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REVIEW

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Cirrhosis and non-hepatic surgery in 2023 – a precision medicine approach

Sean M Morris [a*], Nadir Abbas [a,b*], Daniel-Clement Osei-Bordom [b,c], Simon P Bach [c], Dhiraj Tripathi [a,b] and Neil Rajoriya [a,b]

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ABSTRACT

Introduction: Patients with liver disease and portal hypertension frequently require surgery carrying high morbidity and mortality. Accurately estimating surgical risk remains challenging despite improved medical and surgical management.

Areas covered: This review aims to outline a comprehensive approach to preoperative assessment, appraise methods used to predict surgical risk, and provide an up-to-date overview of outcomes for patients with cirrhosis undergoing non-hepatic surgery.

Expert opinion: Robust preoperative, individually tailored, and precise risk assessment can reduce peri- and postoperative complications in patients with cirrhosis. Established prognostic scores aid stratification, providing an estimation of postoperative mortality, albeit with limitations. VOCAL-Penn Risk Score may provide greater precision than established liver severity scores. Amelioration of portal hypertension in advance of surgery may be considered, with prospective data demonstrating hepatic venous pressure gradient as a promising surrogate marker of postoperative outcomes. Morbidity and mortality vary between types of surgery with further studies required in patients with more advanced liver disease. Patient-specific considerations and practicing precision medicine may allow for improved postoperative outcomes.

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KEYWORDS
liver cirrhosis; portal hypertension; surgery; surgical risk scores; liver prognostic scores; non-hepatic surgery; VOCAL-Penn

1. Introduction

Chronic liver disease imposes a significant healthcare burden worldwide with estimated global prevalence reaching 120 million cases [1]. Patients with cirrhosis frequently require surgery carrying increased mortality and morbidity [2]. Historically, 10% of patients with cirrhosis will undergo surgery during their last two years of life [3]. This number is predicted to rise significantly in the next decade [4] with patients continuing to experience a high burden of surgery-related morbidity and mortality with data demonstrating mortality rates of 8.3–25% compared with 1.1% in matched controls [5]. Surgical eligibility of patients with chronic liver diseases has also risen over time as a result of improvement in the management of cirrhosis alongside enhanced pre-, peri-, and postoperative care. In 2023, patients with liver disease present within the everyday scope of a non-hepatic surgeon [4]. The advent of portal hypertension and cirrhosis present unique challenges for a surgeon undertaking non-hepatic procedures in patients. These include peri- or post-operative risks of infection, coagulopathy, bleeding from varices/porto-systemic collaterals, ascites, precipitation of hepatic encephalopathy (HE), renal impairment, and independent risks associated with the presence of sarcopenia. Each factor requires consideration to avoid adverse surgical outcomes and peri- or postoperative hepatic decompensation [4–6].

Factors determining surgical outcomes broadly include the type of surgery, severity of liver disease, patient demographics, and surgical/anesthetic/intensive care expertise [4,5]. To date, there is a lack of large randomized controlled trials in the field. Regarding liver function, the majority of existing evidence is retrospective with risk stratification based on Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores [7–9]. More recently, surgery-specific tools including the Mayo Postoperative Mortality Risk Score (MRS) and Veteran Outcomes and Costs Associated with Liver disease (VOCAL)-Penn have been developed [10–12]. Indirect measurements of portal pressure may serve as a useful adjunctive tool to predict surgical outcomes [13]. This review discusses existing evidence for surgical outcomes in the setting of cirrhosis, appraises established and novel scoring systems used to risk stratify patients and describes a preoperative risk assessment tool to aid clinicians performing non-hepatic surgery in patients with cirrhosis in the current climate.

2. Pathogenesis of portal hypertension and cirrhosis pertaining to surgery

Cirrhosis encompasses a heterogeneous group of patients with presentations from asymptomatic to decompensated disease, characterized by the development of variceal bleeding,

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Article highlights

- Surgery in patients with liver disease and portal hypertension carries high morbidity and mortality, varying greatly across types of surgery and severity of liver disease.
- Well-established scores such as Child-Turcotte-Pugh and Model for End stage Liver Disease can predict risk but may overestimate mortality.
- Newer surgery specific scores such as Mayo Postoperative Mortality Risk Score and VOCAL-Penn may provide greater precision.
- Hepatic venous pressure gradient as an indicator of risk may be valuable and supports a role for preoperative Transjugular Intrahepatic Portosystemic Stent Shunt but further study is required.
- Global individualized assessment is needed to risk stratify patients and may improve postoperative outcomes.

