3 (2.3)	
2010–2015	416 (31.7)	260 (34.5)	156 (27.9)		120 (30.3)	118 (29.8)		35 (27.3)	35 (27.3)	
2016–2021	810 (61.7)	444 (59.0)	366 (65.5)		248 (62.6)	252 (63.6)		90 (70.3)	90 (70.3)	
ASA score, *n* (%)				.618			.938			NA
1/2	937 (71.5)	542 (72.1)	395 (70.7)		281 (71.0)	279 (70.5)		106 (82.8)	106 (82.8)	
3/4	374 (28.5)	210 (27.9)	164 (29.3)		115 (29.0)	117 (29.5)		22 (17.2)	22 (17.2)	
Tumor type, *n* (%)				< .001			.770			NA
HCC	1121 (85.8)	685 (91.0)	436 (78.8)		355 (89.6)	352 (88.9)		127 (99.2)	127 (99.2)	
ICC/cholangiohepatoma	185 (14.2)	68 (9.0)	117 (21.2)		41 (10.4)	44 (11.1)		1 (0.8)	1 (0.8)	
Median tumor size, mm (IQR)	35.00 (24.00, 52.75)	30.00 (22.00, 47.00)	40.00 (28.00, 60.00)	< .001	34.50 (25.00, 53.25)	35.00 (24.75, 50.00)	.324	30.00 (21.00, 40.00)	30.00 (25.00, 40.75)	.099
Multiple tumors, *n* (%)	168 (12.8)	108 (14.3)	60 (10.8)	.066	36 (9.1)	42 (10.6)	.556	1 (0.8)	1 (0.8)	NA
Concomitant minor surgery excluding cholecystectomy, *n* (%)	26 (2.0)	15 (2.0)	11 (2.0)	1.000	8 (2.0)	9 (2.3)	1.000	1 (0.8)	1 (0.8)	NA
Hilar lymph node dissection, *n* (%)	35 (2.7)	13 (1.7)	22 (3.9)	.022	10 (2.5)	13 (3.3)	.677	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score, (IQR) [range]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [3,8]	< .001	5.00 (4.00, 5.00) [3,8]	5.00 (4.00, 5.00) [3,8]	0.235	5.00 (4.00, 5.00) [3,6]	5.00 (4.00, 5.00) [3,6]	NA
Iwate difficulty, *n* (%)				.054			0.718			NA
Intermediate	107 (8.2)	73 (9.7)	34 (6.1)		27 (6.8)	32 (8.1)		10 (7.8)	10 (7.8)	
High	1191 (90.8)	673 (89.4)	518 (92.7)		365 (92.2)	361 (91.2)		118 (92.2)	118 (92.2)	
Expert	14 (1.1)	7 (0.9)	7 (1.3)		4 (1.0)	3 (0.8)		0 (0.0)	0 (0.0)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CEM*, Coarsened Exact Matching; *HCC*, hepatocellular carcinoma; *ICC*, intrahepatic cholangiocarcinoma; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PSM*, propensity score matching.

Table II
Comparison between perioperative outcomes of MI-LLS in Child-Pugh A cirrhosis versus noncirrhosis

