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ORIGINAL ARTICLE

Minimally invasive versus open liver resection for nonmetastatic hepatocellular carcinoma staged BCLC – B and – C: an Italian multicentric analysis

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Abstract

Background: Recent papers report significant survival gain after liver resection in BCLC-B and -C HCC patients. The results of minimally invasive liver surgery (MILS) in such patients have not been widely investigated so far.

Methods: Data regarding patients undergoing MILS or open liver resection (OLR) for HCC staged BCLC -B and -C were extracted from the HERCOLES database. An inverse probability of treatment weighting (IPTW) method was adopted to balance the confounders. The primary outcome was a composite endpoint including post-hepatectomy liver failure, severe postoperative complications and in-hospital mortality.

Results: 627 patients were included (459 undergoing OLR and 168 receiving MILS). After IPTW, no difference was found in the composite endpoint between MILS and OLR (OR 0.86 [95%CI 0.46-1-60]; p = 0.62). MILS reduced the risk of receiving intra-operative transfusions (OR 0.28 [95%CI 0.13-0.58]; p < 0.001) and of developing postoperative ascites (OR 0.56 [95%CI 0,32-0,98]; p = 0.039), with reduced length of stay (OR 0.82 [95%CI 0.66-1.01]; p = 0.045). The survival analysis showed no differences between MILS and OLR for both OS (p = 0.13) and DFS (p = 0.491).

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Conclusion: MILS was shown to be safe and feasible for selected non-metastatic HCC patients staged BCLC B and C, reducing the risk of perioperative transfusions and postoperative ascites, and shortening the length of stay.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for 85%–90 % of primary hepatic malignancies.[1] It is ranked as the fourth leading cause of cancer-related deaths worldwide, with an incidence that is continuously increasing.[2] HCC develops on liver cirrhosis in more than 90 % of cases, with viral and alcoholic liver disease representing the most common etiology, although recent epidemiological data highlighted the increasing etiological role of obesity, diabetes and metabolic syndrome in liver oncogenesis.[3]

HCC treatment is complex and multimodal. Liver transplantation (LT) is considered the gold standard treatment, offering the possibility to simultaneously treat both liver cancer and the underlying liver disease.[4] However, organ shortage with the subsequent risk of tumor progression and dropout, led to the development of restricted indication to LT, for patients who are not candidates for liver resection or thermal ablations due to uncompensated cirrhosis, to patients with unfavorable prognostic factors on pathological examination after resection and those with recurrent HCC in transplantable patients.[5,6] The multimodal management of HCC patients lies on specifical staging systems, based on tumor's features and liver function, proposed to guide the therapeutic decisions, as well as to stratify the prognosis. The Barcelona Clinic Liver Cancer (BCLC) classification has been endorsed as the best staging system and treatment algorithm for HCC by the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD).[7] This classification combines the underlying liver condition, performance status, and the tumor characteristics (number, size, macrovascular invasion), showing a reliable capacity to categorize patients with different prognosis.[8] According to this staging system, liver resection is indicated only to those patients with early-stage tumors, while patients with multiple, large, or macrovascular invasive HCC are recommended to receive trans-arterial chemo-embolization (TACE) or medical therapy. Thus, according to this staging system the place for liver resection appears very limited. Nonetheless, many papers have shown that liver resection has good survival outcomes even in presence of portal hypertension (PHT), multinodular disease, large nodules or even HCC with macrovascular invasion.[9–12] Indeed, the BCLC staging system has been frequently questioned due to the exclusion of many patients who may benefit from surgical treatment, with important consequences on long term survival.[13,14] Currently, high volume centers have reported BCLC-B and –C staged HCC patients undergoing surgery with satisfying survival outcomes.[15,16]

In this scenario, the role of minimally invasive liver surgery (MILS) in such patients has never been investigated so far. Ideally, a minimally invasive approach could minimize surgical stress and enhance patient recovery, with cirrhotic patients that could benefit from the minimized interruption of collateral shunts end the reduced exposure of the abdominal cavity to the external atmosphere.[17,18] Since its introduction in 1991, MILS has slowly gained a validated role for the treatment of early HCC, being associated with better short-term outcomes and similar oncological survival to the standard open approach.[19–22] However, most cases available in literature included early staged HCC patients, and the role of laparoscopy in the setting of BCLC-B and –C stages is unclear.

The aim of this study was to compare large real-life data from specialized Western institutions about short- and long-term outcomes after open liver resection (OLR) and MILS for HCC staged BCLC-B and –C.