ascites or HE [14,15]. With progressive liver dysfunction, systemic derangements affecting physiology, metabolism, fluid balance, and coagulation present significant clinical challenges in the surgical setting. One of the hallmarks of cirrhosis is the development of portal hypertension – with its measurement derived from the hepatic venous pressure gradient (HVPG) (Figure 1). A normal HVPG is between 1–5 mmHg, and becomes clinically relevant at ≥10 mmHg, known as clinically significant portal hypertension (CSPH). During the development of CSPH, progressive increases in portal pressure leads to porto-systemic shunting. For patients undergoing surgery, this can introduce a number of risks including bleeding, precipitation of HE, loss of first-pass metabolism, exacerbation of hyperdynamic circulation, and increased susceptibility to sepsis [16]. Furthermore, chronic inflammation and bacterial translocation contribute to portal hypertension and propagate the systemic hyperdynamic circulation [17–19]. In the setting of surgery, particularly when the abdominal cavity is breached, the risk of sepsis from bacterial translocation should be considered [19,20]. Perioperative changes in hepatic blood flow as a result of vasodilatory effects of anesthetic drugs and fluid losses during surgery can disrupt a relatively stable homeostatic state preoperatively in a patient with compensated cirrhosis. This may be exacerbated in the setting of emergency surgery [4]. Deranged hemostasis, altered drug pharmacokinetics and neurohormonal mediator imbalance, exacerbating sodium and fluid retention complicate perioperative surgical management. Malnutrition and progressive sarcopenia may compromise postoperative wound healing and rehabilitation. Addressing these factors is challenging, requiring a personalized approach ensuring appropriate risk stratification, identification of

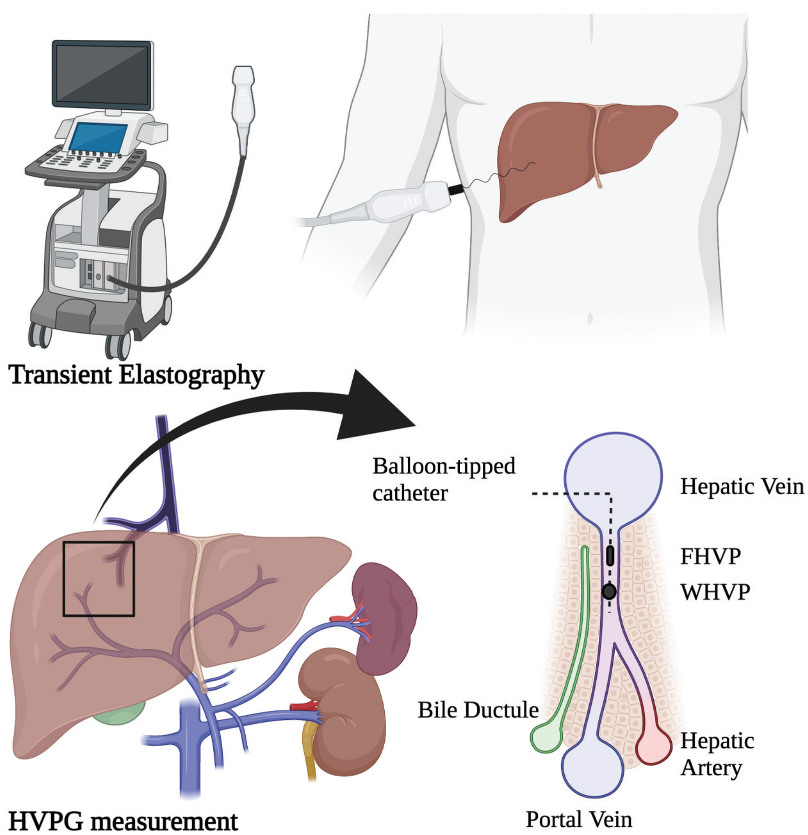

Figure 1. Measurement of portal hypertension (Created with BioRender.com).

Transient elastography is a noninvasive, clinic-based investigation that measures the velocity of a vibration through the liver. Velocity is inversely related to liver stiffness (measured in kPa) and the degree of hepatic fibrosis can be inferred from this measurement [27]. HVPG measurement is an interventional procedure estimating sinusoidal portal pressure from the difference between WHVP and FHVP using a balloon-tipped catheter under ultrasound or fluoroscopic guidance [21]. Measurements are taken from the right hepatic vein, usually via the internal jugular vein, and are often performed concurrently with transjugular core biopsies of the liver.