	All (N = 1312)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM		
		Child A cirrhosis (n = 753)	Noncirrhosis (N = 559)	P value	Child A cirrhosis (n = 396)	Noncirrhosis (N = 396)	P value (paired)	Child A cirrhosis (n = 128)	Noncirrhosis (N = 128)	P value (paired)
Open conversion, n (%)	43 (3.3)	27 (3.6)	16 (2.9)	.568	14 (3.5)	8 (2.0)	.286	6 (4.7)	2 (1.6)	.289
Median operating time, min (IQR)	170.00 (120.00, 230.00)	180.00 (120.00, 240.00)	158.50 (105.00, 210.00)	< .001	179.50 (120.00, 240.00)	156.00 (100.00, 210.00)	.004	174.50 (110.00, 230.00)	155.00 (90.00, 210.00)	.421
Median blood loss, mL (IQR)	100.00 (50.00, 200.00)	100.00 (50.00, 200.00)	100.00 (50.00, 200.00)	.139	100.00 (50.00, 200.00)	100.00 (40.00, 159.50)	.003	100.00 (50.00, 200.00)	50.00 (20.00, 145.00)	.041
Blood loss >500 mL, n (%)	69 (5.5)	40 (5.6)	29 (5.5)	1.000	21 (5.5)	15 (4.0)	.186	11 (8.7)	5 (4.1)	.267
Intraoperative blood transfusion, n (%)	49 (3.7)	31 (4.1)	18 (3.2)	.484	13 (3.3)	9 (2.3)	.522	8 (6.2)	0 (0.0)	.013
Pringle maneuver applied, n (%)	245 (18.9)	134 (18.0)	111 (20.1)	.369	85 (21.7)	67 (17.1)	.093	26 (20.3)	21 (16.8)	.532
Median postoperative stay, d (IQR)	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)	.003	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)	.026	5.00 (4.00, 7.00)	5.00 (4.00, 7.00)	.651
Postoperative morbidity, n (%)	176 (13.4)	105 (13.9)	71 (12.7)	.568	54 (13.6)	43 (10.9)	.284	11 (8.6)	9 (7.0)	.823
Major morbidity (Clavien-Dindo grade >2), n (%)	32 (2.4)	18 (2.4)	14 (2.5)	1.000	9 (2.3)	9 (2.3)	1.000	0 (0.0)	1 (0.8)	1.000
Reoperation, n (%)	11 (0.8)	4 (0.5)	7 (1.3)	.221	3 (0.8)	5 (1.3)	.724	0 (0.0)	0 (0.0)	NA
30-d readmission, n (%)	27 (2.1)	14 (1.9)	13 (2.3)	.704	9 (2.3)	6 (1.5)	.606	3 (2.4)	0 (0.0)	.248
30-d mortality, n (%)	3 (0.2)	0 (0.0)	3 (0.5)	.077	0 (0.0)	3 (0.8)	.248	0 (0.0)	0 (0.0)	NA
In-hospital mortality, n (%)	4 (0.3)	0 (0.0)	4 (0.7)	.033	0 (0.0)	3 (0.8)	.248	0 (0.0)	0 (0.0)	NA
90-d mortality, n (%)	9 (0.7)	3 (0.4)	6 (1.1)	.182	1 (0.3)	4 (1.0)	.371	0 (0.0)	0 (0.0)	NA

CEM, Coarsened Exact Matching; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PSM*, propensity score matching.

unmatched cohort, cirrhosis was associated with a lower median age (63.0 years [55.0–70.0] vs 65 years [55.0–73.0], $P = .033$), a higher proportion of patients with hepatocellular carcinoma (91% vs 78.8%, $P < .001$), smaller tumors (30 mm [22–47] vs 40 mm [28–60], $P < .001$), lower frequency of hilar lymph node dissection (1.7% vs 3.9%, $P = .022$), and higher median Iwate score ($P < .001$; Table I). In the unmatched comparison, patients with CTP A cirrhosis had longer operative times (180.0 min [120.0–240.0] vs 158.5 min [105.0–210.0], $P < .001$), postoperative stay (5.0 days [4.0–7.0] vs 5.0 [4.0–7.0], $P = .003$), and higher in-hospital mortality (0% vs 0.7%, $P = .033$; Table II).

Propensity score matching and CEM with a 1:1 ratio resulted in 396 and 128 matched pairs, respectively. Both groups were well balanced in all baseline characteristics in both matched cohorts (Table I). Cirrhotic patients presented with longer operative time after PSM (179.5 min [120.0–240.0] vs 156.0 min [100.0–210.0], $P = .004$), but not in the CEM (174.5 min [110.0–230.0] vs 155.0 min [90.0–210.0], $P = .421$) analysis. Cirrhosis was consistently associated with higher intraoperative blood loss (PSM: 100.0 mL [50.0–200.0] vs 100.0 mL [40.0–159.5], $P = .003$; CEM: 100.0 mL [50.0–200.0] vs 50.0 mL [20.0–145.0], $P = .041$), and higher transfusion rates (CEM: 6.2% versus 0%, $P = .013$). Duration of hospital stay was significantly longer in PSM analysis (5.0 days [4.0–7.0] vs 5.0 days [4.0–7.0], $P = .026$), but not in CEM analysis (5.0 days [4.0–7.0] vs 5.0 [4.0–7.0], $P = .651$; Table II).

CTP A versus CTP B patients

This study group comprised a total of 811 cirrhotic patients, with 753 in the CTP A group and 58 in the CTP B group. In the unmatched cohort, Child-Pugh B patients had a lower median age (53.50 [47.0–66.8] vs 63 years [55.0–70.0]; $P < .001$) and a higher proportion of patients operated in the last 5 years (Table III). In this unmatched comparison, patients in the CTP B group had the Pringle maneuver more frequently employed (31% vs 18%, $P = .024$) and recorded longer durations of hospital stay (9.0 days [4.6–12.0] vs 5.0 days [4.0–7.0], $P < .001$; Table IV).

