



# Minimally invasive liver surgery for hepatocellular carcinoma in patients with portal hypertension

Daniel Aliseda<sup>1\*</sup> , Gabriel Zozaya<sup>1,2</sup>, Pablo Martí-Cruchaga<sup>1,2</sup>, Juan Lujan<sup>1</sup>, Ana Almeida<sup>1</sup>, Nuria Blanco<sup>1</sup>, Lucas Sabatella<sup>1</sup>, Bruno Sangro<sup>2,3</sup> and Fernando Rotellar<sup>1,2</sup> 

<sup>1</sup>Department of General Surgery, Clínica Universidad de Navarra, University of Navarra, Pamplona, Spain

<sup>2</sup>Institute of Health Research of Navarra (IdisNA), Pamplona, Spain

<sup>3</sup>Liver Unit and Hepato-Pancreato-Biliary Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain

\*Correspondence to: Daniel Aliseda, Department of General Surgery, Clínica Universidad de Navarra, University of Navarra, Av. Pío XII, 36, 31008 Pamplona, Spain (e-mail: dalisedaj@unav.es)

## Introduction

For patients with early stage hepatocellular carcinoma (HCC), liver resection is a mainstay of curative treatment. Patients with a solitary tumour, Child–Pugh A cirrhosis and serum bilirubin of 1 mg/dl are considered ideal candidates for liver resection<sup>1,2</sup>. For patients with portal hypertension, current guidelines recommend careful consideration of liver resection based on the hierarchical interaction of portal hypertension, liver function and resection extent<sup>1,3</sup>. Open liver resection has been used in the majority of published studies on liver resection and portal hypertension. Although there is limited published experience of minimally invasive liver resection (MILR), using MILR in these patients appears to be associated with favourable outcomes<sup>4</sup>. Particularly in patients with Child–Pugh A cirrhosis, but also in patients with more advanced cirrhosis<sup>5</sup>, MILR offers significant advantages in the surgical treatment of HCC including reduced intraoperative bleeding, fewer complications and minimized surgical aggression, which improves recovery<sup>6,7</sup>. If these benefits are also found in patients with portal hypertension, MILR may represent a step forward in the surgical treatment of patients with HCC and portal hypertension.

This systematic review and meta-analysis aimed to summarize the intraoperative, postoperative and survival outcomes of MILR in patients with HCC and portal hypertension.

## Methods

This systematic review was conducted according to the PRISMA guidelines and registered in the PROSPERO (CRD42022300797) platform<sup>8</sup>. Using a rigorous search strategy (see [Supplementary material](#) and [Table S1](#)), three electronic databases (PubMed, MEDLINE (via Ovid) and Scopus) were searched from database inception to 28 December 2022. Inclusion criteria were studies including adults aged  $\geq 18$  years with a diagnosis of HCC undergoing laparoscopic, robotic or hybrid liver surgery and with underlying portal hypertension. Clinically significant portal hypertension (CSPH) was defined as a transjugular hepatic venous pressure gradient (HVPG)  $\geq 10$  mmHg, and indirect signs of portal hypertension were defined as thrombocytopenia ( $<100\,000$

platelets/mm<sup>3</sup>) and splenomegaly or the presence of oesophageal varices at endoscopy. Studies were excluded if platelet count alone or HVPG  $<10$  mmHg was used for the assessment of portal hypertension. Reviews, editorials and case reports with fewer than five patients were also excluded. Data extraction and methodological assessment of the studies are presented in the [Supplementary material](#). Two independent meta-analyses, a pooled meta-analysis of means and proportions and a patient-level survival data meta-analysis were performed to assess perioperative and survival outcomes respectively. A detailed description of the statistical analysis and outcomes of interest can be found in the [Supplementary material](#) (pages 5–6).

## Results

Six studies met the inclusion criteria ([Table S2](#)). [Figure S1](#) and [Table S3](#) show the PRISMA 2020 flowchart and the methodological quality assessment, respectively.

