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ORIGINAL ARTICLE

Early Morbidity and Mortality after Minimally Invasive Liver Resection for Hepatocellular Carcinoma: a Propensity-Score Matched Comparison with Open Resection

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Abstract

Background The impact of minimally invasive surgery on the short-term outcomes of patients with hepatocellular carcinoma (HCC) undergoing liver resection remains poorly defined.

Methods The ACS-NSQIP-targeted hepatectomy database was used to identify patients who underwent liver resection for HCC during 2014–2016. A 1:1 propensity score matching was created between patients who underwent open (OLR) vs. minimally invasive liver resection (MILR) based on age, ASA score, liver resection type, liver texture, and stage of disease. The short-term outcomes of patients undergoing OLR vs. MILR were compared.

Results Among a total cohort of 1816 patients, propensity score matching resulted in 728 liver resections: 364 (50%) OLR and 364 (50%) MILR. Overall morbidity (29% vs. 23%, $P = 0.04$) was greater among patients undergoing OLR compared with MILR, whereas mortality did not differ between the two approaches (2% vs 1%, $P = 0.57$). MILR was associated with significant reductions in hospital LOS (6 vs. 4 days, $P < 0.0001$) but no difference in operative time (188 vs. 171 min, $P = 0.13$). On multivariate logistic regression analysis, age ≥ 65 (OR:1.6, 95%CI: 1.1–2.3, $P = 0.0065$), ASA class ≥ 3 (OR:2.7, 95%CI: 1.5–4.7, $P = 0.0003$), preoperative blood transfusion (OR:9.7, 95%CI: 1.06–90.3, $P = 0.04$), $T \geq 3$ (OR:1.9, 95%CI: 1.09–3.4, $P = 0.02$), operative time > 200 min (OR:1.8, 95%CI: 1.2–2.5, $P = 0.0011$), and OLR (OR:1.4, 95%CI: 1.002–2.03, $P = 0.04$) were associated with increased odds of overall morbidity.

Conclusions MILR for HCC is associated with a shorter hospital LOS and reduced postoperative complication rates, even after controlling for important patient and clinicopathologic confounders, compared to OLR. Efforts to expand the use of MILR for hepatobiliary surgery are warranted.

Keywords Perioperative outcomes · Hepatectomy · Laparoscopic · Robotic · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide.[1] For patients with early stage disease and acceptable liver function, resection offers the best chance for curative intent treatment, especially in situations where transplantation is not feasible. However, despite recent improvements in patient selection and optimization, the technical aspects of liver resection, and perioperative anesthetic care, hepatectomy remains associated with significant rates of morbidity and mortality. This is especially true among patients with underlying liver dysfunction who are at elevated risk of perioperative hemorrhage and post-hepatectomy liver failure (PHLF).[2–7]

The development of minimally invasive surgery (MIS) in other surgical disciplines has resulted in less postoperative pain, shorter length of hospital stay (LOS), and in some cases decreased complication rates.[8–14] The adoption of MIS techniques for liver resection has been somewhat slower but it is

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now accepted as a standard surgical approach at most major medical centers, especially for minor resections in the anterosuperior liver segments. Nevertheless, the safety of minimally invasive liver resection (MILR) continues to be debated as it relates to patients with HCC in the setting of cirrhosis. The results of previous studies comparing the perioperative outcomes of open liver resection (OLR) and MILR for HCC have been limited by important factors including single institutional and unmatched case study designs.[2,15,16]

To overcome these limitations, we set out to use the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) targeted hepatectomy database to compare the perioperative outcomes of patients with HCC undergoing MILR versus OLR. We hypothesized that, after matching for traditional clinicopathologic criteria and advanced stage of disease, there would be no differences in perioperative outcomes between OLR and MILR approaches to HCC. Nevertheless, a more accurate description of the risk factors for early overall morbidity and mortality following liver resection for HCC, especially after accounting for operative approach, may allow for improved patient selection, preoperative optimization, and early recognition and/or prevention of postoperative complications.