Methods

Patients and data

Data regarding consecutive adult patients undergoing liver resection from January 2008 to December 2021 for HCC were retrospectively extracted from the HERCOLES (Hepatocarcinoma Recurrence on the Liver Study Group) database. The inclusion criteria were as follows: adults patients staged BCLC-B and –C HCC with histopathological confirmation, no extrahepatic metastasis. The exclusion criteria were as follows: liver resection extended to other abdominal organs other than gallbladder, histological finding of combined HCC-CCA.

The HE.RC.O.LE.S. register is based on spontaneous collaboration across Italian centers performing liver surgery, without

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restriction on the number of patients treated per year. The register collected nearly 170 variables related to patient comorbidities, underlying liver

Function, radiological and intraoperative findings, postoperative course, histological evaluation, and follow-up information. All data were collected by local researchers and anonymized before their submission to the coordinating center. Data were collected using an electronic database system in each center and then centrally checked.

The HE.RC.O.LE.S. protocol was approved by the Ethical Committee of San Gerardo Hospital (Monza, Italy, "Monza e Brianza Ethical Committee", IRB "HERCOLES2/18") on December 21st, 2018, and also by all centers (clinicaltrial.gov registration number: NCT04053231). The study was conducted in accordance with the principles of the Declaration of Helsinki.

This study was conducted according to the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidelines of the EQUATOR network.[23] Informed consent was obtained prior to every surgical procedure.

Preoperative management

The therapeutic management of each patient was decided by a multidisciplinary team meeting including surgeons, hepatologists, oncologists, and radiologists. Preoperative and postoperative management, as well as surgical procedures, were performed by the same team in the same facility. Preoperative evaluations were similar in both groups and included routine blood tests, liver function, coagulation examinations, serum tumor markers, ICG clearance tests, and triphasic enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). The definition of resectable HCC was based on multidisciplinary team decision, according to comprehensive evaluation of liver function test, ICG clearance test, remnant liver volume, and liver compensation status.

Surgical procedures

The laparoscopic procedures have been described in detail elsewhere.[24–26] The surgical procedures were both parenchymal sparing or anatomical liver resections depending on many factors, such as proximity of major vessels, risk of R1 resection, surgeons' and centers' preference. Laparoscopic ultrasonography was routinely performed to confirm the positions of tumors, prevent the omissions of additional lesions and guide the transection lines. An extracorporeal or intracorporeal Pringle maneuver was prepared to eventually help controlling blood loss. The liver parenchyma was transected by a combination of a harmonic scalpel (Ethicon, Endo-Surgery, USA) and a laparoscopic cavitron ultrasonic surgical aspirator (CUSA, Integra-France) or Ligasure (Medtronic, USA). Intraparenchymal vascular and biliary vessels were secured by clips or sutures. The specimen was placed into a retrieval bag and extracted through a suprapubic incision or a sub-umbilical midline incision.

For the open procedure, a sub-costal incision was performed, with patients in the supine position under general anesthesia and following the same anesthesiologic care. The operating procedure was similar to MILS, and CUSA or clamp crushing was used as the main method for liver parenchyma transection.

Postoperative management and follow-up

Post-operative follow-up data were analyzed. All patients were examined in outpatients' clinics within one month after discharge, undergoing clinical, biological, and imaging evaluations every 3 months after discharge for the first two years, according to the oncological protocols. Following controls were scheduled every 12 months if no relapse was found. In case of tumor recurrence, the case was re-examined by a multidisciplinary team (MDT) with the aim of carrying out curative treatment as much as possible.

Definitions

Comorbidities were summarized by the Charlson Comorbidity Index. Post-operative complications were classified according to the Clavien–Dindo classification,[27] with major postoperative complications defined as major than grade 3a. PHLF was diagnosed and classified according to the International Study Group of Liver Surgery (ISGLS) guidelines.[28] Ascites was defined according to the International Ascites Club definition.[29] The performance status was measured at the first in-patient visit.[30] The presence of cirrhosis was established before surgery by hepatologists according to clinical, biochemical, endoscopic and, when available, pathological information. The presence of esophageal varices was assessed by upper gastrointestinal endoscopy.

The extension of liver resection was defined as minor or major, based on the Brisbane nomenclature.[31] Liver function was estimated using both the model for end stage liver disease (MELD) score and the Child-Turcotte-Pugh (CTP) score during the preoperative patient preparation. The number and size of nodules and presence of vascular invasions were assessed by multiphase contrast CT or magnetic resonance imaging. The presence of neoplastic portal vein thrombosis (PVT) was reported by pathology analysis of the surgical specimen.

Advanced HCC was defined as a patient with an ECOG-PS of 1–3, or with PVT or hepatic vein invasion by the tumor, regardless of the underlying liver function, as defined by BCLC staging system.