### Perioperative outcomes pooled meta-analysis

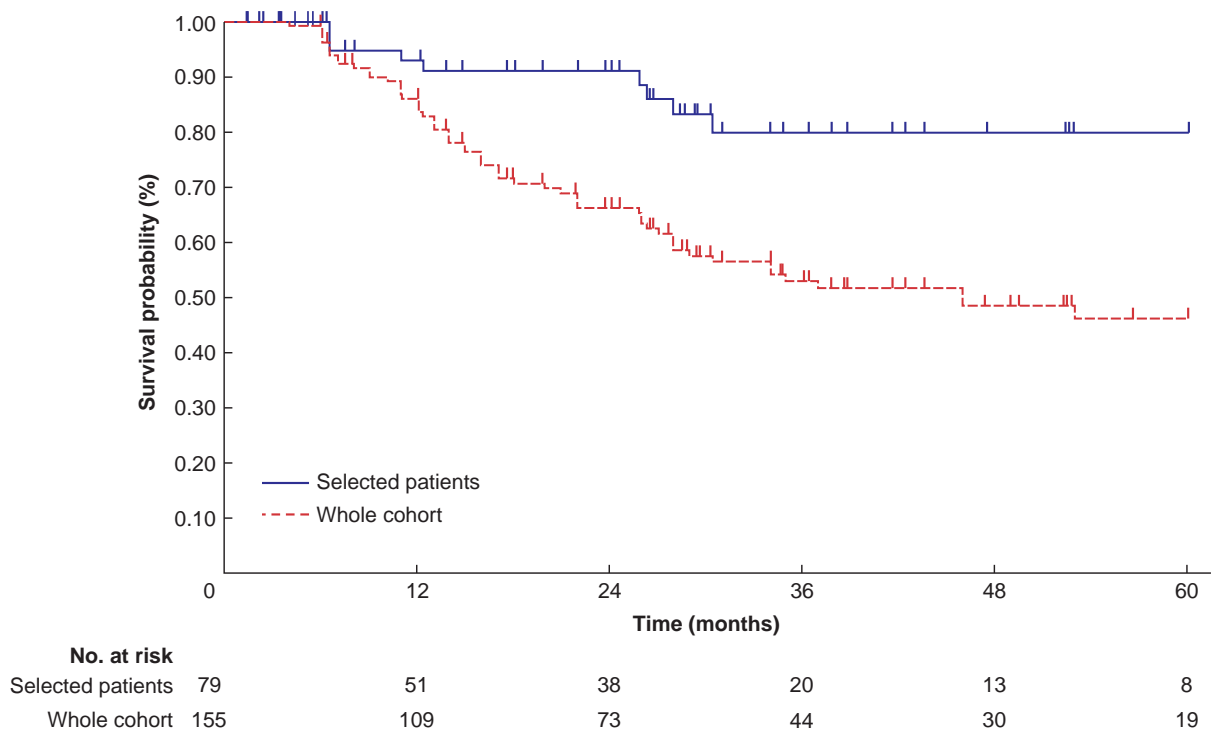
For the meta-analysis of perioperative outcomes, five reports<sup>9–11,13,14</sup> including 168 patients met the inclusion criteria. Baseline patient and tumour characteristics are shown in [Table S4](#). According to the Child–Pugh classification, 147 patients were in class A (87.5 per cent) and 21 were in class B (12.5 per cent). Portal hypertension was defined as HVPG  $\geq 10$  mmHg in two studies<sup>11,13</sup>.

One hundred and sixty-five purely laparoscopic surgeries were performed along with three hybrid surgeries<sup>13</sup>. Minor resections (one or two Couinaud's segments) were performed in 138 patients (82.1 per cent). Sixty-five wedge resections accounted for 38.6 per cent of all surgeries, followed by 70 segmentectomies or bisegmentectomies (41.7 per cent) and three left lateral sectionectomies (1.8 per cent). Three studies<sup>9–11</sup> included major resections (three to four Couinaud's segments), including 14 hemihepatectomies and 16 anatomical resections of three segments. The mean operative time was 197.6 min (95 per cent c.i. 186.3–208.9) ( $I^2 = 93.0$  per cent;  $P < 0.005$ ) ([Fig. S2a](#)). The amount of intraoperative blood loss was 285.1 ml (95 per cent c.i. 246.7–323.4) ( $I^2 = 75.1$  per cent;  $P = 0.003$ ) ([Fig. S2b](#)). The transfusion rate was reported in three studies<sup>10,11,14</sup> with a proportion of 11 per cent (95

