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Impact of liver cirrhosis and portal hypertension on minimally invasive limited liver resection for primary liver malignancies in the posterosuperior segments: an international multicenter study

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Abstract

Introduction: To assess the impact of cirrhosis and portal hypertension (PHT) on technical difficulty and outcomes of minimally invasive liver resection (MILR) in the posterosuperior segments.

Methods: This is a post-hoc analysis of patients with primary malignancy who underwent laparoscopic and robotic wedge resection and segmentectomy in the posterosuperior segments between 2004 and 2019 in 60 centers. Surrogates of difficulty (i.e, open conversion rate, operation time, blood loss, blood transfusion, and use of the Pringle maneuver) and outcomes were compared before and after propensity-score matching (PSM) and coarsened exact matching (CEM).

Results: Of the 1954 patients studied, 1290 (66%) had cirrhosis. Among the cirrhotic patients, 310 (24%) had PHT. After PSM, patients with cirrhosis had higher intraoperative blood transfusion (14% *vs.* 9.3%; p = 0.027) and overall morbidity rates (20% *vs.* 14.5%; p = 0.023) than those without cirrhosis. After coarsened exact matching (CEM), patients with cirrhosis tended to have higher intraoperative blood transfusion rate (12.1% *vs.* 6.7%; p = 0.059) and have higher overall morbidity rate (22.8% *vs.* 12.5%; p = 0.007) than those without cirrhosis. After PSM, Pringle maneuver was more frequently applied in cirrhotic patients with PHT (62.2% *vs.* 52.4%; p = 0.045) than those without PHT.

Conclusion: MILR in the posterosuperior segments in cirrhotic patients is associated with higher intraoperative blood transfusion and postoperative morbidity. This parameter should be utilized in the difficulty assessment of MILR.

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Data access

Data will be available from the corresponding author on reasonable request. It is not available publicly due to ethical and privacy concerns.

Keywords

Laparoscopic liver; posterosuperior segments; Minimally invasive liver; Cirrhosis; Difficulty score

INTRODUCTION

Liver resection (LR) is one of the first-line curative treatments for patients with compensated cirrhosis and primary malignancy. In the setting of LR, cirrhosis has been associated with increased intraoperative bleeding, liver decompensation, morbidity, and mortality.

It has been suggested that minimally-invasive surgery may offer better tolerance in cirrhotic patients as the laparoscopic approach has been shown to decrease the complications after liver surgery [1–7]. Since the seminal consensus meeting in 2008 [8] and its subsequent updates [9, 10], the adoption of minimally invasive liver resection (MILR) has been increasing worldwide. MILR in the anterolateral segments, even in selected patients with cirrhosis, has been considered safe and effective. More recently, MILR in the posterosuperior segments, (the“difficult segments”) have been performed with comparable outcomes to the open approach [11–14]. The extent of resection as well as the quality and quantity of remnant liver have been the main considerations when planning an open LR, while additional factors such as location and size of tumor, and proximity to vessels have been the main considerations when planning a MILR. However, the impact of cirrhosis on the difficulty and outcomes of MILR has still not been clearly defined.

To date, four major difficulty-scoring systems (DSS) are commonly utilized to grade the technical difficulty of MILR [15–19]. Although the Iwate system [18] was the only system to consider the degree of cirrhosis; it considers only Child-Pugh B cirrhosis as a significant factor of difficulty and does not distinguish between patients with Child-Pugh A cirrhosis and those without cirrhosis. Recently, a nationwide multicenter survey showed that cirrhosis was an independent risk factor for impaired outcomes, including mortality, in patients undergoing MILR, even in expert centers [20]. Moreover, center expertise was found as an independent protective factor against postoperative liver failure in cirrhotic patients and was also associated with successful completion of resections of the posterosuperior segments. However, there were several limitations worth highlighting in this study [20]. Firstly, it included MILR for all pathologies including liver metastases and benign tumors which were more likely to be in the non-cirrhotic arm and a potential confounder. Secondly, it included all types and extent of liver resections in the analyses. It has been demonstrated previously that the impact of cirrhosis on the outcomes of MILR differs with the extent and difficulty of the liver resections [21].

Hence, in this study, we aimed to assess the impact of cirrhosis and portal hypertension on the technical difficulty and outcomes of MILR for primary liver malignancies in the posterosuperior segments.

METHODS

Study design

This was a retrospective analysis of 5466 patients from 60 centers who underwent pure laparoscopic and robotic minor liver resections of the posterosuperior segments between 2004 and 2020. Of these, 2515 MI-LLR were performed for hepatocellular carcinoma (HCC), hepatocholangiocarcinoma 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 pure 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. Patients who underwent concomitant minor operations such as hernia repair, local ablation and hilar lymph node dissection were included. Finally, 1954 cases of laparoscopic and robotic LLR of the posterosuperior segments were included in the final analysis.

Definitions

Posterosuperior segments included segments 1/4a/7/8 [22]. Only minor resections were included and these were classified as segmentectomies or wedge/partial resections. Traditional major resections classified as resection of three or more contiguous segments were excluded. Additionally, right anterior and right posterior sectionectomies were also considered as major resections in this study and excluded [23]. Diameter of the largest lesion was used in the cases of multiple tumors. Cirrhosis was defined as F4 fibrosis on pathological examination. Clinically significant portal hypertension was defined based on radiological and clinical criteria such as the presence of ascites, esophageal varices or splenomegaly with a platelet count of less than 100,000/μL as portal venous pressure/hepatic venous pressure gradient was not routinely measured in most centers. In this study only patients with portal hypertension and cirrhosis were analyzed. Data on the hepatic venous gradient was not available. Difficulty of resections were graded according to the Iwate scoring system [18]. Postoperative complications were classified according to the Clavien-Dindo classification and recorded for up to 30 days or during the same hospitalization [24]. The use of the Pringle maneuver, intraoperative blood loss and blood transfusion, conversion rate, and duration of operation were considered surrogates of surgical difficulty.