In the matched cohorts, PSM and CEM with a 1:1 ratio resulted in 49 and 46 matched pairs, respectively. Both groups were well-balanced in all baseline characteristics in the PSM-matched cohort (Table III). In CEM, only the median age was different between the groups (Child-Pugh B: 53.0 years [47.0–64.5] vs Child-Pugh A: 64.0 years [56.5–71.0], $P = .003$; Table III). All perioperative outcomes were similar between the groups, with the exception of a longer hospital stay in Child-Pugh B patients after CEM analysis (9.0 days [6.0–13.5] vs 5.0 days [4.0–7.0], $P < .001$; Table IV).

Cirrhotic patients with versus without PHT

This study group comprised a total of 800 cirrhotic patients, with 670 in the PHT group and 130 in the non-PHT group (Table V). In the unmatched comparison, patients with PHT presented with higher estimated blood loss (100.0 mL [50.0–300.0] vs 100.0 mL [50.0–200.0], $P = .002$), higher frequency of blood loss >500 mL (10.4% vs 4.2%, $P = .003$), and a higher transfusion rate (8.2% vs 3.5%, $P = .015$). Additionally, the Pringle maneuver was more frequently applied in patients with PHT (27.8% vs 16.7%, $P = .002$; Table VI).

Propensity score matching and CEM with a 1:1 ratio resulted in 130 and 73 matched pairs, respectively. Both groups were well-balanced in all baseline characteristics in the matched cohorts (Table V). There were no differences in all the perioperative outcomes analyzed (Table VI).

Table III
Comparison between baseline characteristics of MI-LLS in Child-Pugh A versus Child-Pugh B cirrhosis

	All (N = 811)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM		
		Child A (*N* = 753)	Child B (*N* = 58)	*P* value	Child A (*N* = 49)	Child B (*N* = 49)	*P* value (paired)	Child A (*N* = 46)	Child B (*N* = 46)	*P* value (paired)
Mean age, y (IQR)	62.80 (54.00, 70.00)	63.00 (55.00, 70.00)	53.50 (47.00, 66.75)	< .001	58.00 (49.00, 65.00)	54.00 (47.00, 67.00)	0.719	64.00 (56.50, 71.00)	53.00 (47.00, 64.50)	0.003
Male sex, *n* (%)	615 (75.8)	577 (76.6)	38 (65.5)	.081	39 (79.6)	35 (71.4)	0.289	33 (71.7)	33 (71.7)	NA
BMI (IQR)	24.28 (21.93, 27.34)	24.30 (21.98, 27.50)	23.90 (20.98, 26.60)	.180	23.11 (20.90, 25.61)	23.95 (21.19, 26.98)	0.230	23.80 (21.89, 26.34)	23.73 (21.26, 26.20)	0.898
Robotic, *n* (%)	107 (13.2)	96 (12.7)	11 (19.0)		10 (20.4)	10 (20.4)	1.000	5 (10.9)	5 (10.9)	NA
Laparoscopic, *n* (%)	704 (86.8)	657 (87.3)	47 (81.0)	.252	39 (79.6)	39 (79.6)		41 (89.1)	41 (89.1)	
Previous abdominal surgery, *n* (%)	112 (14.5)	105 (14.7)	7 (12.1)	.723	3 (6.1)	6 (12.2)	0.450	3 (6.5)	3 (6.5)	NA
Year of surgery, *n* (%)				.023			1.000			NA
2004–2009	49 (6.0)	49 (6.5)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
2010–2015	275 (33.9)	260 (34.5)	15 (25.9)		8 (16.3)	9 (18.4)		13 (28.3)	13 (28.3)	
2016–2021	487 (60.0)	444 (59.0)	43 (74.1)		41 (83.7)	40 (81.6)		33 (71.7)	33 (71.7)	
ASA score, *n* (%)				.232			0.343			NA
1/2	579 (71.5)	542 (72.1)	37 (63.8)		36 (73.5)	32 (65.3)		32 (69.6)	32 (69.6)	
3/4	231 (28.5)	210 (27.9)	21 (36.2)		13 (26.5)	17 (34.7)		14 (30.4)	14 (30.4)	
Tumor type, *n* (%)				.810			1.000			NA
HCC	739 (91.1)	685 (91.0)	54 (93.1)		46 (93.9)	46 (93.9)		45 (97.8)	45 (97.8)	
ICC/cholangiohepatoma	72 (8.9)	68 (9.0)	4 (6.9)		3 (6.1)	3 (6.1)		1 (2.2)	1 (2.2)	
Median tumor size, mm (IQR)	30.00 (22.00, 50.00)	30.00 (22.00, 47.00)	35.00 (30.00, 53.75)	.06	35.00 (30.00, 50.00)	31.00 (28.00, 55.00)	0.623	30.50 (24.00, 44.00)	32.00 (30.00, 50.00)	0.422
Multiple tumors, *n* (%)	117 (14.4)	108 (14.3)	9 (15.5)	.959	9 (18.4)	8 (16.3)	1.000	5 (10.9)	5 (10.9)	NA
Concomitant minor surgery excluding cholecystectomy, *n* (%)	15 (1.8)	15 (2.0)	0 (0.0)	.617	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Hilar lymph node dissection, *n* (%)	14 (1.7)	13 (1.7)	1 (1.7)	1.000	0 (0.0)	1 (2.0)	1.000	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score excluding Childs score, (IQR) [range]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [3,7]	.134	5.00 (4.00, 5.00) [3,7]	5.00 (4.00, 5.00) [3,7]	0.903	5.00 (4.00, 5.00) [3,8]	5.00 (5.00, 5.00) [3,7]	0.260
Iwate difficulty exclude Childs score, *n* (%)				.464			NA			NA
Intermediate	77 (9.5)	73 (9.7)	4 (6.9)		3 (6.1)	4 (8.2)		1 (2.2)	1 (2.2)	
High	726 (89.5)	673 (89.4)	53 (91.4)		45 (91.8)	44 (89.8)		44 (95.7)	44 (95.7)	
Expert	8 (1.0)	7 (0.9)	1 (1.7)		1 (2.0)	1 (2.0)		1 (2.2)	1 (2.2)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CEM*, Coarsened Exact Matching; *HCC*, hepatocellular carcinoma; *ICC*, intrahepatic cholangiocarcinoma; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PSM*, propensity score matching.