Material and Methods

ACS-NSQIP Data Acquisition and Study Population

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is a multi-institutional, prospective database, which comprises preoperative, intraoperative, and 30-day postoperative variables. Patients included in the database are randomly sampled from 600 eligible hospitals across the USA. The method of data collection implemented by the ACS-NSQIP has been standardized, resulting in validated data displaying strong reliability.[17] A retrospective review of the 2014–2016 ACS-NSQIP and targeted hepatectomy ACS-NSQIP databases was performed. All adult patients with HCC (ICD-10 C 22.0) who underwent hepatectomy as the index operation were identified using Current Procedural Terminology codes 47120, 47122, 47125, and 47130. Patients were matched between the ACS-NSQIP and targeted hepatectomy ACS-NSQIP databases based on case ID number. Hybrids of minimally invasive approaches were excluded from final analysis. Thirty-four MILRs converted to laparotomy were analyzed on an intention-to-treat basis. A one-to-one propensity score-matched analysis was performed based on operative approach to minimize bias with respect to patient age, ASA class, liver resection type, liver texture, and T and N stage of disease.

Study Variables and Outcomes

Independent variables analyzed included demographics, preoperative health status, relevant comorbidities, preoperative laboratory values, operative variables, and postoperative outcomes. Demographics consisted of age, gender, and ethnicity. Variables related to preoperative health included the American Society of Anesthesiologists (ASA) classification, body mass index (BMI), weight loss (10% of total body weight in 6 months), smoking, chronic corticosteroid use, preoperative sepsis (systemic inflammatory response syndrome or septic shock), and preoperative transfusion. Comorbidities included diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure, hypertension requiring medications, ascites, and bleeding disorder. Preoperative laboratory values consisted of hematocrit, prothrombin time, alkaline phosphatase, total bilirubin, international normalized ratio (INR), and albumin serum levels. Targeted hepatectomy variables included neoadjuvant therapy within 90 days prior to surgery (intra-arterial infusion, liver ablation, or portal vein embolization), viral hepatitis, and preoperative biliary stent placement. Operative variables retrieved from the targeted hepatectomy ACS-NSQIP data were type of resection (trisegmentectomy, total right or left hepatectomy, or partial lobectomy), operative time (OpTime), liver texture (normal, congested, fatty, or cirrhotic), Pringle maneuver performed during resection, biliary reconstruction, concurrent intraoperative ablation, and T and N stage of disease.

Overall morbidity included the following occurring within 30 days of hepatectomy: superficial, deep, or organ/space surgical site infection (SSI), sepsis, respiratory complications [unplanned re-intubation, pneumonia (PNA)], thromboembolism [pulmonary embolism (PE), deep vein thrombosis (DVT)], myocardial infarction (MI), stroke, renal complications [progressive renal insufficiency, urinary tract infection (UTI)], hemorrhage (bleeding requiring transfusion of at least 4 U of packed red blood cells), bile leakage or PHLF. Perioperative mortality was defined as death within 30 days after liver resection. The need for postoperative invasive intervention, peak postoperative bilirubin and INR levels, postoperative drain bilirubin level on or after postoperative day 3, LOS, discharge disposition, and reoperation were also assessed.

Statistical Analysis

The study was designed to assess the impact of MILR on postoperative morbidity and mortality. After 1:1 propensity score matching based on operative approach, univariate analyses were performed to compare demographics, perioperative characteristics, and postoperative variables between the OLR and MILR groups. Categorical variables were compared using the Chi-square or Fisher's test as appropriate whereas continuous variables were compared using the Wilcoxon rank sum test. Categorical variables are presented as numbers and percentages whereas continuous variables are presented as medians and interquartile ranges (IQR). The Chi-square was used to identify significant predictors of postoperative morbidity and mortality for the entire cohort. Multivariable stepwise logistic regression analysis models were constructed to identify risk factors of 30-day overall morbidity and mortality adjusting for relevant patient demographics, comorbidities, stage of disease, and operative approach (OLR vs. MILR). Results are reported as odds ratios (OR) and 95% confident intervals (95%CI). Variables entered the logistic regression models included significant, independent predictors of morbidity, and mortality on univariate analysis. Analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA). A P value of less than 0.05 was considered to be statistically significant.