Statistical analyses

Propensity score matching (PSM) and Coarsened Exact Matching (CEM) were used to estimate the effect of varying degrees of liver cirrhosis on MI-LLR. For PSM, the propensity score is estimated with a mixed effect logistic regression. The fixed effect factors used in calculating the propensity score are the baseline variables stated in Tables 1, 3 and 5 respectively. A random-effects parameter is also included in the model to account for between center variations. For PSM of comparison of Child-Pugh A cirrhotic versus non-cirrhotic liver in Tables 1, patients of one stratum are matched 1:1, using nearest neighbor matching without replacement or discard, utilizing logit link, to patients of the other strata. To improve matching, a small caliper is 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 will be discarded. Similar methodology is employed for PSM comparison in Tables 3 and 5. Due to the small number of patients in Child's B cirrhosis, for Table 3, an additional 1:2 PSM analysis was done. In this 1:2 PSM analysis, some Child's A patients were discarded due to high difference in propensity score from the Child's B patients after matching.

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 neighbor matching without replacement within each stratum, any unmatched units in the stratum will be dropped. This methodology is applied to all 3 CEM models. After matching, balance is 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 is plotted and presented below (Supplementary data S1-S6).

For continuous variables, weighted mean difference is presented, and two sample weighted t-test were used to calculate the standard error and p-values. For categorical variables, generalized linear and ordered logistic regression models were used to calculate the odds ratios, confidence intervals, and p-values. For unpaired comparisons of frequencies of categorical variables, Chi-squared and Fisher's exact tests were used. For the unpaired comparisons of median values and interquartile ranges, Mann-Whitney U test is used, and for the comparisons of mean values and standard deviations, one-way test is used. When appropriate, paired tests are used - McNemar's test is used for categorical variables and Wilcoxon Signed-Rank test is used for continuous. The statistical analyses were performed with RStudio version 1.4.1717, R version 4.1.0.

RESULTS

The study population included 1954 patients. Among these, 1290 (66%) patients had cirrhosis and 664 (34%) did not have cirrhosis. Among the 1290 patients with cirrhosis, 310 (24%) had PHT and 137 (11%) were Child-Pugh B.

Comparison between patients with Child-Pugh A cirrhosis and those without cirrhosis

The demographic, clinicopathological and perioperative data of pre- and post-matching groups are shown in Tables 1 and 2. Common major (grade ≥ 3) postoperative surgical complications included infected collections (n=19), bile leak (n =24), postoperative bleeding (n=3) and liver decompensation (n=4).

Before matching, patients with cirrhosis more frequently had ASA score ≥ 3 and HCC, and less frequently underwent robotic LR, segmentectomy and hilar lymph node dissection

(Table 1). Patients with cirrhosis tended to undergo less complex hepatectomies (Table 1). Patients with cirrhosis tended to have higher overall morbidity (p = 0.055; Table 2).

After matching, both groups were well balanced for all variables (Table 2, Supplementary Figures 1 and 2). After PSM, patients with cirrhosis had a higher intraoperative blood transfusion rate (14% *vs.* 9.3%; p = 0.027) and overall morbidity rate (20% *vs.* 14.5%; p = 0.023) than those without cirrhosis. After CEM, patients with cirrhosis tended to have higher intraoperative blood transfusion rate (12.1% *vs.* 6.7%; p = 0.059) and have higher overall morbidity rate (22.8% *vs.* 12.5%; p = 0.007; Table 2) than those without cirrhosis. There was no significant difference in other perioperative outcomes including median blood loss, need for Pringle maneuver, open conversion rate, median operating time, postoperative stay, readmission rate and postoperative mortality between both groups after matching (Table 2).

Comparison between Child-Pugh A and B cirrhotic patients

Tables 3 and 4 showed the demographic, clinicopathological and perioperative data of pre- and post-matching groups. Before PSM matching, patients with Child-Pugh B cirrhosis had less frequently history of abdominal surgery, surgery in the late era (≥ 2016), and had more frequently multiple tumors than those with Child-Pugh A (Table 3). Patients with Child-Pugh score B cirrhosis underwent more complex hepatectomies (Table 3). Patients with Child-Pugh B cirrhosis tended to have higher intraoperative blood transfusion (22.6% *vs.* 11.2%; p<0.001).

In the post-matching analysis, patients with Child-Pugh A cirrhosis and patients with Child-Pugh B cirrhosis both have similar baseline and preoperative characteristics. In the 1:1 PSM and 1:2 analysis, all key perioperative outcomes such as operation time, postoperative morbidity, blood transfusion rate, reoperation rate, postoperative length of stay and postoperative mortality were similar between the 2 groups.

Comparison between patients with and without portal hypertension

The demographic, clinicopathological and perioperative data of pre- and post-matching groups are shown in Tables 5 and 6. Before matching, comparison between the two groups showed higher prevalence of Child-Pugh B, ASA score ≥ 3 in the PHT group, whereas male sex was lower in the non-PHT group (Table 5). Before and after matching, Iwate "High" and "Expert" level resections were comparable between both groups. Before matching, Pringle maneuver was more frequently applied in the PHT group (64.2% *vs.* 54%; p = 0.002). The other perioperative outcomes were similar between both groups (Table 6).

After matching, both groups were well balanced for all variables (Table 5, Supplementary Figures 3 and 4). After PSM, Pringle maneuver was more frequently applied in the PHT group (62.2% *vs.* 52.4%; p = 0.045) than in the non-PHT group. After CEM, Pringle maneuver tended to be more frequently applied in the PHT group, but this was not significant (66.1% *vs.* 56.1%; p = 0.2). After matching, the other perioperative outcomes were similar between both groups (Table 6).