Abbreviations: HVPG, hepatic venous pressure gradient; FHVP, free hepatic venous pressure; WHVP, wedge hepatic vein pressure preoperative risk factors and consideration of alternative treatment options.

3. Preoperative clinical assessment

Preoperative assessment requires a detailed history, examination, and appropriate investigations to identify previously undiagnosed asymptomatic chronic liver disease – only then can risk stratification be performed pertaining to cirrhosis [5]. Formal assessment of surgical risk in patients with underlying liver disease includes a review of: the severity of liver disease, current medical history, category of surgical urgency (emergency vs. elective), nutritional status, liver function, and assessment of coagulopathy and renal dysfunction [22]. Challenges remain to determine (i) whether a surgical procedure can be performed safely in the presence of cirrhosis, or (ii) if surgery can be deferred until after liver transplantation in an appropriate candidate, or (iii) is surgery contraindicated. Several contraindications to elective surgery exist including acute or fulminant liver failure, acute viral or alcoholic hepatitis and American Society of Anesthesiologists (ASA) class V [6].

The presence of portal hypertension is an independent risk factor for perioperative mortality [23] and thus should be evaluated during preoperative workup in accordance with international guidelines [24–26]. Noninvasive markers of portal hypertension in preoperative assessment include combinations of platelet count, ultrasound/CT imaging to assess for presence of ascites, collateral vessels and splenomegaly, and liver stiffness measurements (LSM) obtained by transient elastography (TE) (Figure 1) [24,27,28]. Invasive measurement of portal pressure such as HVPG (Figure 1), if available, is considered the gold standard to diagnose CSPH [29]. In a prospective study, HVPG >10 mmHg and LSM >21kPa were found to be equally effective in predicting liver cirrhosis decompensation [30]. HVPG however is available in limited institutions and not recommended in the American Gastroenterological Association (AGA) guidelines due to paucity of data in non-hepatic surgery. Noninvasive assessment using TE and presence of thrombocytopenia may be of value in predicting portal hypertension, excluding CSPH with LSM <15kPa and platelets ≥150x10^9/L (negative predictive value >90%), whereas LSM values ≥25kPa are sufficient to rule in CSPH (positive predictive value >90%) [24]. TE however to date has not been used in surgical prognostication scores thus its relevance should be an adjunct for the global overall assessment of surgical cirrhosis patients. Of note it cannot be used accurately in the setting of non-fasted state, acute alcohol use or ascites. In patients high risk for CSPH, the authors advocate consideration of HVPG measurement where available to inform decision making and patient counseling. A schematic algorithm for preoperative assessment of liver disease patients to aid precision-decision making is detailed in Figure 2. Specific considerations in Peirioperative optimization of a patient with liver cirrhosis undergoing non-hepatic surgery are outside the remits of this review but requires close liaison between the surgical, anesthetic and gastroenterology/hepatology teams (Figure 3).