Results

Overall Cohort

Among 1816 patients who underwent hepatectomy for HCC in the 2014–2016 targeted hepatectomy ACS-NSQIP database, 1288 (71%) underwent OLR while 528 (29%) underwent MILR. Complete demographic and clinicopathologic data for the entire cohort are available in supplementary Table 1. Patients who underwent an OLR were more likely to have higher rates of preoperative weight loss (5% vs. 3%, $P =$ 0.03), neoadjuvant therapy (13% vs. 8%, $P = 0.0024$), or obstructive jaundice (2% vs. 0.5%, $P = 0.0111$), trisegmentectomy (10% vs. 1%, $P < 0.0001$), biliary reconstruction (4% vs. 1%, $P = 0.0065$), Pringle maneuver during resection (30% vs. 13%, $P < 0.0001$), and longer OpTime (210 vs. 170 min, $P < 0.00001$) than patients who underwent MILR. In contrast, MILRs were more frequently performed in the context of a cirrhotic liver (35% vs. 45%, $P = 0.0001$) and required only partial hepatectomy (57% vs. 85%, $P < 0.0001$).

Clinicopathological and Operative Characteristics

After a 1:1 propensity score matching, the data of 728 patients who underwent hepatectomy for HCC were analyzed: 364 (50%) patients underwent OLR and 364 (50%) patients underwent MILR. The OLR and MILR groups did not differ with regard to age, liver resection type, liver texture, biliary reconstruction, concurrent intraoperative ablation, or T and N stage of disease, suggesting satisfactory propensity score matching. Relevant clinicopathologic and operative characteristics are summarized in Table 1. The median patient age for the entire cohort was 64 years (IQR: 58–71) with 72% male and 48% Caucasian patients. Overall, most patients had cirrhosis (64%) and underwent partial hepatectomy (86%). Patients who underwent an OLR were more likely to have had preoperative biliary stent placement (2% vs. 0%, $P =$ 0.03) and more frequently had Pringle maneuver used during resection (30% vs. 13%, $P < 0.0001$) compared with patients who underwent MILR, though there was no difference in OpTime (188 vs. 171 min, $P = 0.13$).

Postoperative Outcomes

Detailed information on postoperative outcomes is reported in Table 2. Overall morbidity (29% vs. 23%, $P = 0.04$) was higher among patients undergoing OLR than MILR whereas short-term mortality did not differ between the two groups (2% vs. 1%, $P = 0.57$). Specifically, patients undergoing OLR experienced higher rates of ventilator dependence (3% vs. 0.5%, $P = 0.01$), superficial surgical site infection (4% vs. 1%, $P = 0.01$), bleeding requiring transfusion (15% vs. 10%, $P = 0.05$), and need for a postoperative invasive intervention (8% vs. 3%, $P = 0.0085$) than patients who underwent MILR. In contrast, there was no significant difference in biliary fistula or PHLF between the two groups. LOS was significantly longer after OLR compared to MILR (6 vs. 4 days, $P < 0.0001$).

Predictors of 30-Day Overall Morbidity After Hepatectomy for HCC

On univariate analysis, MILR was associated with reduced incidence of overall postoperative morbidity compared with OLR (OR: 0.66, 95%CI: 0.45–0.97, $P = 0.03$). On stepwise multivariate logistic regression analysis, age ≥ 65 (OR: 1.63, 95%CI: 1.14–2.31, $P = 0.0065$), ASA class of ≥ 3 (OR: 2.74, 95%CI: 1.58–4.73, $P = 0.0003$), preoperative blood transfusion (OR: 9.78, 95%CI: 1.06–90.3, $P = 0.04$), OLR (OR: 1.42, 95%CI: 1–2.03, $P = 0.04$), $T \geq 3$ (OR: 1.93, 95%CI: 1.09–3.40, $P = 0.02$), and OpTime > 200 min (OR: 1.80, 95%CI: 1.26–2.56, $P = 0.0011$) were risk factors for increased postoperative morbidity after hepatectomy for HCC (Table 3).