Received: December 16, 2022. Revised: January 20, 2023. Accepted: February 26, 2023

© The Author(s) 2023. Published by Oxford University Press on behalf of BJS Society Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fig. 1** Kaplan-Meier overall survival curves and number-at-risk table for the whole cohort and for selected patients with hepatocellular carcinoma and portal hypertension who underwent minimally invasive liver resection

per cent c.i. 2.0–24.0 per cent) ( $I^2 = 51.9$  per cent;  $P = 0.13$ ) (Fig. S2c). The conversion rate was reported in four studies<sup>9–11,14</sup> with a rate of 6 per cent (95 per cent c.i. 2.0–11.0 per cent) ( $I^2 = 0.0$  per cent;  $P = 0.48$ ) (Fig. S2d). The operative details are summarized in Table S5.

### Postoperative outcomes

A summary of the postoperative outcomes is shown in Table S6. The mean duration of hospital stay was 8 days (95 per cent c.i. 7.6–8.5) ( $I^2 = 97.8$  per cent;  $P < 0.005$ ) (Fig. S3a). The overall morbidity rate was 38 per cent (95 per cent c.i. 28.0–50.0) ( $I^2 = 45.6$  per cent;  $P = 0.12$ ) (Fig. S3b). The major complication rate (Clavien–Dindo  $\geq$  III) was 10 per cent (95 per cent c.i. 5.0–15.0) ( $I^2 = 0.0$  per cent;  $P = 0.95$ ) (Fig. S3c). The comprehensive complication index was 9.3 (95 per cent c.i. 7.2–11.5) ( $I^2 = 0.3$  per cent;  $P = 0.404$ ) (Fig. S3d). None of the studies reported mortality during the first 90 days after surgery. R0 resection was reported in four studies<sup>9–11,13</sup> and was achieved at 95 per cent (95 per cent c.i. 90.0–98.0) ( $I^2 = 0.0$  per cent;  $P = 0.59$ ) (Fig. S4).

### Liver-specific complications

The overall rate of postoperative haemorrhage was 2 per cent (95 per cent c.i. 0.0–7.0 per cent) ( $I^2 = 10.3$  per cent;  $P = 0.34$ ) (Fig. S5a). All patients who experienced postoperative haemorrhage required transfusion, but no surgical or invasive intervention was necessary in any patient. The proportion of liver failure was 5 per cent (95 per cent c.i. 1.0–11.0 per cent) ( $I^2 = 0.0$  per cent;  $P = 0.59$ ) (Fig. S5b) with one patient requiring admission to the ICU and the rest of the patients not requiring invasive interventions. The postoperative ascites rate was 7 per cent (95 per cent c.i. 1.0–16.0 per cent) ( $I^2 = 39.9$  per cent;  $P = 0.17$ ) (Fig. S5c) with more than 90 per cent of patients exhibiting transient ascites treated with diuretics. Two studies<sup>11,13</sup> reported on unresolved liver decompensation

(3 months after surgery), with a rate of 5 per cent (95 per cent c.i. 0.0–14.0 per cent) ( $I^2 = 0.0$  per cent) (Fig. S5d). These patients were managed with medical treatment without the need for salvage transplantation. Finally, three studies reported that 50 per cent of all Clavien–Dindo  $\geq 3$  complications were due to liver-specific complications, which are summarized in Table S7.