DISCUSSION

LR in the posterosuperior segments represents one of the most challenging situations in MILR, especially in patients with liver cirrhosis. The main findings of this study were as follows: 1) both robotic and laparoscopic segmentectomies and wedge resections were associated with acceptable outcomes in selected patients with cirrhosis and even in the presence of PHT, 2) the presence of cirrhosis was associated with significantly higher intraoperative blood transfusion and postoperative morbidity rates compared to non cirrhotics, and 3) Pringle maneuver was more frequently used in the presence of PHT. However, the mortality rate did not differ significantly even with the presence of cirrhosis in this series, which was contrary with a recent French nationwide series gathering data from more than 3000 patients, which reported a significant increased mortality rate in the cirrhotic population [20]. A likely explanation for this difference in results was that the present study only focused on minor liver resections and did not include major hepatectomies.

MI-LLR in the posterosuperior segments in cirrhotic patients is technically challenging for the following reasons: 1) these segments are located in the upper right part of the abdominal cavity under the ribs, which makes them difficult to access, 2) the cirrhotic parenchymal texture is hard and dysmorphic, which makes the liver difficult to mobilize and to transect, and 3) cirrhosis is usually associated with a low platelet count and clinically significant PHT, which renders these procedures more susceptible to bleed. The current DSS of MILR are mainly based on the procedure-related (extent of resection [17, 18]) and tumor-related variables (difficult location, size and proximity to major vessels [18]). The Iwate system is the only classification of surgical difficulty of MILR which considered cirrhosis as a difficulty variable. However, it only considered Child-Pugh B cirrhosis as a factor influencing difficulty [18]. In other words, the current DSS for MILR do not consider cirrhosis as a factor per se influencing the technical difficulty of MILR [19].

However, in real-life practice, most surgeons consider that cirrhosis has an impact on technical difficulty of MILR [25]. Several studies have reported the impact of cirrhosis on the outcomes of MILR [20, 21, 26, 27]. However, several biases have precluded any robust conclusions. These reports were obtained from mono- [21, 27] or multicentric [20, 26] series in which DSS (if any) were heterogeneously used (Institut Mutualiste Montsouris (IMM) system in the study by Hobeika et al. [20], or both IMM and Iwate systems in the study by Goh et al. [21], none in the other studies [20, 26, 27]). Major limitations of many these previous studies were the small sample size and the absence of matching [27]. Furthermore, in these previous studies, a major confounding factor was the inclusion of patients with other pathologies including benign lesions and colorectal liver metastases in the non-cirrhotic cohort [20],[21]. These studies also included patients who underwent various extents of liver resections including both major and minor hepatectomies [27]. Intuitively, it is likely that the degree of impact of cirrhosis on outcomes would depend on the extent and complexity of the MILR.

To our knowledge, this is the first multicentric study to assess specifically the impact of cirrhosis on the outcomes of minimally invasive minor LR in the posterosuperior segments in patients with primary malignancy. MI-LLR in the posterosuperior segments in patients with cirrhosis was associated with higher transfusion rate and postoperative morbidity rate. These results deserve several comments. As expected, MI-LLR in patients with cirrhosis is associated with worse outcomes compared to those without cirrhosis, which is in accordance with previous series [20, 21]. Second, our study confirms that the differences in outcomes between MI-LLR in cirrhosis *vs.* non cirrhosis was more pronounced in patients undergoing more difficult resections [20, 21].More interestingly, the study by Hobeika et al. has stratified the analyses according to the extent of posterosuperior liver resection (i.e, wedge resection of the posterosuperior segments (grade I of the IMM system) *vs.* segmentectomy of the posterosuperior segments (grade III of the IMM system). This however was not the case in the present series as both segmentectomy and wedge resection of the posterosuperior segments were not analyzed separately. Third, the higher rate of intraoperative blood transfusion also contributed to the higher rate of postoperative morbidity [28].

The second aspect to consider during MILR for cirrhosis is the presence of PHT. The EASL guidelines [29] proposed a risk algorithm for postoperative liver decompensation following LR including three variables in the following order: presence of PHT, extent of resection and MELD score. In the present study, we found that MI-LLR in the posterosuperior segments in selected cirrhotic patients with PHT was associated with safe outcomes (hospital stay = 6 days, morbidity rate = 21.9%, major morbidity rate = 6.8%, 30-day readmission = 2.9%, 90-day mortality = 0.3%); and more interestingly, PHT did not increase the risk of complications after MILR. This is in accordance with a recent study showing that the laparoscopic approach was the sole independent predictor of achieving a textbook outcome in a series of 79 high-risk patients with PHT (all with hepatic venous gradient ≥ 10 mmHg) who underwent resection of HCC [30].

The third aspect concerns the outcomes of MI-LLR in patients with Child-Pugh B cirrhosis. This requires the following comments. First, only 11% (7% of the series) of cirrhotic patients were Child-Pugh B. Second, MI-LLR in the posterosuperior segments in well-selected patients with Child-Pugh B cirrhosis was feasible with reasonably good outcomes (hospital stay = 7 days, morbidity rate = 19.7%, major morbidity rate = 9.5%, 30-day readmission = 2.7%, 90-day mortality = 0.2%). All together, these results demonstrated that Child-Pugh B cirrhosis patients with tumors located in the posterosuperior segments should not be excluded from potentially curative limited resection.

Finally, we acknowledge several limitations with this study. Firstly, its retrospective nature over a long time period could result in information bias. Secondly, although two matching modalities including PSM and CEM were used in this study to improve the robustness of the analyses, residual bias cannot be entirely mitigated in the absence of randomization. Thirdly, a pooled analysis of data from multiple Western and Eastern centers introduces some inherent selection bias resulting from differing practices (Eastern centers tend to propose surgery while Western centers tend to refer Child-Pugh B cirrhosis patients for liver transplantation), and also difference in surgeon and center experience.

In conclusion, MI-LLR for tumors located in the posterosuperior segments in patients with cirrhosis was associated with higher intraoperative blood transfusion and postoperative morbidity, but overall acceptable outcomes compared to non-cirrhotics. This parameter should be utilized in the difficulty assessment of MILR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declarations

We confirm all the authors are accountable for all aspects of the work

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Table 1.