Table IV
Comparison between perioperative outcomes of MI-LLS in Child-Pugh A versus Child-Pugh B cirrhosis

	All ($N = 811$)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM		
		Child A ($N = 753$)	Child B ($N = 58$)	*P* value	Child A ($N = 49$)	Child B ($N = 49$)	*P* value (paired)	Child A ($N = 46$)	Child B ($N = 46$)	*P* value (paired)
Open conversion, *n* (%)	29 (3.6)	27 (3.6)	2 (3.4)	1.000	1 (2.0)	2 (4.1)	1.000	1 (2.2)	2 (4.3)	1.000
Median operating time, min (IQR)	180.00 (120.00, 238.25)	180.00 (120.00, 240.00)	177.50 (115.00, 210.00)	.183	173.00 (120.00, 208.00)	170.00 (100.00, 210.00)	.550	180.00 (144.50, 221.50)	180.00 (116.25, 210.00)	.085
Median blood loss, mL (IQR)	100.00 (50.00, 200.00)	100.00 (50.00, 200.00)	100.00 (50.00, 300.00)	.214	100.00 (50.00, 300.00)	100.00 (50.00, 300.00)	.736	100.00 (21.25, 200.00)	100.00 (50.00, 300.00)	.110
Blood loss >500 mL, *n* (%)	43 (5.5)	40 (5.6)	3 (5.3)	1.000	7 (14.3)	3 (6.2)	.289	1 (2.4)	3 (6.7)	.617
Intraoperative blood transfusion, *n* (%)	36 (4.4)	31 (4.1)	5 (8.6)	.172	5 (10.2)	4 (8.2)	1.000	0 (0.0)	5 (10.9)	.074
Pringle maneuver applied, *n* (%)	152 (19.0)	134 (18.0)	18 (31.0)	.024	9 (18.4)	17 (34.7)	.136	13 (28.9)	15 (32.6)	.814
Median postoperative stay, d (SD)	5.05 (4.00, 8.00)	5.00 (4.00, 7.00)	9.00 (4.60, 12.00)	< .001	7.00 (5.00, 10.00)	8.00 (4.00, 11.00)	.210	5.00 (4.00, 7.00)	9.00 (6.00, 13.50)	< .001
Postoperative morbidity, *n* (%)	115 (14.2)	105 (13.9)	10 (17.2)	.618	6 (12.2)	9 (18.4)	.579	4 (8.7)	8 (17.4)	.343
Major morbidity (Clavien-Dindo grade >2), *n* (%)	19 (2.3)	18 (2.4)	1 (1.7)	1.000	0 (0.0)	1 (2.0)	1.000	0 (0.0)	1 (2.2)	1.000
Reoperation, *n* (%)	5 (0.6)	4 (0.5)	1 (1.7)	.311	0 (0.0)	1 (2.0)	1.000	0 (0.0)	1 (2.2)	1.000
30-d readmission, *n* (%)	16 (2.0)	14 (1.9)	2 (3.4)	.323	0 (0.0)	2 (4.1)	.480	0 (0.0)	1 (2.2)	1.000
30-d mortality, *n* (%)	1 (0.1)	0 (0.0)	1 (1.7)	.072	0 (0.0)	1 (2.0)	1.000	0 (0.0)	1 (2.2)	1.000
In-hospital mortality, *n* (%)	1 (0.1)	0 (0.0)	1 (1.7)	.072	0 (0.0)	1 (2.0)	1.000	0 (0.0)	1 (2.2)	1.000
90-d mortality, *n* (%)	4 (0.5)	3 (0.4)	1 (1.7)	.257	0 (0.0)	1 (2.0)	1.000	0 (0.0)	1 (2.2)	1.000