Statistical analysis

Primary outcome was a composite endpoint including post-hepatectomy liver failure (PHLF), severe postoperative complications and in-hospital mortality. Secondary outcomes were the following perioperative outcomes: rate of intraoperative transfusions. mean length of hospital stay, rate of total postoperative complications, rate of severe postoperative complications, rate and severity of postoperative ascites, mean comprehensive

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complication index, 90-day mortality, rate of R1 resections, rate of re-operations, as well as survival results.

To avoid the impact of known potential confounders on outcomes, an inverse probability weighted treatment analysis was performed. Propensity score, that is the probability for each patient to be operated by open or laparoscopic surgery, was calculated for each patient using logistic regression based on the following covariates: age, gender, ECOG performance status, the Charlson comorbidity index, ASA score, presence of liver cirrhosis, MELD score, Child-Pugh score, BCLC class (B vs C), the number of HCC nodules, the type of hepatectomy performed (major vs minor), blood platelet levels (above or belove 100.000), the presence of esophageal or gastric varices, the presence of macroscopic portal invasion.[32] Patients with missing data for these covariates were excluded from the analysis, under the assumption of data missing completely at random. Therefore, for each patient, a stabilized inverse probability treatment weight was calculated for each patient and two weighted pseudo-populations of patients undergoing open or laparoscopic surgical resections were obtained with balanced confounding variables.[33] The Standardized mean differences across the two treatments were calculated for each covariate in the unweighted and weighted populations to check covariate balance after weighting. The impact of the laparoscopic approach on postoperative binary and continuous outcomes was assessed using an univariate logistic and linear regressions, with the association reported as Odds Ratio (OR) along with 95 % confidence interval. Univariate cox regression analyses were performed within the weighted population to assess the impact of laparoscopic surgery type on overall survival and disease-free survival, and the associations reported as Hazard Ratios and relative 95 % CI. Patient overall and disease-free survival within the weighted population, stratified according to type of treatment, were graphically plotted using Kaplan Meier curves. Continuous data are expressed as mean and standard deviation (SD). Group comparisons were performed using Student's T test or Wilcoxon's rank test, depending on the distribution of the variable. Categorical data were expressed as frequencies and associated percentages. Comparisons between groups were performed using Pearson's chi-squared test or Fisher's exact test, depending on the expected value of the variable of interest. All p values =< 0.05 were considered as statistically significant. Statistical analyses vere conducted using R version 4.0.3 (The R foundation for statistical computing).

Results

Patients and data characteristics

The HERCOLES database included 5441 patients undergoing liver resection for HCC. After removing BCLC-A patients and cases with missing data for the variables using for IPWT, and applying exclusion criteria, 627 patients staged BCLC-B (n = 430; 68.6 %) or −C (n = 197; 31.4 %) were eligible for this study. Of the included patients, 459 patients (73.2 %) underwent OLR and 168 patients (26.8 %) received MILS (Fig. 1).

Baseline characteristics before and after weighting

Before the IPTW, the two cohorts significantly differed for the higher rate of BCLC-C patients in the OLR group (37.3 % vs 15.5 %, p < 0.001). Similarly, OLR group showed a higher rate of tumors with macrovascular invasion (22.0 % vs 10.1 %, p < 0.001), a higher tumor size (70.11 ± 48.22 mm vs 60.56 ± 58.38 mm, p = 0.041), a higher number of major liver resections (38.1 % vs 17.3 %, p < 0.001). On the contrary, MILS patients had a higher mean MELD score (2.51 vs 2.18, p < 0.001),