Comparison between baseline characteristics of MILR in Child-Pugh A cirrhosis *vs.* non-cirrhosis

		Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
	All (N = 1817)	**Child A Cirrhosis (N = 1153)**	**Non-cirrhosis (N = 664)**	**P-value**	**Child A Cirrhosis (N = 516)**	**Non-cirrhosis (N = 516)**	**P-value (paired)**	**Child A Cirrhosis (N = 224)**	**Non-cirrhosis (N = 224)**	**P-value (paired)**
Mean age (SD), yrs	64.00 [55.00, 71.00]	63.00 [55.64, 71.00]	64.00 [54.00, 72.00]	0.920	63.60 [56.00, 70.00]	63.56 [54.00, 71.00]	0.747	64.00 [57.00, 69.25]	64.00 [56.75, 70.00]	0.538
Male sex, n (%)	1353 (74.5)	854 (74.1)	499 (75.2)	0.650	382 (74.0)	389 (75.4)	0.671	182 (81.2)	182 (81.2)	NA
Robotic, n (%)	243 (13.4)	120 (10.4)	123 (18.5)		134 (26.0)	127 (24.6)	1.000	42 (18.8)	42 (18.8)	
Laparoscopic, n (%)	1574 (86.6)	1033 (89.6)	541 (81.5)	**<0.001**	433 (83.9)	434 (84.1)		210 (93.8)	210 (93.8)	NA
Previous abdominal surgery, n (%)	336 (19.0)	204 (18.4)	132 (19.9)	0.449	96 (18.6)	101 (19.6)	0.750	24 (10.7)	24 (10.7)	NA
Year of surgery, n (%)										
2004–2009	30 (1.7)	15 (1.3)	15 (2.3)	0.069	7 (1.4)	9 (1.7)	0.558	23 (10.3)	23 (10.3)	NA
2010–2015	378 (20.8)	255 (22.1)	123 (18.5)		92 (17.8)	103 (20.0)		201 (89.7)	201 (89.7)	
2016–2021	1409 (77.5)	883 (76.6)	526 (79.2)		417 (80.8)	404 (78.3)				
ASA score, n (%)										
1/2	1282 (70.6)	787 (68.3)	495 (74.5)	**0.005**	387 (75.0)	381 (73.8)		181 (80.8)	181 (80.8)	NA
3/4	535 (29.4)	366 (31.7)	169 (25.5)		129 (25.0)	135 (26.2)	0.718	43 (19.2)	43 (19.2)	
Tumor type, n (%)										
HCC	1666 (91.7)	1096 (95.1)	570 (85.8)	**<0.001**	487 (94.4)	490 (95.0)	0.742	217 (96.9)	217 (96.9)	NA
ICC/cholangiohepatoma	151 (8.3)	57 (4.9)	94 (14.2)		29 (5.6)	26 (5.0)		7 (3.1)	7 (3.1)	
Median tumor size, mm [IQR]	28.00 [20.00, 40.00]	30.00 [20.00, 40.00]	30.00 [21.50, 40.00]	0.596	30.00 [20.00, 40.00]	29.50 [20.00, 40.00]	0.667	25.00 [20.00, 34.00]	25.00 [20.00, 35.00]	0.391
Multiple tumors, n (%)	142 (7.8)	100 (8.7)	42 (6.3)	0.090	29 (5.6)	33 (6.4)	0.703	2 (0.9)	2 (0.9)	NA
Wedge/partial, n (%)	1068 (58.8)	710 (61.6)	358 (53.9)	**0.002**	273 (52.9)	288 (55.8)	0.377	137 (61.2)	137 (61.2)	NA

		Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
	All (N = 1817)	**Child A Cirrhosis (N = 1153)**	**Non-cirrhosis (N = 664)**	**P-value**	**Child A Cirrhosis (N = 516)**	**Non-cirrhosis (N = 516)**	**P-value (paired)**	**Child A Cirrhosis (N = 224)**	**Non-cirrhosis (N = 224)**	**P-value (paired)**
Segmentectomy, n (%)	749 (41.2)	443 (38.4)	306 (46.1)		243 (47.1)	228 (44.2)		87 (38.8)	87 (38.8)	
Concomitant minor surgery excluding cholecystectomy, n (%)	94 (5.2)	46 (4.0)	48 (7.2)	**0.004**	21 (4.1)	15 (2.9)	0.405	0 (0.0)	0 (0.0)	NA
Hilar lymph node dissection, n (%)	42 (2.3)	10 (0.9)	32 (4.8)	**<0.001**	8 (1.6)	3 (0.6)	0.228	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score, [IQR](range)	6.00 [5.00, 9.00] (3, 11)	7.00 [5.00, 9.00] (3, 11)	7.00 [5.00, 9.00] (4, 11)	0.551	7.00 [5.00, 9.00] (3, 11)	6.00 [5.00, 9.00] (4, 11)	0.423	6.00 [5.00, 9.00] (4, 10)	6.00 [5.00, 9.00] (4, 10)	NA
Iwate difficulty, n (%)				**<0.001**			NA			NA
Low	2 (0.1)	1 (0.1)	1 (0.2)		1 (0.2)	1 (0.2)		0 (0.0)	0 (0.0)	
Intermediate	997 (54.9)	686 (59.5)	311 (46.8)		251 (48.6)	270 (52.3)		134 (59.8)	134 (59.8)	
High	695 (38.2)	416 (36.1)	279 (42.0)		222 (43.0)	204 (39.5)		77 (34.4)	77 (34.4)	
Expert	123 (6.8)	50 (4.3)	73 (11.0)		42 (8.1)	41 (7.9)		13 (5.8)	13 (5.8)	

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; CEM, coarsened exact matching; SD, standard deviation; NA, not available; ASA, American Society of Anesthesiologists; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; IQR, interquartile range.