CEM, Coarsened Exact Matching; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PSM*, propensity score matching.

Discussion

To the best of our knowledge, this represents the first study specifically evaluating the impact of liver cirrhosis, the severity of cirrhosis, and PHT on the difficulty and perioperative outcomes of patients undergoing MI-LLS. Based on our data, the presence of liver cirrhosis (CTP A) did not increase the risk of conversion, but significantly increased operative time, blood loss, and transfusion requirements in the matched cohorts. Additionally, the presence of cirrhosis was associated with a longer duration of hospital stay. Notably, there was no significant difference between postoperative morbidity and major morbidity rates despite the poorer perioperative outcomes. This minimal impact on postoperative outcomes is likely due to the large future liver remnant after LLS.

The LLS was the first minimally invasive anatomical liver resection performed and simultaneously reported by Azagra et al[26] and Kaneko et al[27] in 1996. Subsequently, multiple studies have demonstrated the advantages of MILR over open surgery in terms of decreased perioperative morbidity, blood loss, and length of stay.[28,29] With its favorable anatomical location and predictable anatomy, MI-LLS has been proven to be a highly standardizable operation with a gentler-than-average learning curve (as opposed to other types of hepatectomies).[13,30–33] For these reasons, MI-LLS is now considered the gold standard approach in most specialized liver surgery centers.[16,34]

A plethora of well-powered studies have confirmed the safety and feasibility of MI-LLS over the past decade.[7,11,35] Recent population-based studies and 2 randomized controlled trials have been published supporting the use of MI-LLS.[36–39] In a recent meta-analysis, Macacari et al[12] demonstrated that laparoscopic LLS was associated with less blood loss, lower transfusion rates, and shorter hospital stays compared with those undergoing open surgery in a study that included 3,415 patients in 23 different studies. Subsequent studies specifically comparing robotic and laparoscopic approaches to LLS found similar perioperative outcomes.[40] Today, MI-LLS is categorized as a low- to intermediate-difficulty procedure according to most difficulty scoring systems for MILR.[20–23,41]

However, the impact of cirrhosis and its severity on the difficulty and outcomes of MILRs is controversial. Physiologic changes such as hardened parenchymal texture, raised portal pressure, hypoalbuminemia, ascites, coagulopathy, and thrombocytopenia commonly make liver resection more challenging in cirrhotic patients.[42,43] Notably, however, studies with small sample sizes did not show significant differences in outcomes comparing patients who underwent MILRs with and without cirrhosis.[44,45]

In contrast, a large recent multicenter PSM study reported worse outcomes in a cirrhotic cohort undergoing MILR,[46] whereas Tong et al[47] found a two-fold increase in the risk of open conversion and postoperative complications in patients with cirrhosis undergoing MILR. Similarly, Goh et al[18] found that MILRs in cirrhotic patients were associated with an increased open conversion rate, prolonged operative time, increased blood loss, increased transfusion rate, prolonged hospital stays, and an overall increase in postoperative morbidity. Additionally, it was observed in this study that the differences in outcomes between MILR in cirrhotics versus non-cirrhotics were more pronounced in patients undergoing more difficult resections. However, several of these studies were limited, as these included MILR for various pathologies such as benign disease and metastases, which are important confounding factors as these pathologies occurred much more frequently in the non-cirrhotic cohort compared with the cirrhotic cohort.