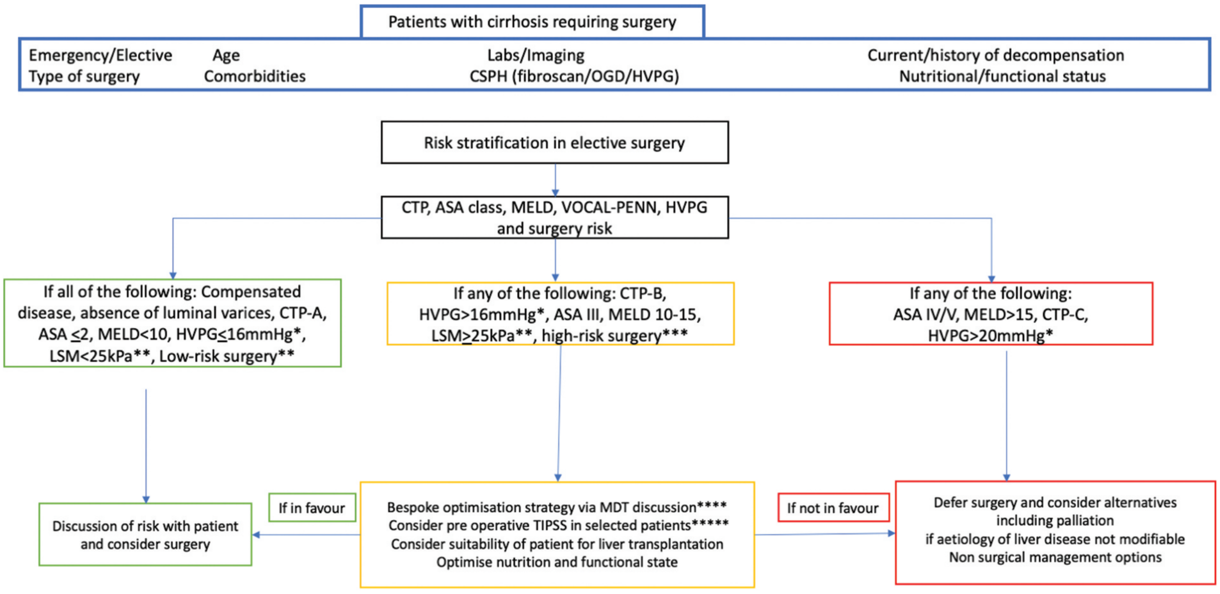

Figure 2. Algorithm for assessment of patients with cirrhosis undergoing elective surgery.

*HVPG measurement is preferable where available

**High-risk surgery includes cardiovascular, thoracic and open abdominal surgeries

***Low-risk surgery comprises laparoscopic, abdominal wall surgeries, and orthopedic surgeries

****Includes addressing individual risk factors such as alcohol intake, increased BMI, measures to improve ASA status and portal decompression, e.g. TIPSS in suitable patients.

***** Only available in selected centers

Abbreviations: ASA, American Society of Anesthesiology score; CTP, Child-Turcotte-Pugh score; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; MDT, multidisciplinary team discussion; OGD, oesophago-gastro-duodenoscopy; TIPSS, transjugular intrahepatic porto-systemic stent shunt

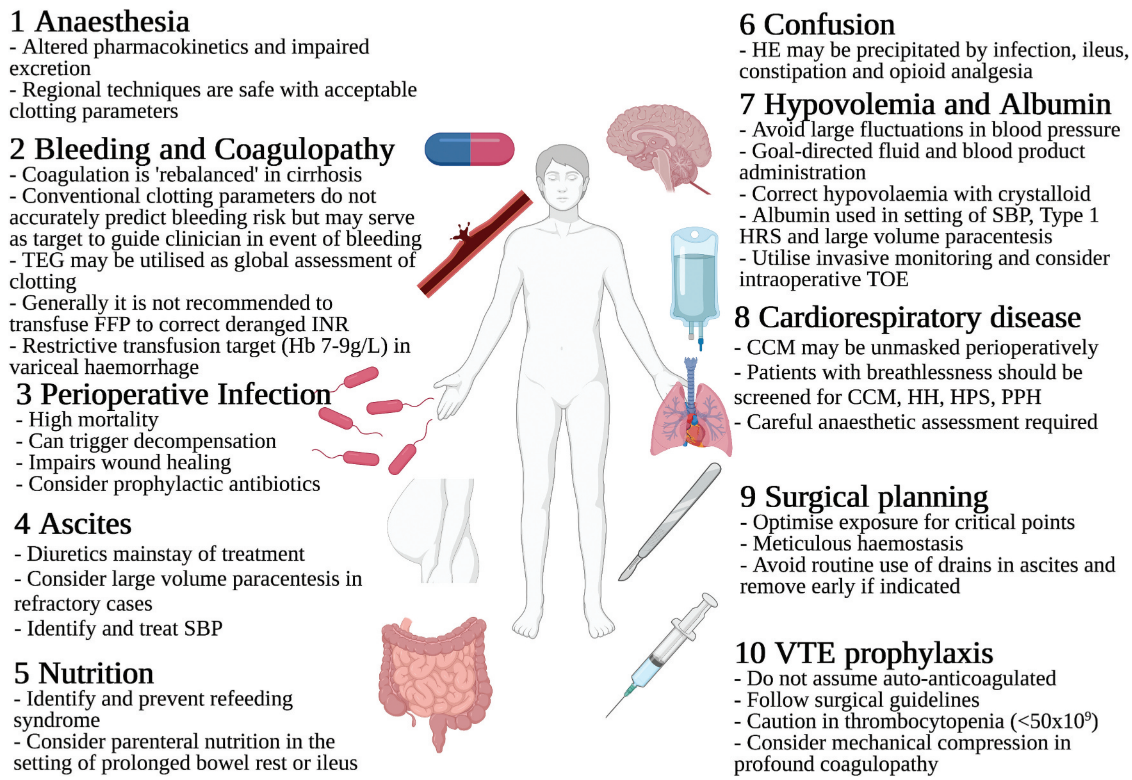

Figure 3. Perioperative considerations for optimization of patients with liver cirrhosis and portal hypertension undergoing non-hepatic surgery (Created with BioRender.com).