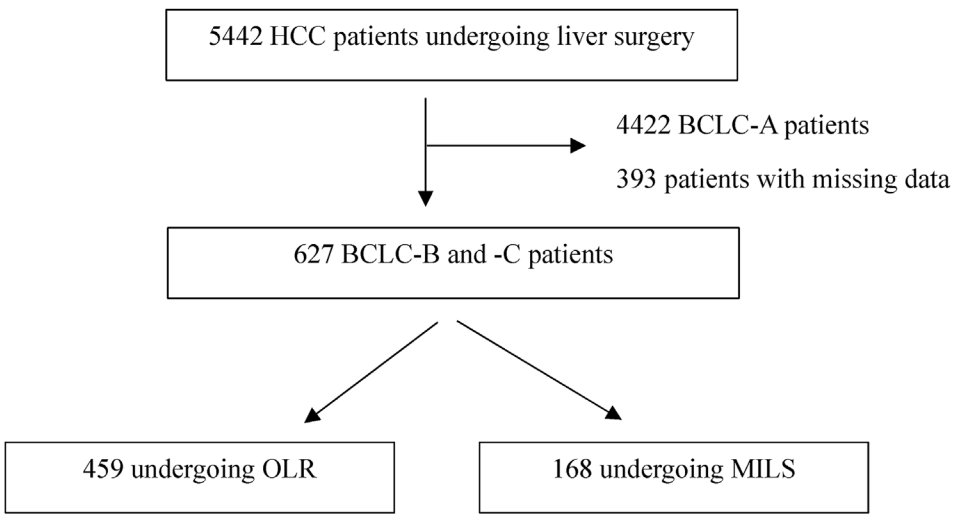


Figure 1 Diagram of the included population. HCC: hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer staging system; OLR: open liver resection; MILS: minimally invasive liver surgery

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a higher mean CTP score (p = 0.007), a higher number of patients with esophageal varices (26.2 % vs 13.7 %, p < 0.001). Comparisons between baseline characteristics are available in Table 1.

After IPTW, there were no differences in all patients' and tumors' characteristics (Fig. 2).

Postoperative outcomes

No difference was found in the composite endpoint between the MILS and the OLR (14.7 % vs 12.8 %; OR 0.82 [95%CI 0.45–1.59]; p = 0.621). MILS was found to reduce the risk of receiving intra-operative transfusions (6.9 % vs 20.9 %, respectively; OR 0.27 [95%CI 0.13–0.58]; p < 0.001), as well as of developing postoperative ascites (23.7 % vs 14.9 %, OR 0,56 [95%CI 0.32–0.98]; p = 0.039). Similarly, MILS was associated with reduced length of hospital stay (11.23 ± 11.93 vs 13.72 ± 12.22 days, respectively; OR 0.81 [95%CI 0.66–1.00]; p = 0.045). Finally, the minimally invasive access was significantly associated with a lower rate of R1 resections (8.2 % vs 15.1 %; OR 0.50 [95 % CI [0.27–0.95]; p = 0.031).

Table 1 Patients' and tumors' characteristics before the inverse probability of treatment weighting: in bold the statistically significant p-values. ECOG-PS: Eastern Cooperative Oncology Group- Performance Status; SD: standard deviation;CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists; MELD: Model for End-stage Liver Disease; BCLC: Barcelona Clinic Liver Cancer staging system; CTP: Child-Turcotte-Pugh

	Before IPTW			**After IPTW**		
	OLR (n = 459)	**MILS (n = 168)**	**p-value**	**OLR (n = 458.29)**	**MILS (n = 158.41)**	**p-value**
Age, mean (SD)	65.32 (11.35)	66.85 (8.97)	0.117	65.79 (11.03)	66.72 (9.01)	0.326
Female sex, n (%)	74 (16.1)	41 (24.4)	**0.034**	84.3 (18.4)	30.3 (19.1)	0.847
ECOG-PS, n (%)			0.155			0.912
0	296 (64.5)	117 (69.6)		302.4 (66.0)	102.4 (64.7)	
1	140 (30.5)	48 (28.6)		136.8 (29.9)	50.3 (31.7)	
2	23 (5.0)	3 (1.8)		19.1 (4.2)	5.7 (3.6)	
CCI, mean (SD)	6.07 (2.00)	6.27 (1.60)	0.238	6.11 (1.97)	6.15 (1.62)	0.820
ASA Score			0.09			0.636
1	5 (1.1)	0 (0.0)		3.7 (0.8)	0.0 (0.0)	
2	181 (39.4)	62 (36.9)		177.7 (38.8)	59.1 (37.3)	
3	268 (58.4)	100 (59.5)		270.5 (59.0)	96.6 (61.0)	
4	5 (1.1)	6 (3.6)		6.4 (1.4)	2.7 (1.7)	
Cirrhosis, n (%)	350 (76.3)	133 (79.2)	0.509	350.9 (76.6)	120.7 (76.2)	0.930
MELD score, mean (SD)	8.36 (2.18)	9.16 (2.51)	**<0.001**	8.56 (2.32)	8.74 (2.19)	0.398
BCLC-C, n (%)	171 (37.3)	26 (15.5)	**<0.001**	144.4 (31.5)	45.2 (28.5)	0.571
Number of nodules, n (%)			**0.016**			0.712
1	208 (45.3)	60 (35.7)		189.7 (41.4)	68.5 (43.3)	
2	129 (28.1)	43 (25.6)		136.4 (29.8)	40.1 (25.3)	
3	59 (12.9)	26 (15.5)		62.2 (13.6)	21.0 (13.3)	
4	63 (13.7)	39 (23.2)		69.9 (15.3)	28.7 (18.1)	
Tumor size in mm,	70.11 (48.22)	60.56 (58.38)	**0.041**	67.47 (46.63)	62.22 (57.13)	0.322
Major liver resection, n (%)	175 (38.1)	29 (17.3)	**<0.001**	149.9 (32.7)	45.6 (28.8)	0.448
CTP Score, n (%)			**0.007**			0.943
5	255 (55.5)	67 (39.9)		233.4 (50.9)	76.1 (48.0)	
6	161 (35.1)	69 (41.1)		169.7 (37.0)	61.6 (38.9)	
7	22 (4.8)	18 (10.7)		28.3 (6.2)	12.7 (8.0)	
8	14 (3.1)	10 (6.0)		18.2 (4.0)	5.9 (3.7)	
9	7 (1.5)	4 (2.4)		7.3 (1.6)	2.1 (1.3)	
Platelets lower than $100 \times 10^3/mm^3$, n (%)	231 (50.3)	86 (51.2)	0.919	229.8 (50.2)	77.9 (49.2)	0.851
Esophageal varices, n (%)	63 (13.7)	44 (26.2)	**<0.001**	76.1 (16.6)	27.0 (17.1)	0.894
Macrovascular invasion, n (%)	101 (22.0)	17 (10.1)	**0.001**	86.7 (18.9)	28.5 (18.0)	0.841