Predictors of Short-Term Mortality After Hepatectomy for HCC

On univariate analysis, MILR was not associated with a reduced incidence of postoperative mortality compared to OLR (OR: 0.66, 95%CI: 0.17–2.56, $P = 0.54$). On stepwise multivariate logistic regression analysis, myocardial infarction (OR: 34.02, 95%CI: 4.88–237, $P = 0.0004$), PHLF (OR: 8.49, 95%CI: 1.72–41.8, $P = 0.0086$), postoperative renal failure (OR: 31.01, 95%CI: 4.36–220, $P = 0.0006$), and postoperative sepsis (OR: 15.01, 95%CI: 3.02–74.55, $P = 0.0009$), but not OLR (OR: 3.05, 95% CI: 0.44–20.9, $P = 0.25$), were associated with increased odds of mortality (Table 4).

Table 1 Comparison of demographics, comorbidities, laboratory data, and clinical characteristics of propensity score matched patients undergoing OLR vs. MILR

	OLR (n = 364)	MILR (n = 364)	P value
Demographics			
Median age in years, *n* (IQR)	64 (59–71)	64 (58–70)	0.3605
Male gender, *n* (%)	276 (76%)	249 (68%)	*0.0315*
Caucasian race, *n* (%):	181 (50%)	170 (47%)	0.9609
ASA classification, *n* (%):			
• I	1 (1%)	1 (1%)	0.2351
• II	67 (18%)	74 (20%)	
• III	271 (74%)	250 (69%)	
• IV	25 (7%)	39 (10%)	
Median body mass index (kg/m^2), *n* (IQR)	27 (24–31)	27 (23–32)	0.8293
Comorbidities			
> 10% loss body weight in last 6 months, *n* (%)	11 (3%)	9 (2%)	0.6502
Diabetes mellitus with oral agents or insulin, *n* (%)	102 (28%)	104 (28%)	0.8693
Current smoker within 1 year, *n* (%)	92 (25%)	118 (32%)	*0.0407*
Severe chronic obstructive pulmonary disease, *n* (%)	33 (9%)	24 (7%)	0.2144
Congestive heart failure in 30 days before surgery, *n* (%)	2 (0.5%)	3 (0.8%)	0.6536
Hypertension requiring medications, *n* (%)	224 (61%)	203 (56%)	0.1140
Viral hepatitis, *n* (%)	204 (58%)	215 (61%)	0.3738
Preoperative biliary stent, *n* (%)	6 (2%)	0 (0%)	*0.0306*
Ascites within 30 days, *n* (%)	4 (1%)	6 (2%)	0.5242
Preoperative sepsis, *n* (%)	0 (0%)	3 (1%)	0.0826
Steroid use for a chronic condition, *n* (%)	9 (2%)	7 (2%)	0.6131
Bleeding disorders, *n* (%)	21 (6%)	25 (7%)	0.5423
Preoperative transfusion, *n* (%)	3 (1%)	2 (1%)	0.6536
Neoadjuvant therapy, *n* (%)	36 (10%)	30 (8%)	0.4526
Laboratory data			
Median serum albumin in g/dL, *n* (IQR)	4 (3.7–4.3)	4 (3.7–4.3)	0.3756
Median total bilirubin in mg/dL, *n* (IQR)	0.6 (0.4–0.8)	0.6 (0.4–0.9)	0.9720
Median alkaline phosphatase in U/L, *n* (IQR)	89 (73–120)	84 (66–112)	0.0185
Median international normalized ratio, *n* (IQR)	1.03 (1–1.1)	1.08 (1–1.1)	0.3652
Median hematocrit, % (IQR)	41 (38–44)	41 (37–44)	0.7413
Median prothrombin time, *n* (IQR)	11.6 (11–13)	11.7 (11–14)	0.7328
Clinical/operative			
Resection type, *n* (%):			
Trisegmentectomy	4 (1%)	5 (1%)	0.9801
Right hepatectomy	19 (5%)	19 (5%)	
Left hepatectomy	29 (8%)	27 (8%)	
Partial hepatectomy	312 (86%)	313 (86%)	
Median OpTime in minutes, *n* (IQR)	188 (140–239)	171 (131–250)	0.1367
Liver texture, *n* (%):			
Normal	82 (22%)	79 (22%)	0.7825
Congested	1 (1%)	2 (1%)	
Fatty	51 (14%)	44 (12%)	
Cirrhotic	230 (63%)	239 (65%)	
Pringle maneuver during resection, *n* (%)	109 (30%)	47 (13%)	*< 0.0001*
Biliary reconstruction, *n* (%)	7 (2%)	3 (1%)	0.2059
Concurrent intraoperative ablation, *n* (%)	42 (11%)	34 (9%)	0.3322
T stage 3≥, *n* (%)	32 (9%)	31 (9%)	0.8951
Node positive stage, *n* (%)	5 (1%)	4 (1%)	0.7373