1 Anesthesia [31]; *2 Bleeding and coagulopathy* [32–34]; *3 Perioperative infection* [35,36]; *4 Ascites* [5]; *5 Nutrition* [37–39]; 6 *Confusion; 7 Hypovolemia* [31,40–42]; *8 Cardiorespiratory disease* [43–46]; *9 Surgical planning* [4]; 10 *VTE prophylaxis* [47,48]

Abbreviations: TEG, thromboelastography; FFP, fresh frozen plasma; INR, international normalized ratio; Hb, hemoglobin; SBP, spontaneous bacterial peritonitis; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; TOE, transesophageal echocardiography; CCM, cirrhotic cardiomyopathy; HH, hepatic hydrothorax; HPS, hepatopulmonary syndrome; PPH, porto-pulmonary hypertension; VTE, venous thromboembolism

4. Reducing portal pressure

In compensated cirrhosis, the risk of decompensation increases with development of CSPH and the degree of portal hypertension, defined by HVPG, may serve as a guide to reflect surgical risk. In the study by Reverter et al [13], patients with HVPG >16 and ≥20 mmHg were considered *high risk* and *very high risk* respectively for surgical intervention. Reducing portal pressure can be achieved through use of nonselective beta blockers or transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion, intended to lower risk of refractory ascites and recurrent or uncontrolled variceal bleeding [49]. TIPSS is an interventional fluoroscopic procedure where a stent is inserted across a tract created between the hepatic and portal vein [49]. There a number of complications, particularly development of HE (in up to 1/3 of patients), that require careful consideration [49]. In theory, preoperative reduction in portal pressure to facilitate subsequent surgery, especially abdominal, may reduce intraoperative bleeding (decompression of collaterals) and postoperative complications pertaining to portal hypertension. HVPG-guided beta blocker administration, with responders defined as achieving >10-20% decrease from baseline or absolute pressure <12 mmHg, experience reduced risk of decompensation and increased survival [50,51]. To date, HVPG-guided reduction in portal pressure with beta blockers prior to non-hepatic surgery has not been investigated. Similarly, a marked paucity of data on safety and efficacy of TIPSS prior to surgery is recognized by the current guidelines [49,52]. To date, few studies have evaluated feasibility of preoperative TIPSS [53–58] and only a small number compare postoperative outcomes to controls [53,57,58]. Furthermore, criteria to determine whom might benefit from preoperative TIPSS is debated. Goel et al [55] reported on 21 patients who underwent preoperative TIPSS to facilitate non-hepatic surgical procedures. At the time of TIPSS, 71% were CTP-A with the remainder being CTP-B. TIPSS had excellent technical success (100%) and significant hemodynamic response (portal pressure decreased from a median of 21.5 mmHg to 16 mmHg; p = 0.001). Eighty-six percent could proceed with the planned surgical procedure (median duration from TIPSS: 38 days) and eventually 57% of the entire cohort had no perioperative liver/portal hypertension-related complications. In a systematic review (19 studies, 64 patients) of outcomes for non-hepatic surgery in patients undergoing preoperative TIPSS [56], the procedure had a 100% success rate, with all patients undergoing planned surgery with a median delay of 30 days. Perioperative mortality and morbidity was 8% and 59.4% respectively with an overall 1-year survival of 80%. The authors concluded that TIPSS may allow planned surgery for patients with cirrhosis previously deemed inoperable, but larger studies were required. In a comparative study Tabchouri et al [57] conducted a retrospective analysis of postoperative outcomes for 66 patients with cirrhosis undergoing preoperative TIPSS. The proportion of patients exhibiting severe postoperative complications and 90-day mortality (TIPSS vs. controls) was 18% vs. 23%, p = 0.392 and 7.5% vs. 7.8%, p = 0.644 respectively. The observed lack of mortality benefit may be accounted for by the initial higher CTP score in the TIPSS group (p = 0.043). Recently Chang et al [58] evaluated postoperative development of acute-on-chronic liver failure (ACLF), a syndrome associated with systemic inflammation and multiorgan failure and mortality in patients with or without preoperative TIPSS. Forty-five patients with preoperative TIPSS (inserted for refractory ascites or hemorrhage) were 1:1 propensity matched to patients without TIPSS. Patients in the no-TIPSS group had higher rates of ACLF at 28-days (p = 0.016) and 90-days (p = 0.020) in addition to 1-year mortality (p = 0.023). Further studies are required to understand the need for prophylactic portal decompression in cirrhotic patients undergoing surgery. Referral to an experienced high volume TIPSS center (minimum 10 cases per annum or at least 20 per annum for complex cases – Budd-Chiari syndrome, portal vein thrombosis, transplant recipients) [49], along with a strict patient selection remains the cornerstone for successful preoperative TIPSS to facilitate surgery. Pooled multicentric studies may help future recommendations in this evolving area.