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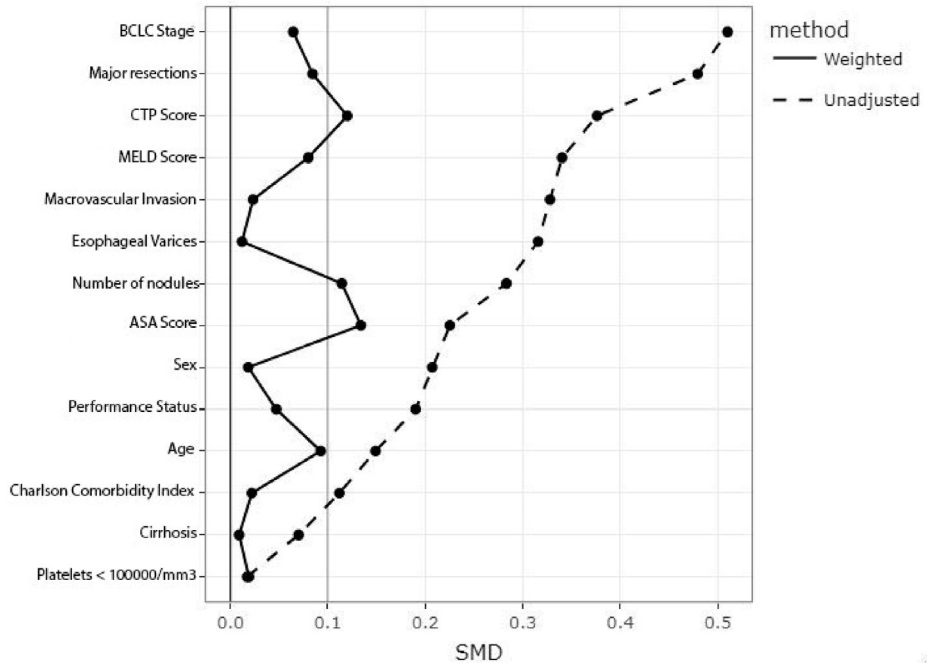


Figure 2 Standardized mean differences for each covariate across the treatments contrasts in the unweighted and weighted populations. ECOG-PS: Eastern Cooperative Oncology Group- Performance Status; CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists; MELD: Model for End-stage Liver Disease; BCLC: Barcelona Clinic Liver Cancer staging system; CTP: Child-Turcotte-Pugh

No difference was found between the two groups when comparing the risk of severe postoperative complications according to Clavien-Dindo classification (12.2 % after MILS vs 13.3 % after OLR; OR 0.86 [95%CI 0.45–1.62]; p = 0.63) and the 90-day mortality (OR 0.79 [95%CI 0.35–1.76] p = 0.570) (Table 2).

Survival analysis

After a median follow-up of 64 months (range 1–192), the survival analysis showed no differences between MILS and OLR in both DFS (HR 1.11 [95%CI 0.82–1.49] p = 0.491) and OS (HR 0.81 [95%CI 0.61–1.06] p = 0.130) (Fig. 3).