Table 2.

Comparison between perioperative outcomes of MILR in Child-Pugh A cirrhosis *vs.* non-cirrhosis

		Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:1 CEM		
	All (N = 1817)	**Child A Cirrhosis (N = 1153)**	**Non-cirrhosis (N = 664)**	**P-value**	**Child A Cirrhosis (N = 516)**	**Non-cirrhosis (N = 516)**	**P-value (paired)**	**Child A Cirrhosis (N = 224)**	**Non-cirrhosis (N = 224)**	**P-value (paired)**
Open conversion, n (%)	105 (5.8)	68 (5.9)	37 (5.6)	0.856	37 (7.2)	30 (5.8)	0.450	13 (5.8)	7 (3.1)	0.239
Median operating time [IQR], min	224.00 [164.00, 305.00]	233.50 [167.25, 330.00]	230.00 [168.50, 317.00]	0.469	233.50 [167.25, 330.00]	225.00 [166.50, 310.00]	0.499	208.00 [160.00, 300.00]	220.00 [155.00, 300.00]	0.292
Median blood loss [IQR], ml	193.50 [50.00, 350.00]	200.00 [50.00, 400.00]	190.00 [60.00, 400.00]	0.646	200.00 [50.00, 400.00]	192.50 [60.00, 400.00]	0.445	150.00 [50.00, 300.00]	150.00 [50.00, 350.00]	0.908
Blood loss > 500 mls, n (%)	258 (14.7)	159 (14.3)	99 (15.4)	0.587	87 (17.5)	82 (16.4)	1.000	29 (13.4)	32 (14.5)	0.766
Intraoperative blood transfusion, n (%)	196 (10.8)	129 (11.2)	67 (10.1)	0.513	72 (14.0)	48 (9.3)	**0.027**	27 (12.1)	15 (6.7)	0.059
Pringle maneuver applied, n (%)	1020 (56.9)	647 (56.9)	373 (57.0)	0.981	307 (60.6)	281 (55.3)	0.101	138 (62.4)	126 (56.8)	0.257
Mean postoperative stay, d [IQR]	6.00 [4.00, 9.00]	6.00 [4.93, 9.00]	6.00 [4.00, 8.00]	0.061	6.00 [4.93, 9.00]	6.00 [4.00, 8.00]	0.125	6.00 [4.00, 9.00]	6.00 [5.00, 8.54]	0.999
Postoperative morbidity, n (%)	333 (18.3)	227 (19.7)	106 (16.0)	0.055	103 (20.0)	75 (14.5)	**0.023**	51 (22.8)	28 (12.5)	**0.007**
Major morbidity (Clavien-Dindo grade> 2), n (%)	94 (5.2)	59 (5.1)	35 (5.3)	0.977	39 (7.6)	29 (5.6)	0.268	16 (7.1)	13 (5.8)	0.689
Reoperation, n (%)	11 (0.6)	7 (0.6)	4 (0.6)	1.000	5 (1.0)	2 (0.4)	0.371	2 (0.9)	1 (0.4)	1.000
30-day readmission, n (%)	53 (2.9)	31 (2.7)	22 (3.3)	0.539	20 (3.9)	18 (3.5)	0.868	9 (4.0)	5 (2.2)	0.423
30-day mortality, n (%)	2 (0.1)	1 (0.1)	1 (0.2)	1.000	1 (0.2)	1 (0.2)	1.000	0 (0.0)	0 (0.0)	NA
In-hospital mortality, n (%)	5 (0.3)	2 (0.2)	3 (0.5)	0.362	2 (0.4)	1 (0.2)	1.000	0 (0.0)	1 (0.4)	1.000
90-day mortality, n (%)	4 (0.2)	2 (0.2)	2 (0.3)	0.626	2 (0.4)	2 (0.4)	1.000	0 (0.0)	1 (0.4)	1.000

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; CEM, coarsened exact matching; IQR, interquartile range; d, days

Table 3.

Comparison between baseline characteristics of MILR in Child-Pugh A *vs.* Child-Pugh B cirrhosis

		Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:2 PSM (nearest neighbour, calipers used)		
	All (N = 1290)	**Childs A (N = 1153)**	**Childs B (N = 137)**	**P-value**	**Childs A (N = 65)**	**Childs B (N = 65)**	**P-value**	**Childs A (N = 121)**	**Childs B (N = 68)**	**P-value**
Mean age (SD), yrs	63.00 [55.00, 71.00]	63.00 [55.64, 71.00]	60.00 [48.00, 68.00]	0.533	62.00 [54.00, 70.00]	64.30 [55.00, 72.00]	0.485	64.00 [56.00, 71.00]	64.65 [55.75, 72.20]	0.737
Male sex, n (%)	964 (74.7)	854 (74.1)	110 (80.3)	0.139	50 (76.9)	52 (80.0)	0.814	95 (78.5)	54 (79.4)	1.000
Robotic, n (%)	138 (10.7)	120 (10.4)	18 (13.1)		15 (23.1)	13 (20.0)		26 (21.5)	14 (20.6)	
Laparoscopic, n (%)	1152 (89.3)	1033 (89.6)	119 (86.9)	0.406	58 (89.2)	55 (84.6)	0.606	106 (87.6)	58 (85.3)	0.821
Previous abdominal surgery, n (%)	211 (16.9)	204 (18.4)	7 (5.1)	**<0.001**	3 (4.6)	5 (7.7)	0.683	9 (7.4)	5 (7.4)	1.000
Year of surgery, n (%)										
2004–2009	19 (1.5)	15 (1.3)	4 (2.9)		2 (3.1)	2 (3.1)		3 (2.5)	2 (2.9)	
2010–2015	304 (23.6)	255 (22.1)	49 (35.8)		15 (23.1)	18 (27.7)		31 (25.6)	19 (27.9)	
2016–2021	967 (75.0)	883 (76.6)	84 (61.3)	**<0.001**	48 (73.8)	45 (69.2)	0.880	87 (71.9)	47 (69.1)	0.908
ASA score, n (%)										
1/2	886 (68.7)	787 (68.3)	99 (72.3)		38 (58.5)	42 (64.6)		75 (62.0)	43 (63.2)	
3/4	404 (31.3)	366 (31.7)	38 (27.7)	0.391	27 (41.5)	23 (35.4)	0.571	46 (38.0)	25 (36.8)	0.989
Tumor type, n (%)										
HCC	1231 (95.4)	1096 (95.1)	135 (98.5)		63 (96.9)	64 (98.5)		119 (98.3)	66 (97.1)	
ICC/cholangiohepatoma	59 (4.6)	57 (4.9)	2 (1.5)	0.080	2 (3.1)	1 (1.5)	1.000	2 (1.7)	2 (2.9)	0.620
Median tumor size, mm (IQR)	25.00 [19.00, 40.00]	25.00 [18.00, 35.25]	25.00 [20.00, 37.00]	0.989	30.00 [18.00, 40.00]	25.00 [20.00, 37.00]	0.811	28.00 [18.00, 40.00]	25.00 [19.75, 39.00]	0.828
Multiple tumors, n (%)	124 (9.6)	100 (8.7)	24 (17.5)	**0.002**	7 (10.8)	9 (13.8)	0.789	20 (16.5)	9 (13.2)	0.695
Wedge/partial liver resection, n (%)	791 (61.3)	710 (61.6)	81 (59.1)		39 (60.0)	42 (64.6)		75 (62.0)	44 (64.7)	
Segmentectomy, n (%)	499 (38.7)	443 (38.4)	56 (40.9)	0.642	26 (40.0)	23 (35.4)	0.710	46 (38.0)	24 (35.3)	0.830

		Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:2 PSM (nearest neighbour, calipers used)		
	All (N = 1290)	**Childs A (N = 1153)**	**Childs B (N = 137)**	**P-value**	**Childs A (N = 65)**	**Childs B (N = 65)**	**P-value**	**Childs A (N = 121)**	**Childs B (N = 68)**	**P-value**
Concomitant minor surgery excluding cholecystectomy, n (%)	49 (3.8)	46 (4.0)	3 (2.2)	0.475	6 (9.2)	3 (4.6)	0.505	6 (5.0)	3 (4.4)	1.000
Hilar lymph node dissection, n (%)	11 (0.9)	10 (0.9)	1 (0.7)	1.000	2 (3.1)	1 (1.5)	1.000	2 (1.7)	1 (1.5)	1.000
Median Iwate difficulty score excluding Childs score, [IQR] (range)	6.00 [5.00, 8.00] (3, 11)	6.00 [5.00, 8.00] (4, 11)	5.00 [5.00, 8.00] (3, 10)	0.892	6.00 [5.00, 9.00]	5.00 [5.00, 8.00]	0.394	6.00 [5.00, 9.00]	5.00 [5.00, 8.00]	0.991
Iwate difficulty exclude Childs score, n (%)										
Low	1 (0.1)	1 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)				
Intermediate	725 (56.2)	686 (59.5)	39 (28.5)		31 (47.7)	35 (53.8)		62 (51.2)	35 (51.5)	
High	469 (36.4)	416 (36.1)	53 (38.7)		22 (33.8)	18 (27.7)		35 (28.9)	20 (29.4)	
Expert	95 (7.4)	50 (4.3)	45 (32.8)	**<0.001**	12 (18.5)	12 (18.5)	0.210	24 (19.8)	13 (19.1)	1.000

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; SD, standard deviation; ASA, American Society of Anesthesiologists; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; IQR, interquartile range.

Table 4.

Comparison between perioperative outcomes of MILR in Child-Pugh A *vs.* B cirrhosis

		Entire unmatched cohort			1:1 PSM (nearest neighbour)			1:2 PSM (nearest neighbour, calipers used)		
	All (N = 1290)	**Childs A (N = 1153)**	**Childs B (N = 65)**	**P-value**	**Childs A (N = 65)**	**Childs B (N = 65)**	**P-value**	**Childs A (N = 121)**	**Childs B (N = 68)**	**P-value**
Open conversion, n (%)	72 (5.6)	68 (5.9)	4 (2.9)	0.172	4 (6.2)	1 (1.5)	0.371	5 (4.1)	1 (1.5)	0.422
Median operating time [IQR], min	222.00 [164.00, 300.00]	220.00 [163.00, 300.00]	205.00 [150.00, 255.00]	0.269	220.00 [170.00, 285.00]	205.00 [150.00, 255.00]	0.141	225.00 [175.00, 305.00]	210.00 [150.00, 276.00]	0.191
Median blood loss [IQR], ml	200.00 [50.00, 380.00]	197.00 [50.00, 350.00]	200.00 [65.00, 350.00]	0.745	200.00 [50.00, 300.00]	200.00 [65.00, 350.00]	0.596	196.50 [50.00, 390.50]	200.00 [92.50, 400.00]	0.525
Blood loss > 500 mls, n (%)	184 (14.8)	159 (14.3)	25 (18.8)	0.210	8 (12.3)	9 (13.8)	1.000	20 (16.9)	11 (16.7)	1.000
Intraoperative blood transfusion, n (%)	160 (12.4)	129 (11.2)	31 (22.6)	**<0.001**	7 (10.8)	11 (16.9)	0.386	19 (15.7)	12 (17.6)	0.887
Pringle maneuver applied, n (%)	717 (56.4)	647 (56.9)	70 (52.6)	0.403	35 (58.3)	32 (51.6)	0.458	66 (57.4)	34 (52.3)	0.615
Mean postoperative stay, d [IQR]	6.00 [4.49, 10.00]	6.00 [4.00, 9.00]	7.00 [5.00, 12.00]	0.645	7.00 [5.00, 10.00]	7.00 [5.00, 12.00]	0.593	7.00 [5.00, 12.00]	7.50 [5.00, 12.00]	0.655
Postoperative morbidity, n (%)	262 (20.3)	227 (19.7)	35 (25.5)	0.135	18 (27.7)	12 (18.5)	0.286	30 (24.8)	14 (20.6)	0.633
Major morbidity (Clavien-Dindo grade> 2), n (%)	72 (5.6)	59 (5.1)	13 (9.5)	0.056	5 (7.7)	4 (6.2)	1.000	8 (6.6)	5 (7.4)	1.000
Reoperation, n (%)	8 (0.6)	7 (0.6)	1 (0.7)	0.594	0 (0.0)	1 (1.5)	1.000	0 (0.0)	1 (1.5)	0.360
30-day readmission, n (%)	37 (2.9)	31 (2.7)	6 (4.4)	0.396	3 (4.6)	4 (6.2)	1.000	4 (3.3)	5 (7.4)	0.287
30-day mortality, n (%)	2 (0.2)	1 (0.1)	1 (0.7)	0.201	1 (1.5)	0 (0.0)	1.000	1 (0.8)	1 (1.5)	1.000
In-hospital mortality, n (%)	4 (0.3)	2 (0.2)	2 (1.5)	0.058	1 (1.5)	1 (1.5)	1.000	1 (0.8)	2 (2.9)	0.294
90-day mortality, n (%)	4 (0.3)	2 (0.2)	2 (1.5)	0.058	1 (1.5)	1 (1.5)	1.000	1 (0.8)	2 (2.9)	0.294