5. Surgical risk prediction models in liver cirrhosis

To aid clinicians in risk stratification of patients with cirrhosis undergoing surgery, existing scores have been repurposed and new systems have been developed (Table 1) – however most published evidence relies on retrospective, single center

Table 1. Scores for severity of liver disease.

Score	Components		
Child-Turcotte-Pugh (CTP) [7,8]			
Score	1	2	3
Albumin (g/L)	>35	28–35	<28
Bilirubin(μmol/L)	<34	34–50	>50
Clotting (INR)	<1.7	1.7–2.2	>2.2
Ascites	None	Diuretic responsive	Diuretic resistant
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Class	A	B	C
Total score	5–6	7–9	10–15
Model for End-stage Liver Disease (MELD) [9]			
Creatinine (μmol/L)			
Bilirubin (μmol/L)			
Clotting (INR)			
Dialysis at least twice in past week			
Formula = (0.957 x ln (Serum Cr) + 0.378 x ln (Serum Bilirubin) + 1.120 x ln (INR) + 0.643) x 10 (if hemodialysis, value for Creatinine is automatically set to 4.0)			
MELD-Na [73]			
Creatinine (μmol/L)			
Bilirubin (μmol/L)			
Clotting (INR)			
Sodium (mmol/L) †			
Dialysis at least twice in past week			
Formula = MELD score − Na − 0.025 x MELD x (140-Na) +140			
†Sodium is limited in a range of 125–140, and if outside of these bounds, is set to the nearest limit			
ASA [75]			
ASA I – Normal healthy patient			
ASA II – Patient with mild systemic disease			
ASA III – Patient severe systemic disease that is not a constant threat to life			
ASA IV – Patient with severe systemic disease that is a constant threat to life			
ASA V – Moribund patient not expected to survive with or without surgery			
ADOPT-LC [64]			
Age (Years)			
Charlson Comorbidity index			
CTP Class			
Anesthesia duration			
Formula not available			
Mayo Postoperative Mortality Risk Score (MRS) [10]			
Age			
ASA Score			
Bilirubin (mg/dl)			
Creatinine (mg/dl)			
INR			
Etiology of cirrhosis			
VOCAL-Penn [11]			
Age (Years)		*BMI >30*	
Albumin (g/L)		*NAFLD etiology*	
Bilirubin (μmol/L)		*ASA score*	
Platelet count (x10^9/L)		*Emergency surgery*	
Surgery type			
Formula not available			

Abbreviations: ASA, American society of Anesthesiology Score; BMI, body mass index; CTP, Child-Turcotte-Pugh score; INR, international normalized ratio, NAFLD, nonalcoholic fatty liver disease.

case series that are vulnerable to reporting bias, population demographics and institutional experience [59,60]. Recently, alternative methods of risk stratification have been explored in the form of HVPG measurements [13]. All the risk models to date, however, do not take into account specific conditions relating to liver disease including hepatocellular carcinoma, portal vein thrombosis, hepatopulmonary syndrome and porto-pulmonary hypertension with the latter two being major considerations for general anesthesia.