Table 2 Postoperative outcomes in BCLC B and C patients before and after the inverse probability of treatment weighting: in bold the statistically significant p-values. PHLF: post-hepatectomy liver failure; SD: standard deviation; R1: microscopic positive margins on the pathologic examination of the specimen

	Before IPTW			After IPTW			
	OLR (n = 459)	MILS (n = 168)	p-value	OLR (n = 458.29)	MILS (n = 158.41)	OR [95%CI]	p-value
Composite endpoint, n (%)	71 (15.5)	18 (10.7)	0.167	67.2 (14.7)	20.3 (12.8)	0,86 [0,46–1,60]	0.622
Intraoperative transfusions, n (%)	96 (21.6)	12 (7.3)	**<0.001**	92.8 (20.9)	10.7 (6.9)	0,28 [0,13–0,58]	**<0.001**
Length of hospital stay, mean (SD)	13.85 (12.37)	10.29 (11.53)	**0.001**	13.72 (12.22)	11.23 (11.93)	0,82 [0,66–1,01]	**0.045**
PHLF, n (SD)	24 (5.2)	6 (3.6)	0.512	23.2 (5.1)	5.3 (3.4)	0,64 [0,24–1,74]	0.388
Postoperative ascites, n (%)	108 (23.6)	24 (14.3)	**0.037**	108.4 (23.7)	23.5 (14.9)	0,56 [0,32–0,98]	**0.039**
Comprehensive complications index, mean (SD)	21.07 (24.84)	16.86 (22.55)	0.073	20.75 (24.72)	17.81 (22.84)	0,86 [0,66–1,12]	0.242
Complications, n (%)	315 (68.6)	103 (61.3)	0.104	313.3 (68.4)	102.1 (64.5)	0,84 [0,56–1,26]	0.401
Severe postoperative complications, n (%)	64 (13.9)	17 (10.1)	0.258	61.2 (13.3)	19.6 (12.4)	0,92 [0,48–1,74]	0.790
R1 resection, n (%)	74 (16.4)	15 (9.0)	**0.029**	68.1 (15.1)	12.9 (8.2)	0,50 [0,27–0,95]	**0.031**
Reoperations, n (%)	19 (4.2)	7 (4.3)	1.000	18.7 (4.2)	6.5 (4.2)	1,01 [0,38–2,72]	0.977
90-days mortality, n (%)	38 (8.3)	11 (6.6)	0.597	37.4 (8.2)	10.4 (6.6)	0,79 [0,36–1,77]	0.569

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Discussion

From this analysis of a large multicentric Italian database, we firstly investigated with an inverse probability of treatment weighted analysis the outcomes of MILS in HCC patients staged BCLC-B and −C. The analysis showed clear advantages of the minimally invasive approach, namely a lower rate of intraoperative transfusions and postoperative ascites, with a shorter length of hospital stay, and without affective other short- and long-term outcomes.

The optimalmanagement of BCLC-B and −C still remains controversial given the variability of tumor status within these groups of patients. Indeed, the intermediate and advanced HCC stages, as proposed by the BCLC group, includes a heterogeneous range of patients with preserved liver function who can be allocated to this stage for one among different reasons: a multinodular disease, the presence of PVT, extrahepatic tumor spread or an ECOG-PS > 0. Subsequently, this staging system allocates in the same group patients with very different prognoses, and with or without feasibility of liver resection with acceptable results.[34] Many previous studies have shown that patients with multiple hepatocellular carcinomas can undergo surgery with favorable long-term outcomes, in particular when compared to TACE.[35–37] Furthermore, previous studies showed how liver resection for large HCC have better outcomes than TACE, even when exceeding 10 cm.[38–40] A recent meta-analysis by Zhou et al. including 3609 patients reported improved 1-year OS, 3-year OS, and 5-year OS for liver resection over TACE ($p < 0.001$).[41] Similarly, recent papers including also large multicentric studies showed that selected cases with macrovascular infiltration and PHT may undergo liver resection with satisfactory results.[9,42–44] Finally, a strong support to surgical management for such patients comes from these large real-life data: in the included Italian tertiary HPB centers a total of 430 BCLC-B patients and 197 BCLC-C patients underwent surgery after MDT discussion, with favorable survival outcomes, as shown by our survival analysis. However, due to the aforementioned high variability and the design of our study, our analysis cannot lead to strong absolute conclusions about long term survival in advanced HCC patients: there are too many variables to be taken into account. Further prospective studies with an appropriated design should focus on this argument.