To date, there has been a woeful lack of high-quality evidence studying the effects of cirrhosis and PHT on the perioperative outcomes of MI-LLS. The largest study to date is a recent multicenter study reporting on 2,245 patients undergoing MI-LLS. Wang

Table V
Comparison between baseline characteristics of MI-LLS in patients with cirrhosis with and without PHT

	All ($N = 800$)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM		
		Cirrhosis PHT ($N = 630$)	Cirrhosis no PHT ($N = 170$)	*P* value	Cirrhosis PHT ($N = 130$)	Cirrhosis no PHT ($N = 130$)	*P* value	Cirrhosis PHT ($N = 73$)	Cirrhosis No PHT ($N = 73$)	*P* value (paired)
Mean age, y (IQR)	62.65 (54.00, 70.00)	63.00 (55.25, 70.00)	62.00 (54.00, 70.00)	.692	62.45 (55.00, 69.75)	61.00 (54.00, 67.75)	.463	62.90 (55.00, 70.00)	61.00 (55.00, 67.00)	.341
Male sex, *n* (%)	606 (75.8)	130 (76.5)	476 (75.6)	.884	100 (76.9)	103 (79.2)	.755	64 (87.7)	64 (87.7)	NA
BMI (IQR)	24.27 (21.95, 27.30)	24.42 (21.84, 27.70)	24.22 (21.97, 27.20)	.864	24.11 (21.51, 27.42)	24.24 (21.45, 27.10)	.686	24.76 (4.39)	24.28 (3.56)	.448
Robotic, *n* (%)	107 (13.4)	23 (13.5)	84 (13.3)	1	19 (14.6)	16 (12.3)	.710	4 (5.5)	4 (5.5)	NA
Laparoscopic, *n* (%)	693 (86.6)	147 (86.5)	546 (86.7)		111 (85.4)	114 (87.7)		69 (94.5)	69 (94.5)	
Previous abdominal surgery, *n* (%)	108 (14.2)	25 (14.7)	83 (14.0)	.926	20 (15.4)	14 (10.8)	.391	5 (6.8)	5 (6.8)	NA
Childs A, *n* (%)	742 (92.8)	142 (83.5)	600 (95.2)	.926	118 (90.8)	113 (86.9)	.383	73 (100.0)	73 (100.0)	NA
Childs B, *n* (%)	58 (7.2)	28 (16.5)	30 (4.8)		12 (9.2)	17 (13.1)		0 (0.0)	0 (0.0)	
Year of surgery, *n* (%)				.941			.909			NA
2004–2009	49 (6.1)	10 (5.9)	39 (6.2)		8 (6.2)	9 (6.9)		4 (5.5)	4 (5.5)	
2010–2015	269 (33.6)	59 (34.7)	210 (33.3)		46 (35.4)	47 (36.2)		25 (34.2)	25 (34.2)	
2016–2021	482 (60.2)	101 (59.4)	381 (60.5)		76 (58.5)	74 (56.9)		44 (60.3)	44 (60.3)	
ASA score, *n* (%)				.001			.298			NA
1/2	575 (72.0)	104 (61.2)	471 (74.9)		90 (69.2)	81 (62.3)		51 (69.9)	51 (69.9)	
3/4	224 (28.0)	66 (38.8)	158 (25.1)		40 (30.8)	49 (37.7)		22 (30.1)	22 (30.1)	
Tumor type, *n* (%)				.163			.814			NA
HCC	729 (91.1)	160 (94.1)	569 (90.3)		122 (93.8)	120 (92.3)		73 (100.0)	73 (100.0)	
ICC/cholangiohepatoma	71 (8.9)	10 (5.9)	61 (9.7)		8 (6.2)	10 (7.7)		0 (0.0)	0 (0.0)	
Median tumor size, mm (IQR)	30.00 (22.00, 49.00)	30.00 (22.00, 50.00)	30.00 (22.00, 48.00)	.887	30.00 (21.00, 43.75)	30.00 (20.00, 45.00)	.638	30.00 (20.00, 39.00)	30.00 (20.00, 38.00)	.825
Multiple tumors, *n* (%)	115 (14.4)	24 (14.1)	91 (14.4)	1	19 (14.6)	19 (14.6)	1.000	5 (6.8)	5 (6.8)	NA
Concomitant minor surgery excluding cholecystectomy, *n* (%)	15 (1.9)	1 (0.6)	14 (2.2)	.214	1 (0.8)	1 (0.8)	1.000	0 (0.0)	0 (0.0)	NA
Hilar lymph node dissection, *n* (%)	13 (1.6)	3 (1.8)	10 (1.6)	.744	1 (0.8)	3 (2.3)	.617	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score, (IQR) [range]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [2,8]	5.00 (4.00, 5.00) [3,7]	.877	5.00 (4.00, 5.00) [3,7]	5.00 (4.00, 5.00) [3,7]	.715	5.00 (4.00, 5.00) [3,6]	5.00 (4.00, 5.00) [3,6]	NA
Iwate difficulty, *n* (%)				.687			NA			NA
Intermediate	72 (9.0)	17 (10.0)	55 (8.7)		14 (10.8)	12 (9.2)		6 (8.2)	6 (8.2)	
High	714 (89.2)	149 (87.6)	565 (89.7)		114 (87.7)	115 (88.5)		67 (91.8)	67 (91.8)	
Expert	14 (1.8)	4 (2.4)	10 (1.6)		2 (1.5)	3 (2.3)		0 (0.0)	0 (0.0)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CEM*, Coarsened Exact Matching; *HCC*, hepatocellular carcinoma; *ICC*, intrahepatic cholangiocarcinoma; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PHT*, portal hypertension; *PSM*, propensity score matching.