5.1. Child-Turcotte-Pugh classification

The CTP score is frequently used to classify severity of liver disease, relying on three objective components (bilirubin, albumin and prothrombin time) and two more subjective components (ascites and HE) – especially on retrospective analysis [7,8]. CTP has been evaluated in non-hepatic surgery extensively and correlates with postoperative mortality. Historically, postoperative mortality has been reported in CTP-A, B and C patients at 10%, 30% and 80% respectively [61,62]. Garrison et al [61] reviewed 100 consecutive patients with cirrhosis undergoing laparotomy for biliary, peptic ulcer and colonic procedures, with CTP score predicting survival with 89% accuracy. Mansour et al [62] reported similar results following retrospective analysis of 92 patients with cirrhosis undergoing cholecystectomy, hernia or gastrointestinal tract procedures. Fifty-seven parameters were evaluated as predictors of mortality including procedure type, co-morbidities, preoperative blood results and severity of liver disease. The most accurate predictor of outcome was preoperative CTP score. More recently Telem et al [63] evaluated a cohort of 100 cirrhotic patients undergoing abdominal surgery (cholecystectomy, umbilical herniorrhaphy and colectomy), reporting CTP classification correlated well with postoperative morbidity but similar 30-day mortality rates for CTP-B & C classes (CTP-A 2%, CTP-B/C 12%). Lower mortality rates were attributed to institutional expertise in liver transplantation and multidisciplinary perioperative care. Only 17% of the cohort were, however, classed as CTP-C and the majority of these patients underwent umbilical herniorrhaphy. In a separate cohort of 2197 patients undergoing a range of surgical interventions (60% intra-abdominal), a CTP score of ≥7.5 (sensitivity 69%, specificity 80%) and ≥9.5 (sensitivity 72%, specificity 77%) was a reasonable predictor of in-hospital mortality for elective and emergency surgery respectively [64]. Overall, there is agreement that CTP provides a good estimation of surgical risk in patients with cirrhosis [5,52]. Surgery is well tolerated in CTP-A patients, in the absence of thrombocytopenia or CSPH and it may be permissible in CTP-B patients with preoperative optimization (except for high-risk cardiac surgery or extensive hepatic resection). Patients with CTP-C cirrhosis undergoing surgery are however under-represented in the literature, relying on historical data [61,62] with further studies required. It is clear however CTP-C patients are high risk for surgery, and not a group recommended for surgery in the author's institute. The presence of ascites has been shown to correlate with worse outcomes irrespective of CTP score [63]. Several drawbacks of the CTP scoring system exist limiting its utility in non-hepatic surgery. These include inter-observer variability due to the subjectivity of ascites and HE components, equal weighting for each parameter in the score, and a large range for each class lending to ceiling and floor effects.

5.2. Model for end-stage liver disease

The MELD scoring system (Table 1) predicted mortality after TIPSS [9], and was later adopted to estimate short-term survival for liver transplantation candidates [65]. It has advantages over CTP as a risk stratification system in the fact that it produces a continuous variable with greater discrimination. Following its survival validation in multiple settings, studies have been published demonstrating its utility in predicting mortality following non-hepatic surgery [10,66–71]. In a retrospective study from Befeler et al [68] analyzing 53 patients who underwent extrahepatic surgery (laparoscopic cholecystectomy, open cholecystectomy or exploratory laparotomy), MELD was shown to be an independent predictor of poor outcomes ($p < 0.001$) (death, liver transplant within 90 days of surgery or hospital stay >21 days). On comparison between MELD and CTP, similar Receiver Operating Characteristic (ROC) curves were constructed (AUROC 0.826 vs. 0.814 respectively). Using a cut off of >14, however, demonstrated good correlation (sensitivity 77%, specificity 80%) yielding a better positive likelihood ratio than CTP-B or C ($p < 0.05$) and a better negative likelihood ratio than CTP-C ($p < 0.05$), establishing its utility as a clinical tool [68]. In a retrospective analysis of 133 cirrhotic patients, MELD score was a predictor of 30-day (cut off value 19.5, sensitivity 75%, specificity 72.6%), 90-day (cut off value 18.5, sensitivity 74.1%, specificity 73.6%) and 1-year mortality (cut off value 16.5, sensitivity 68.6%, specificity 63.0%) [71]. Northup et al [69] demonstrated approximately a 1% increase in mortality per MELD point to a score of 20. For each MELD point >20, mortality increased by 2%. Teh et al [10] conducted the largest retrospective study of predictors of perioperative mortality in patients with cirrhosis (n = 772) undergoing abdominal, orthopedic and cardiovascular surgery. MELD, age and ASA score were statistically significant predictors of outcome on multivariate analysis. In contrast to Northup et al [69]. this study found that 30-day and 90-day mortality increased by 14% for each MELD point at scores >8, exhibiting an almost linear relationship.

The AGA clinical practice update has provided evidence for a range of MELD cutoffs for surgical type (Table 2), however heterogeneity between studies and types of surgery requires a patient-specific approach beyond MELD score alone [52]. The risk of mortality for MELD scores appears almost linear,

Table 2. MELD scores and increased risk for various surgical procedures.