After exclusion of the patients with extrahepatic extension of the tumor, other significant differences in baseline characteristics, such as tumor burden, MELD and CTP score, may have justified the surgical approach made in clinical practice, apart from the surgeons' preference. Indeed, in this study the laparoscopic group included more patients with worse liver function. This is coherent with the common belief that this kind of patients can benefit from MILS thanks to less invasive manipulation, a higher preservation of intra-abdominal and abdominal wall collateral circulation, and a lower perspiration to the external air of the abdominal fluids, that could lead to better postoperative outcomes in cirrhotic patients.[17,45] Our analysis included also CTP B and C patients, showing satisfying results. It would be interesting in the future to specifically focus with dedicated prospective designed studies on the postoperative cirrhotic decompensation and rate of ascites after MILS for HCC patients with impaired liver function. The number of nodules and the tumor size, representing a different extent of disease, and reflected in a different rate of major liver resections performed between the two pre-weighting cohorts, may have represented another important reason for choosing OLR instead of MILS. To overcome the impact of these disparities in our analysis, we adopted the IPTW method to weight baseline differences and create two well balanced pseudo-populations of BCLC-B and −C patients treated with OLR and MILS.

After weighting the two groups, the laparoscopic approach was associated with lower rates of intraoperative transfusions. Such finding confirms also in the setting of BCLC-B and −C patients an important and well-established advantage of laparoscopic approach over the open technique.[22,46] Furthermore, such results may have an important clinical relevance, as reduced blood losses and intraoperative transfusions have been shown to be associated with impaired outcomes after liver resection.[47,48]

Similarly, the MILS population experienced significantly lower rates of postoperative ascites, confirming also in the setting of BCLC-B and −C staged patients many previous findings from recent literature.[49,50] Indeed, Famularo et al. in a recent study involving 2144 HCC patients reported significant results about the protective role of laparoscopic surgery on developing postoperative ascites (OR = 0.445, 95%CI = 0.295–0.668, $p < 0.001$), underlining how postoperative ascites was associated with a higher 90-day mortality (9.1 % vs 1.9 %, $p < 0.001$). In our study, the lower rate of postoperative ascites may be related to the significantly shorter length of hospital stay showed by the MILS group. This result is also coherent with many previous studies comparing MILS and OLR, suggesting a possible correlation with a reduced postoperative pain, early ambulation, and early recovery of gastrointestinal function.[21] Moreover, a reduced length of hospital stay could lead to a significant reduction of the economic costs related to the HCC treatment. However economic aspects were not within the aims of our study: further efforts should investigate such an important field.

Finally, both short-term postoperative and survival outcomes (in terms of PHLF, severe postoperative complications, 90-days mortality) and long-term oncological outcomes (in terms of both DFS and OS) did not significantly differ between the two included populations, after a median follow-up longer than 5 years. This testifies the safety of the minimally invasive approach in selected patients with advanced staged nonmetastatic HCC. Such satisfactory results are coherent with a previous propensity-score matched study investigating the outcomes of LLR in BCLC-B patients, as well as with a recent study by Cassese et al. focused