ASA American Society of Anesthesiologists, *italics* p<0.05

Discussion

The application of minimally invasive platforms to hepatobiliary surgery has been relatively slow both because of the technical challenges associated with MILR, as well as concerns for perioperative safety, especially with regards to minimizing blood loss, obtaining appropriate oncologic margins, and avoiding biliary injury or fistula. These issues are especially pertinent in patients with HCC where the avoidance of major hemorrhage and PHLF has important implications for short- and long-term outcomes. In this population-based propensity score matched analysis of patients undergoing MILR vs. OLR for HCC, we noted several interesting observations. First, in the overall cohort, almost 1/3 of patients undergoing resection of HCC had a MIS approach. Second, MILR was associated with a decreased overall postoperative morbidity (23% vs. 29%) even after propensity score matching and controlling for confounding factors on stepwise logistic regression analysis (OR: 0.70, 95%CI:

Table 2 Comparison of 30-day postoperative complications of propensity score matched patients with HCC undergoing OLR vs. MILR

	OLR (*n* = 364)	MILR (*n* = 364)	*P* value
Bile leakage, *n* (%)	14 (4%)	15 (4%)	0.8556
Peak postoperative bilirubin, *n* (IQR)	1.1 (0.7–2.1)	0.9 (0.6–1.6)	0.1429
Peak postoperative international normalized ratio, *n* (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.9703
Post hepatectomy invasive intervention, *n* (%)	28 (8%)	12 (3%)	*0.0085*
Post hepatectomy liver failure, *n* (%)	18 (5%)	18 (5%)	1.0000
Superficial surgical site infection, *n* (%)	15 (4%)	4 (1%)	*0.0106*
Deep incisional surgical site infection, *n* (%)	5 (1.3%)	1 (0.2%)	0.1011
Organ/space surgical site infection, *n* (%)	10 (3%)	8 (2%)	0.6331
Unplanned re-intubation, *n* (%)	8 (2%)	5 (1%)	0.4011
Ventilator dependence, *n* (%)	10 (3%)	2 (0.5%)	*0.0199*
Pneumonia, *n* (%)	14 (4%)	12 (3%)	0.6896
Progressive renal insufficiency, *n* (%)	7 (2%)	4 (1%)	0.3621
Urinary tract infection, *n* (%)	5 (1%)	8 (2%)	0.4011
Stroke, *n* (%)	1 (0.2%)	0 (0%)	0.3170
Myocardial infarction, *n* (%)	8 (2%)	4 (1%)	0.2443
Cardiac arrest, *n* (%)	2 (0.5%)	2 (0.5%)	1.0000
Bleeding requiring transfusion, *n* (%)	53 (15%)	37 (10%)	0.0516
Deep venous thrombosis/thrombophlebitis, *n* (%)	2 (0.5%)	5 (1.3%)	0.2545
Sepsis, *n* (%)	15 (4%)	12 (3%)	*0.5563*
Median LOS in days, *n* (IQR)	6 (4–7)	4 (3–6)	*< 0.0001*
Discharge destination to home, *n* (%)	335 (92%)	343 (94%)	0.4863
30-day readmission	31 (8%)	30 (8%)	0.8936
Reoperation, *n* (%)	9 (2%)	7 (2%)	0.6131
30-day overall morbidity, *n* (%)	107 (29%)	83 (23%)	*0.0428*
Mortality, *n* (%)	8 (2%)	5 (1%)	0.5776