### Patient-level survival data meta-analysis

Five studies<sup>9,10,12–14</sup> were included in the survival analysis, including 155 patients. Unadjusted overall survival (OS) rates at 1, 3 and 5 years were 86.1 per cent (95 per cent c.i. 78.8–91.0), 53.0 per cent (95 per cent c.i. 43.3–61.9) and 46.3 per cent (95 per cent c.i. 35.7–56.2) respectively (Fig. 1). However, in selected patients (the majority of Child–Pugh A cirrhosis, tumours  $< 5$  cm and excluding advanced HCC stages), the unadjusted OS was 93.0 per cent (95 per cent c.i. 82.4–97.3), 79.9 per cent (95 per cent c.i. 64.0–89.3) and 79.9 per cent (95 per cent c.i. 64.0–89.3) at 1, 3 and 5 years respectively (Fig. 1). Four studies reported<sup>10,12–14</sup> HCC recurrence after a mean follow-up of 24.4 ( $\pm 8.0$ ) months. The tumour recurrence rate was 31 per cent (95 per cent c.i. 15.0–49.0) ( $I^2 = 61.1$  per cent;  $P = 0.05$ ) (Fig. S6). The detailed survival outcomes are shown in Table S8.

### Discussion

In patients with HCC and portal hypertension, MILR demonstrates reaching optimal rates of intraoperative and postoperative outcomes with minimal liver-specific complications. In addition, the results are similar to current benchmarks for laparoscopic liver surgery<sup>15</sup>. Furthermore, this study suggests that in well-selected patients, MILR achieves excellent long-term OS outcomes.

MILR is associated with less liver mobilization, better preservation of perihepatic collateral circulation, the

pneumoperitoneum assisting effect and limitation of insensible fluid loss secondary to small incisions, among others<sup>16,17</sup>. These properties are particularly relevant in cirrhotic patients in whom MILR has been shown to decrease blood loss and complications, such as ascites and posthepatectomy liver failure<sup>6,7</sup>. The advantages of MILR over open liver resection are particularly relevant for patients with portal hypertension. Most of the modest published results in these patients are based on open liver resection. Performing laparoscopy in HCC patients with portal hypertension has already shown better postoperative outcomes compared with open surgery, as well as being an independent factor to achieve textbook outcomes<sup>4,14,18</sup>. In addition to the intra- and postoperative benefits, MILR may also offer advantages in the surgical management of recurrence. In the case of repeat liver resection or salvage liver transplantation, MILR reduces severe adhesions, making repeat hepatectomy or retransplantation safer<sup>19</sup>.

Therefore, the results observed in this meta-analysis suggest that MILR in HCC patients with portal hypertension is a safe, effective and promising approach. If supported by more robust studies and in well-selected patients, MILR could represent a significant advance towards the curative treatment of patients with HCC and portal hypertension.

## Funding

The authors have no funding to declare.

## Disclosures

The authors declare no conflict of interest.

## Supplementary material

Supplementary material is available at *BJS* Open online.

## Data availability

Data to reproduce this report is available in the published studies.

## Author contributions

Daniel Aliseda (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Gabriel Zozaya (Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing—review & editing), Pablo MartC3AD-Cruchaga (Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing—review & editing), Juan Lujan (Conceptualization, Data curation, Investigation, Validation, Visualization, Writing—review & editing), Ana Almeida (Data curation, Investigation, Validation, Visualization, Writing—review & editing), Nuria Blanco (Data curation, Investigation, Validation, Visualization, Writing—review & editing), Lucas Sabatella (Data curation, Investigation, Validation, Visualization, Writing—review & editing), Bruno Sangro (Conceptualization, Data curation, Investigation, Supervision, Validation, Visualization, Writing—review & editing) and Fernando Rotellar (Conceptualization, Data curation, Investigation, Supervision, Validation, Visualization, Writing—review & editing).