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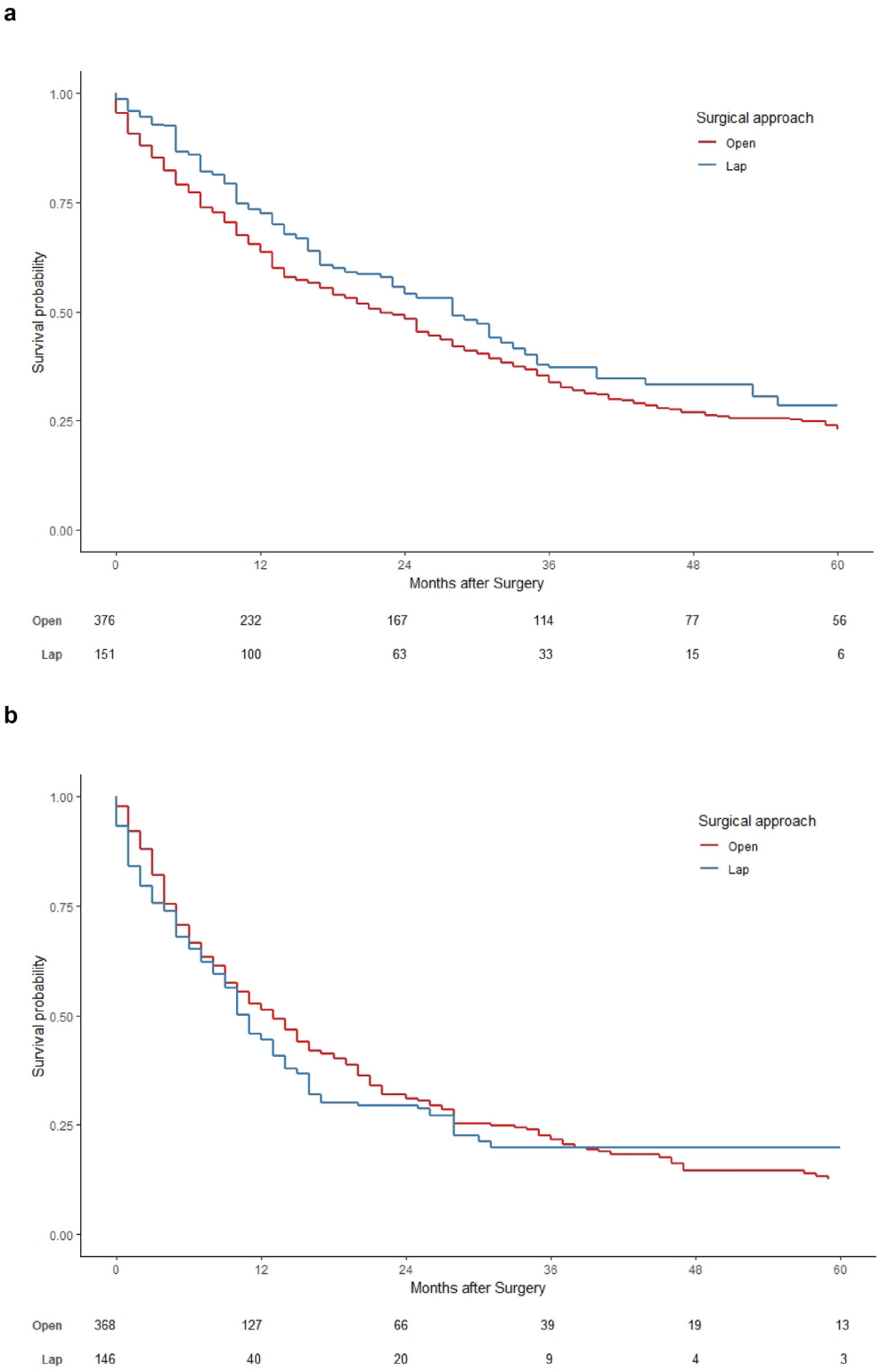


Figure 3 Cumulative Overall Survival (a) and Disease-Free Survival (b) within the two cohorts

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on multinodular HCC and including both BCLC-B and –C patients.[11,51]

This study suffers from several limitations. Firstly, its retrospective and observational nature makes it vulnerable to the confounding effects of both unintended biases and selection biases. Of note, a randomized controlled trial comparing MILS and OLR in BCLC-B and –C patients would be difficult to conduct since in this setting current guidelines haven't still approved surgical indication. Thus, the adoption of the IPTW-based analysis from a large database was the only method to obtain the second-best evidence available on this issue, by mitigating possible biases. Secondly, the lack of some important data about the location of the tumors (liver segments, proximity to major vessels) made it impossible to compare the technical difficulty of the resections between the two cohorts.

A prospective database analyzing in a consecutive way all liver resections from different centers could provide interesting information on that, especially the indication for MILS. Unfortunately, the available published or current registers only refer to minimally invasive procedures of selected cases.

Another criticism deals with the indication for surgery, which was not predefined by rules shared among centers. Since surgical feasibility also depends on the technical skills of the surgeons and the experience of the center, it is possible that the surgical indications for similar patients may not have been the same in all reference centers. The pre-surgery intention-to-transplant (whether surgery served as bridging or downstaging therapy) and the occurrence of liver transplants in the months/years following surgery, a factor potentially impacting both DFS and OS, remain unknown. Nonetheless, IPTW ensured comparability between the patients of the OLR and MILS groups in terms of age, extent of intrahepatic disease, liver function, and portal hypertension, equating their likelihood of receiving a transplant.

Patients classified as technically resectable BCLC-B and –C probably require a high level of expertise if they are to be approached with minimally invasive techniques. However, the design and methods of this study, together with the lack of data on learning curves and surgeons' experience, do not allow solid conclusions to be drawn. Further studies, with prospective design and larger sample sizes, should focus on these aspects.

Conclusion

MILS was shown to be safe and feasible in well-selected non-metastatic BCLC-B and –C patients. When compared to OLR, MILS is able to reduce the need for intraoperative transfusions and the rate of postoperative ascites, shortening the length of stay after surgery, while not affecting either the risk of severe post-operative complications or survival outcomes. Accordingly, in the case-by-case tailored approach to the advanced HCC patients with preserved liver function, a minimally invasive treatment should always be considered whenever feasible.

Authors' contribution

All the following authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content; gave their final approval of the version to be published.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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