ASA American Society of Anesthesiologists, *LOS* length of hospital stay, *italics* $p<0.05$

0.492–0.998, $P = 0.0486$). Third, MILR was associated with a significantly reduced LOS (4 vs. 6 days) without an increase in operative time, which suggests that hospitalization cost saving benefits may be possible with the MIS approach. Finally, while surgical approach was not associated with postoperative mortality, the study identified several predictors of increased short-term mortality, for which early postoperative recognition may allow targeted preventive management.

The results of this propensity score matched analysis are generally consistent with prior work comparing MILR to OLR. Ciria et al. recently reviewed the literature experience of over 9000 MILRs for any histological diagnosis and concluded that MILR is safe and associated with improved short-term outcomes compared to OLR.[18] Fewer studies have evaluated the impact of MILR specifically among patients with HCC.[19–23] Chen et al. compared MILR for HCC with open resection.[19] These authors concluded that MILR can be applied for challenging major resections in patients with cirrhotic liver disease with less postoperative pain and shorter hospital stays without compromising oncological outcomes. Other investigators have also reported that MILR is associated with comparable oncologic outcomes to OLR for HCC and that laparoscopic resection for malignancy is safe with a similar operative time as open hepatectomy.[23–25] In aggregate, these studies tend to suggest that MILR is associated with reductions in postoperative LOS, and perhaps other short-term benefits, when performed for HCC.

Compared to previous similar analyses, the strengths of this current study consist of the larger number of patients included as well as the use of multi-institutional data, which allowed for a more even case mix. Most importantly, its propensity score matching design allowed for comparison of two groups while minimizing baseline differences in patient and tumor characteristics. Despite this matching, patients who underwent OLR experienced a significantly higher complication rate following liver resection. Furthermore, the association between MILR and improved overall postoperative morbidity persisted on multivariate analysis after controlling for these important pre- and postoperative factors. In particular, MILR was associated with a shorter LOS, which confirms that MIS results in reduced postoperative pain, earlier ambulation and oral intake, faster recovery, and discharge even after challenging operations.[10,25–27]

Table 3 Significant predictors of 30-day morbidity among patients undergoing hepatectomy for HCC based on multivariate stepwise logistic regression analysis

30-day morbidity	OR	95% CI	P value
Age ≥ 65	*1.630*	*1.146–2.319*	*0.0065*
ASA class ≥ 3	*2.740*	*1.587–4.731*	*0.0003*
Preoperative transfusion	*9.786*	*1.060–90.365*	*0.0443*
Open operative approach	*1.427*	*1.002–2.032*	*0.0486*
T stage ≥ 3	*1.932*	*1.097–3.400*	*0.0225*
Operative time > 200 min	*1.801*	*1.264–2.566*	*0.0011*

ASA American Society of Anesthesiologists, *italics* $p<0.05$

There are several reasons why MILR may lead to improved outcomes especially among patients with HCC. First, the use of MILR in cirrhotic patients avoids the disadvantages of utilizing a large transabdominal incision, thereby preserving wall portosystemic shunts and reducing portal vein pressure, which may contribute to a reduced incidence of PHLF. MILR may also be associated with a more gentle intraoperative manipulation of the liver. More importantly, minimization of EBL during MILR may prevent the unintended consequences of blood transfusions in patients with chronic liver disease, which is confirmed by our results.[28] Since these findings suggest that MILR is independently associated with improved postoperative morbidity, efforts to expand the use of MILR among hepatobiliary surgeons are warranted. Future work dedicated to the field of hepatopancreatobiliary MIS should focus on innovative approaches for educating trainees and disseminating skills to established surgeons, identifying novel ways of safely shortening the steep learning curve while simultaneously evaluating patient's outcomes to ensure that safety is not compromised during implementation of minimally invasive technology.[29]