Table VI
Comparison between perioperative outcomes of MI-LLS in cirrhosis patients with and without PHT

	All ($N = 800$)	Entire unmatched cohort			1:1 PSM (nearest neighbor matching)			1:1 CEM			
		Cirrhosis PHT ($N = 630$)	Cirrhosis NPHT ($N = 170$)	*P* value	Cirrhosis PHT ($N = 130$)	Cirrhosis NPHT ($N = 130$)	*P* value	Cirrhosis PHT ($N = 73$)	Cirrhosis NPHT ($N = 73$)	*P* value (paired)
Open conversion, *n* (%)	28 (3.5)	10 (5.9)	18 (2.9)	.095	7 (5.4)	1 (0.8)	0.077	2 (2.7)	2 (2.7)	1.000
Median operating time, min (IQR)	180.00 (120.00, 240.00)	177.00 (120.00, 239.00)	180.00 (120.00, 240.00)	.624	180.00 (120.00, 240.00)	168.00 (125.00, 210.00)	0.386	165.00 (119.00, 210.00)	170.00 (133.00, 219.00)	.752
Median blood loss, mL (IQR)	100.00 (50.00, 300.00)	100.00 (50.00, 200.00)	100.00 (50.00, 200.00)	.002	100.00 (50.00, 300.00)	100.00 (50.00, 200.00)	0.194	100.00 (50.00, 200.00)	50.00 (45.00, 150.00)	.276
Blood loss >500 mL, *n* (%)	42 (5.5)	17 (10.4)	25 (4.2)	.003	12 (9.4)	8 (6.3)	0.646	5 (7.1)	3 (4.5)	.724
Intraoperative blood transfusion, *n* (%)	36 (4.5)	14 (8.2)	22 (3.5)	.015	9 (6.9)	3 (2.3)	0.149	6 (8.2)	1 (1.4)	.074
Pringle maneuver applied, *n* (%)	151 (19.1)	47 (27.8)	104 (16.7)	.002	30 (23.1)	22 (17.2)	0.349	12 (16.7)	10 (13.9)	.823
Median postoperative stay, d (IQR)	5.85 (4.00, 8.00)	5.00 (4.00, 8.00)	6.00 (4.00, 8.00)	.911	5.00 (4.00, 8.00)	5.00 (4.00, 8.00)	0.558	5.00 (4.00, 6.00)	5.00 (4.00, 7.00)	.356
Postoperative morbidity, *n* (%)	113 (14.1)	31 (18.2)	82 (13.0)	.107	21 (16.2)	15 (11.5)	0.405	9 (12.3)	7 (9.6)	.789
Major morbidity (Clavien-Dindo grade> 2), *n* (%)	19 (2.4)	3 (1.8)	16 (2.5)	.778	2 (1.5)	3 (2.3)	1.000	1 (1.4)	2 (2.7)	1.000
Reoperation, *n* (%)	5 (0.6)	2 (1.2)	3 (0.5)	.288	1 (0.8)	0 (0.0)	1.000	1 (1.4)	1 (1.4)	1.000
30-d readmission, *n* (%)	16 (2.0)	4 (2.4)	12 (1.9)	.757	3 (2.3)	3 (2.3)	1.000	2 (2.8)	2 (2.8)	1.000
30-d mortality, *n* (%)	1 (0.1)	1 (0.6)	0 (0.0)	.213	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
In-hospital mortality, *n* (%)	1 (0.1)	1 (0.6)	0 (0.0)	.213	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
90-d mortality, *n* (%)	4 (0.5)	2 (1.2)	2 (0.3)	.2	1 (0.8)	0 (0.0)	1.000	1 (1.4)	0 (0.0)	1.000

CEM, Coarsened Exact Matching; *MI-LLS*, minimally-invasive LLS; *NA*, not applicable; *PHT*, portal hypertension; *PSM*, propensity score matching.

et al reported an overall open conversion rate of 2.8% with male sex, larger tumor size, and clinically significant PHT identified as independently significant predictive factors on multivariate analysis. This study reported that the presence of cirrhosis had no significant association with the risk of requiring open conversion.[48] This data suggest that only advanced cirrhosis with PHT impacts the conversion risk of MI-LLS. Of note, this study failed to analyze other noteworthy perioperative variables commonly associated with MILR, including operative time, blood loss, use of Pringles maneuver, duration of hospital stay, morbidity, and mortality.