## References

1. European Association for the Study of the Liver. *EASL Clinical Practice Guidelines: management of hepatocellular carcinoma*. *J Hepatol* 2018;**69**:182–236
2. Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M et al. Trends in perioperative outcome after hepatic resection. *Ann Surg* 2009;**249**:995–1002
3. Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. *JAMA Surg* 2016;**151**:846–853
4. Azoulay D, Ramos E, Casellas-Robert M, Salloum C, Lladó L, Nadler R et al. Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension. *JHEP Rep* 2021;**3**:100190
5. Troisi RI, Berardi G, Morise Z, Cipriani F, Ariizumi S, Sposito C et al. Laparoscopic and open liver resection for hepatocellular carcinoma with Child–Pugh B cirrhosis: multicentre propensity score-matched study. *Brit J Surg* 2021;**108**:196–204
6. Ciria R, Gomez-Luque I, Ocaña S, Cipriani F, Halls M, Briceño J et al. A systematic review and meta-analysis comparing the short- and long-term outcomes for laparoscopic and open liver resections for hepatocellular carcinoma: updated results from the European guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017. *Ann Surg Oncol* 2019;**26**:252–263
7. Kabir T, Tan ZZ, Syn NL, Wu E, Lin JD, Zhao JJ et al. Laparoscopic versus open resection of hepatocellular carcinoma in patients with cirrhosis: meta-analysis. *Br J Surg* 2021;**109**:21–29
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71
9. Guo Z-Y, Hong Y, Tu B, Cheng Y, Wang X-M. Laparoscopic liver resection for hepatocellular carcinoma complicated with significant portal hypertension: a propensity score-matched survival analysis. *Hepatobiliary Pancreat Dis Int* 2022; <https://doi.org/10.1016/j.hbpd.2022.03.012> [Epub ahead of print]
10. Zheng J, Feng X, Liang Y, Cai J, Shi Z, Kirih MA et al. Safety and feasibility of laparoscopic liver resection for hepatocellular carcinoma with clinically significant portal hypertension: a propensity score-matched study. *Surg Endosc* 2021;**35**:3267–3278
11. Casellas-Robert M, Lim C, Lopez-Ben S, Lladó L, Salloum C, Codina-Font J et al. Laparoscopic liver resection for hepatocellular carcinoma in Child–Pugh A patients with and without portal hypertension: a multicentre study. *World J Surg* 2020;**44**:3915–3922
12. Lim C, Osseis M, Lahat E, Doussot A, Sotirov D, Hemery F et al. Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study. *Surg Endosc* 2019;**33**:811–820
13. Molina V, Sampson-Dávila J, Ferrer J, Fondevila C, del Gobbo RD, Calatayud D et al. Benefits of laparoscopic liver resection in patients with hepatocellular carcinoma and portal hypertension: a case-matched study. *Surg Endosc* 2018;**32**:2345–2354
14. Harada N, Maeda T, Yoshizumi T, Ikeda T, Kayashima H, Ikegami T et al. Laparoscopic liver resection is a feasible treatment for patients with hepatocellular carcinoma and portal hypertension. *Anticancer Res* 2016;**36**:3489–3497
15. Hobeika C, Fuks D, Cauchy F, Goumard C, Gayet B, Laurent A et al. Benchmark performance of laparoscopic left lateral sectionectomy and right hepatectomy in expert centers. *J Hepatol* 2020;**73**:1100–1108
16. Morise Z, Sugioka A, Kawabe N, Umamoto S, Nagata H, Ohshima H et al. Pure laparoscopic hepatectomy for hepatocellular

- carcinoma patients with severe liver cirrhosis. *Asian J Endosc Surg* 2011;**4**:143–146
17. Brytska N, Han H-S, Shehta A, Yoon Y-S, Cho JY, Choi Y. Laparoscopic liver resection for hepatitis B and C virus-related hepatocellular carcinoma in patients with Child B or C cirrhosis. *Hepatobiliary Surg Nutr* 2015;**4**:373–378
  18. Ruzzenente A, Bagante F, Ratti F, Alaimo L, Marques HP, Silva S et al. Minimally invasive versus open liver resection for hepatocellular carcinoma in the setting of portal vein hypertension: results of an international multi-institutional analysis. *Ann Surg Oncol* 2020;**27**:3360–3371
  19. Mohan R, Kabir T, Wu AGR, Lim KI, Goh BKP. Analysis of perioperative outcomes following laparoscopic repeat liver resection compared to laparoscopic primary liver resection based on a single surgeon's experience: a 1:2 propensity score-matched study. *Surg Oncol* 2020;**35**:382–387