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; IQR, interquartile range; d, days.

Table 5.

Comparison between baseline characteristics of MILR in cirrhotic patients with and without portal hypertension

		Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
	All (N = 1283)	**Cirrhosis PHT (N = 310)**	**Cirrhosis NPHT (N = 973)**	**P-value**	**Cirrhosis PHT (N = 227)**	**Cirrhosis NPHT (N = 227)**	**P-value**	**Cirrhosis PHT (N = 116)**	**Cirrhosis NPHT (N = 116)**	**P-value (paired)**
Mean age (SD), yrs	63.00 [55.00, 71.00]	64.15 [56.25, 71.00]	63.00 [54.00, 71.00]	0.836	63.00 [55.50, 71.00]	63.00 [55.00, 70.60]	0.658	63.62 [56.00, 69.62]	63.00 [55.00, 70.00]	0.432
Male sex, n (%)	960 (74.8)	218 (70.3)	742 (76.3)	**0.043**	168 (74.0)	174 (76.7)	0.566	93 (80.2)	93 (80.2)	NA
Robotic, n (%)	138 (10.8)	35 (11.3)	103 (10.6)		59 (26.0)	53 (23.3)		23 (19.8)	23 (19.8)	
Laparoscopic, n (%)	1145 (89.2)	275 (88.7)	870 (89.4)	0.808	199 (87.7)	201 (88.5)	0.885	113 (97.4)	113 (97.4)	NA
Previous abdominal surgery, n (%)	210 (16.9)	63 (20.3)	147 (15.8)	0.079	46 (20.3)	54 (23.8)	0.403	13 (11.2)	13 (11.2)	NA
Childs A, n (%)	1144 (89.3)	253 (81.6)	891 (91.8)		193 (85.0)	190 (83.7)		111 (95.7)	111 (95.7)	
Childs B, n (%)	137 (10.7)	57 (18.4)	80 (8.2)	**<0.001**	34 (15.0)	37 (16.3)	0.755	5 (4.3)	5 (4.3)	NA
Year of surgery, n (%)										
2004–2009	19 (1.5)	5 (1.6)	14 (1.4)		3 (1.3)	3 (1.3)				
2010–2015	304 (23.7)	68 (21.9)	236 (24.3)		44 (19.4)	46 (20.3)		13 (11.2)	13 (11.2)	
2016–2021	960 (74.8)	237 (76.5)	723 (74.3)	0.668	180 (79.3)	178 (78.4)	0.750	103 (88.8)	103 (88.8)	NA
ASA score, n (%)										
1/2	884 (68.9)	187 (60.3)	697 (71.6)		152 (67.0)	143 (63.0)		79 (68.1)	79 (68.1)	
3/4	399 (31.1)	123 (39.7)	276 (28.4)	**<0.001**	75 (33.0)	84 (37.0)	0.391	37 (31.9)	37 (31.9)	NA
Tumor type, n (%)										
HCC	1222 (95.2)	300 (96.8)	922 (94.8)		221 (97.4)	220 (96.9)		116 (100.0)	116 (100.0)	
ICC/cholangiohepatoma	61 (4.8)	10 (3.2)	51 (5.2)	0.194	6 (2.6)	7 (3.1)	1.000	0 (0.0)	0 (0.0)	NA
Median tumor size, mm (IQR)	25.00 [19.00, 40.00]	26.00 [20.00, 40.00]	25.00 [18.00, 40.00]	0.664	26.00 [20.00, 40.00]	26.00 [20.00, 35.00]	0.940	25.00 [20.00, 32.00]	25.00 [20.00, 31.25]	0.802

		Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
	All (N = 1283)	**Cirrhosis PHT (N = 310)**	**Cirrhosis NPHT (N = 973)**	**P-value**	**Cirrhosis PHT (N = 227)**	**Cirrhosis NPHT (N = 227)**	**P-value**	**Cirrhosis PHT (N = 116)**	**Cirrhosis NPHT (N = 116)**	**P-value (paired)**
Multiple tumors, n (%)	124 (9.7)	28 (9.0)	96 (9.9)	0.747	17 (7.5)	18 (7.9)	1.000	0 (0.0)	0 (0.0)	NA
Wedge/partial liver resection, n (%)	790 (61.6)	194 (62.6)	596 (61.3)		140 (61.7)	138 (60.8)		82 (70.7)	82 (70.7)	
Segmentectomy, n (%)	493 (38.4)	116 (37.4)	377 (38.7)	0.725	87 (38.3)	89 (39.2)	0.918	34 (29.3)	34 (29.3)	NA
Concomitant minor surgery excluding cholecystectomy, n (%)	49 (3.8)	10 (3.2)	39 (4.0)	0.649	9 (4.0)	9 (4.0)	1.000	0 (0.0)	0 (0.0)	NA
Hilar lymph node dissection, n (%)	11 (0.9)	2 (0.6)	9 (0.9)	1.000	2 (0.9)	1 (0.4)	1.000	0 (0.0)	0 (0.0)	NA
Median Iwate difficulty score, [IQR] (range)	6.00 [5.00, 8.00] (4, 11)	6.00 [5.00, 9.00] (4, 11)	6.00 [5.00, 8.00] (4, 11)	0.904	6.00 [5.00, 9.00] (4, 11)	6.00 [5.00, 9.00] (4, 11)	0.990	6.00 [5.00, 8.00] (4, 10)	6.00 [5.00, 8.00] (4, 10)	NA
Iwate difficulty, n (%)										
Low	1 (0.1)	0 (0.0)	1 (0.1)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Intermediate	724 (56.4)	166 (53.5)	558 (57.3)		121 (53.3)	121 (53.3)		79 (68.1)	79 (68.1)	
High	466 (36.3)	116 (37.4)	350 (36.0)		87 (38.3)	85 (37.4)		36 (31.0)	36 (31.0)	
Expert	92 (7.2)	28 (9.0)	64 (6.6)	0.385	19 (8.4)	21 (9.3)	0.161	1 (0.9)	1 (0.9)	NA

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; CEM, coarsened exact matching; SD, standard deviation; PHY, portal hypertension; NPHT no portal hypertension NA, not available; ASA, American Society of Anesthesiologists; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; IQR, interquartile range

Table 6.

Comparison between perioperative outcomes of MILR in cirrhotic patients with and without portal hypertension

		Entire unmatched cohort			1:1 PSM (nearest neighbour matching)			1:1 CEM		
	All (N = 1283)	**Cirrhosis PHT (N = 310)**	**Cirrhosis NPHT (N = 973)**	**P-value**	**Cirrhosis PHT (N = 227)**	**Cirrhosis NPHT (N = 227)**	**P-value**	**Cirrhosis PHT (N = 116)**	**Cirrhosis NPHT (N = 116)**	**P-value (paired)**
Open conversion, n (%)	72 (5.6)	22 (7.1)	50 (5.1)	0.245	13 (5.7)	5 (2.2)	0.099	5 (4.3)	5 (4.3)	1.000
Median operating time [IQR], min	222.00 [165.00, 300.00]	206.00 [150.00, 280.00]	224.50 [165.75, 300.00]	0.165	206.00 [150.00, 280.00]	220.00 [162.00, 300.00]	0.222	202.00 [150.00, 271.25]	205.50 [160.00, 267.75]	0.757
Median blood loss [IQR], ml	200.00 [50.00, 380.00]	150.00 [50.00, 400.00]	200.00 [50.00, 350.00]	0.928	150.00 [50.00, 400.00]	170.00 [50.00, 330.00]	0.670	150.00 [77.50, 400.00]	200.00 [75.00, 333.00]	0.829
Blood loss > 500 mls, n (%)	183 (14.8)	53 (17.7)	130 (13.8)	0.120	35 (15.6)	30 (13.7)	0.583	17 (15.3)	16 (13.9)	0.838
Intraoperative blood transfusion, n (%)	158 (12.3)	37 (11.9)	121 (12.4)	0.889	29 (12.8)	33 (14.5)	0.658	10 (8.6)	11 (9.5)	1.000
Pringle maneuver applied, n (%)	714 (56.5)	197 (64.2)	517 (54.0)	**0.002**	140 (62.2)	118 (52.4)	0.045	76 (66.1)	64 (56.1)	0.200
Mean postoperative stay, d [IQR]	6.00 [4.68, 10.00]	6.00 [4.02, 11.00]	6.00 [4.20, 10.00]	0.166	6.00 [4.02, 11.00]	6.00 [4.00, 9.00]	0.235	6.00 [5.00, 8.00]	6.00 [4.00, 8.25]	0.573
Postoperative morbidity, n (%)	260 (20.3)	68 (21.9)	192 (19.8)	0.453	45 (19.8)	46 (20.3)	1.000	20 (17.2)	18 (15.5)	0.831
Major morbidity (Clavien-Dindo grade> 2), n (%)	72 (5.6)	21 (6.8)	51 (5.2)	0.381	14 (6.2)	15 (6.6)	1.000	3 (2.6)	3 (2.6)	1.000
Reoperation, n (%)	8 (0.6)	2 (0.6)	6 (0.6)	1.000	2 (0.9)	0 (0.0)	0.480	0 (0.0)	0 (0.0)	NA
30-day readmission, n (%)	37 (2.9)	9 (2.9)	28 (2.9)	1.000	7 (3.1)	6 (2.6)	1.000	2 (1.7)	4 (3.4)	0.683
30-day mortality, n (%)	2 (0.2)	0 (0.0)	2 (0.2)	1.000	0 (0.0)	1 (0.4)	1.000	0 (0.0)	0 (0.0)	NA
In-hospital mortality, n (%)	6 (0.5)	1 (0.3)	5 (0.5)	1.000	0 (0.0)	2 (0.9)	0.480	0 (0.0)	0 (0.0)	NA
90-day mortality, n (%)	4 (0.3)	1 (0.3)	3 (0.3)	1.000	0 (0.0)	2 (0.9)	0.480	0 (0.0)	0 (0.0)	NA

Footnotes:

MILR indicates minimally invasive liver resection; PSM, propensity score matching; CEM, coarsened exact matching; SD, standard deviation; NA, not available; ASA, American Society of Anesthesiologists; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; IQR, interquartile range