Benefits of the minimally invasive approach for hepatectomy in patients with higher grades of cirrhosis (CTP B) were recently demonstrated in a multicenter study that showed lower blood loss, less morbidity, and fewer major complications in the MILR cohort compared with their open liver resection counterparts.[49] Notably, this study found MILR to be associated with a significantly shorter median duration of postoperative hospital stay compared with the open liver resection group (7.5 days vs 18 days), with no differences in overall or disease-free survival. This study, however, reported that patients with more advanced cirrhosis (CTP B9) or PHT presented with a significantly higher rate of postoperative morbidity. Unfortunately, this study failed to present subgroup analyses regarding the type of hepatectomy performed (minor versus technical major versus traditional major).[49] Although CTP B cirrhosis was associated with increased difficulty in the Iwate score,[9] other studies failed to report similar findings. Cipriani et al[44] compared CTP A ($n = 100$) and B ($n = 25$) patients who underwent MILR due to hepatocellular carcinoma and found no differences in the perioperative outcomes. Our results showed that MI-LLS in CTP B patients is not associated with significant differences in perioperative outcomes, except for a longer duration of hospital stay compared with CTP patients. This suggests that on the identification of cirrhotic patients at increased risk of undergoing liver resection, MI-LLS may be performed safely with similar outcomes in both CTP A and B patients in properly selected patients at experienced centers. With improved collaboration between surgeons and gastroenterologists, anesthetic knowledge of intraoperative physiology in cirrhotics, and the advent of subspecialized nursing care, our study suggests that the intuitively increased morbidity associated with increasing levels of hepatic dysfunction can be effectively mitigated once these patients with compensated cirrhosis are identified preoperatively.

Portal hypertension has been previously reported to be associated with increased intraoperative difficulty and poorer perioperative outcomes in patients undergoing MILR.[44,49] This is reflected in the abovementioned study by Wang et al that reported the significantly increased risk of open conversion in patients with PHT undergoing MI-LLS.[48] In our study PHT was not associated with a higher conversion rate or poorer postoperative outcomes. Possible explanations could be the relatively low technical difficulty of LLS and the experience of the centers included in this study. Furthermore, the relatively large future liver remnant associated with this procedure likely had minimal impact on the postoperative portal pressure and hepatic function. Moreover, improved patient selection and preoperative screening allow surgeons to now be more cognizant of high-risk patients with limited physiological reserves who should be treated with a lower threshold for open conversion before the onset of clinically significant intraoperative deterioration that may affect the recovery course.

Our study presents several limitations, including its retrospective nature resulting in a higher likelihood of selection bias and confounding factors. Furthermore, as an international multicenter study, heterogeneity in surgical technique, perioperative management, and healthcare systems between centers affords an additional layer of bias. Nonetheless, this represented “real world” data

and increased the generalizability of our findings. Additionally, the long study period also raises concerns regarding confounding factors of advancing surgical technology, anesthetic knowledge and expertise, and surgeon experience. Unsurprisingly, surgical training, equipment, and protocol have evolved during the 17-year study period. Despite a large number of patients being included in this study, subgroups like CTP B cirrhosis had a small sample size after matching, which increased the risk of type 1 and type 2 errors. Despite the limitations, the restriction of our study group to a highly focused subset of hepatectomies (LLS) only in patients with primary liver malignancies allows our study to analyze the impact of liver cirrhosis on perioperative outcomes of MILR more precisely and reduce the impact of confounding factors. This is unlike previous studies, which included patients undergoing various types of MILR with different pathologies. Propensity score matching and CEM also allowed us to reduce the impact of confounding biases. Lastly, it must be added that there is no internationally recognized standard method for measuring blood loss, and its scientific validity is limited. However, the transfusion rate was found to be significantly higher in cirrhotics after 1:1 CEM supporting the clinical significance of these findings.

In conclusion, the increased technical difficulties associated with MI-LLS in patients with cirrhosis are evidenced by their significantly increased blood loss, higher transfusion rate, and longer postoperative stay compared with patients without cirrhosis. Hence, the presence of cirrhosis should be included in future difficulty scoring systems. This information would also be important for new surgeons embarking on MILR and for future auditing and benchmarking of MILR.

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Conflict of interest/Disclosure

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Supplementary materials

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