Additionally, the results of this study allow for the critical analysis of predictors of postoperative morbidity in a relatively large series of patients undergoing liver resection for HCC. Advanced age, patient comorbidities, preoperative transfusion, and the open approach were independently associated with increased postoperative morbidity.[2,15,30–33] In contrast to the results of previous studies, preoperative obstructive jaundice, postoperative blood transfusion, the Pringle maneuver, the extent of hepatectomy, and cirrhosis were not associated with a higher incidence of postoperative complications in our study.[2,15,32,34–36] Nevertheless, cirrhosis is recognized as a clinically important feature that influences patient morbidity after hepatic resection when compared with patients with a healthy liver. Therefore, surgeons should always consider underlying liver disease when planning the extent and type of hepatic resection. On the other hand, an advanced T stage of disease (≥ 3) and an operative duration of more than 3 h progressively increased the odds of developing postoperative complications. While the predictive power of prolonged operative time is probably related to a variety of factors, including the extent of dissection, difficulty of resection, biliary reconstruction and surgical skills, longer operative time still correlated with greater overall morbidity when stratified by type of surgery.

While pre- and intra-operative clinical factors were reliable predictors of postoperative morbidity, early mortality following surgery for HCC was largely driven by the occurrence of postoperative complications. Indeed, in our study, no preoperative demographic, clinical, or operative factors remained associated with mortality on multivariate analysis. Predictors of postoperative mortality were myocardial infarction, sepsis, and postoperative liver and renal failure. PHLF and renal failure are known independent predictors of mortality following hepatectomy.[35–37] The results of this study demonstrate that isolated renal dysfunction was an important risk factor for early mortality independently from the development of PHLF, though previous studies have shown that the predictive value for mortality is significantly higher when failure of both organ systems occurs simultaneously.[38] Renal dysfunction following liver resection usually occurs as a consequence of hepatorenal syndrome but may also result from hypovolemia, low central venous pressure during resection or injury from inflammatory mediators during hepatectomy.[36,39] Postoperative sepsis also carried a high risk for mortality following hepatectomy. Postoperative septic complications are often associated with liver dysfunction, although their temporal relationship is poorly defined. Liver dysfunction may facilitate bacterial translocation and infection while at the same time sepsis itself may cause or worsen liver failure.[40–43]

Despite efforts to eliminate bias, balance factors, and adjust for different case-mix samples by propensity score matching, our study has limitations. The main limitation is its retrospective, non-randomized, design, which limits the interpretation of causality of the findings. While the strengths of the ACS-NSQIP database rely on its multi-institutional design with relatively robust sample sizes, it lacks important surgeon and hospital-related information. Indeed, given the learning curve associated with MILR and the importance of hospital volume, all of which may influence postoperative outcomes, the absence of this information limits our conclusions. Furthermore, the ACS-NSQIP database lacks important perioperative-related information such as preoperative portal vein thrombosis, the duration of Pringle

Table 4 Significant predictors of 30-day mortality among patients undergoing hepatectomy for HCC based on multivariate stepwise logistic regression analysis

Mortality	OR	95% CI	*P* value
Myocardial infarction	*34.024*	*4.880–237.242*	*0.0004*
Postoperative liver failure	*8.492*	*1.721–41.893*	*0.0086*
Postoperative renal failure	*31.013*	*4.360–220.597*	*0.0006*
Postoperative sepsis	*15.018*	*3.025–74.556*	*0.0009*

italics, $p<0.05$

maneuver during resection, and the use of postoperative antithrombotic prophylaxis, which may have also influenced outcomes. Finally, while we chose to include patients who underwent conversion to open resection in the MILR group in an "intention-to-treat" type of analysis, the reasons for conversion were not available and remain a potentially important confounder.

In conclusion, this propensity score matched analysis of patients undergoing hepatectomy for HCC demonstrates that MILR is associated with significantly reduced overall morbidity and hospital LOS, but not mortality, compared with OLR. These findings suggest the continued application of MIS techniques to complex hepatobiliary pathology should be pursued and that expanding access to MILR may improve future post-hepatectomy outcomes for patients with HCC.

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Author's Contributions All authors made substantial contributions to the: conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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