Type of Surgery	MELD Score
All surgical procedures	>14
Cholecystectomy	>15
Abdominal wall herniorrhaphy	>13
Coronary artery bypass grafting	>13.5
Colonic resection	>9

(adapted from [52])
Abbreviations: MELD: model for end stage liver disease.

particularly for MELD>8, which may facilitate extrapolation [10,69]. In both studies there were few patients with MELD >25, thus postoperative mortality modeling may be less accurate for advanced cirrhosis [10,69]. MELD, unlike CTP score, does not take into account associated clinical factors such as ascites and presence of HE, thus potentially limiting its use in abdominal surgery, whereby additive risks of portal hypertension exist. The impact of ascites on mortality and morbidity was evaluated in a large retrospective study of 16,877 patients undergoing colectomy [72]. Patients were stratified by MELD score into low, medium and high risk (MELD <9, 9–15 and >15 respectively). Compared with low-risk patients without ascites, the presence of ascites increased risk of postoperative mortality in low (with ascites odds ratio (OR) 9.40 (3.53–25.01) $p < 0.0001$), moderate (without ascites OR 1.47 (1.14–1.89) $p < 0.0031$; with ascites OR 5.62 (2.95–10.72) $p < 0.0001$) and high-risk patients (without ascites OR 3.04 (2.24–4.13) $p < 0.0001$; with ascites OR 9.91 (5.29–18.58) $p < 0.0001$).

5.3. MELD-Na

MELD-Na (Table 1) incorporates serum sodium into the existing MELD score, introduced in 2008, to improve the precision in predicting mortality for patients on the liver transplant waiting list aiding organ allocation [73]. One retrospective analysis of 133 patients undergoing gastrointestinal and urological surgery compared 30-day, 90-day and 1-year mortality [71]. In this study, MELD-Na was found to be an accurate predictor of mortality at each of these time points (30-day AUROC 0.77, cut off value 24.5, sensitivity 75%, specificity 74.5%, $p = 0.001$; 90-day AUROC 0.74, cut off value 21.5, sensitivity 66.7%, specificity 67.0%, $p = 0.001$; 1-year AUROC 0.67, cut off value 20.5, sensitivity 60%, specificity 60.2%, $p = 0.003$), however MELD (all time points $p < 0.001$) and MRS (all time points $p < 0.001$) demonstrated superior performance. In a study by Causey et al [74], CTP, MELD and MELD-Na were assessed in a retrospective study of 64 patients undergoing a range of non-transplant surgical procedures for malignant and nonmalignant indications. When used to predict mortality at 1 year, CTP was the most sensitive (78% vs 67% for MELD and MELD-Na) whereas MELD-Na was the most specific (70% vs 63% (MELD) and 46% (CTP)) scoring system. At 1-year a MELD-Na score of >14.5 corresponded to a 4.5-fold increased risk of death (95% confidence interval (CI), 1.4–14.6). A predicted probabilities curve, based on MELD-Na, demonstrated a linear increase in 1-year mortality with increasing MELD-Na scores highlighting potential utility in the preoperative assessment. Although data suggests MELD-Na may serve as a suitable adjunct to risk stratification, it has not been adopted within the AGA guidelines [52].

5.4. The American Society of Anesthesiologists status

The ASA physical status classification is a measure of risk of administering anesthesia that has been utilized since the 1940s (Table 1) [75]. It is based on functional status and comorbidities of the patient but lacks specific guidance on how to classify cirrhosis [9]. As a systemic illness, compensated cirrhosis is proposed to be classified as ASA class III, whereas decompensated states should be ASA class IV. Teh et al [10] identified ASA as an independent risk factor with ASA class V (moribund patient who is not expected to survive without an operation) being the strongest predictor of 7-day postoperative mortality, whilst MELD score being the best predictor at 30-, 90-days and 1-year survival. The MRS score is derived from a combination of MELD, ASA class and age. Recently, ASA class, HVPG and high-risk surgery (open abdominal and cardiovascular) have been found to be independently associated with 1-year mortality [13].

5.5. Adequate operative treatment for liver cirrhosis (ADOPT-LC) score

The ADOPT-LC score (Table 1) was devised using age, CTP score, Charlson comorbidity index, duration of anesthesia and emergency indication. They were derived from study from Sato et al [64] from 2197 patients undergoing elective (89.8%) or emergency surgery (n = 10.2%). These patients underwent abdominal, breast, orthopedic, cardiovascular, and urological surgery. On multivariate analysis the ADOPT-LC components were all predictive of inpatient mortality. The ADOPT-LC score (Table 1) demonstrated in the setting of elective surgery excellent discrimination during internal validation (AUROC 0.881, n = 986). Moreover, the ADOPT-LC outperformed CTP score (AUROC 0.803, $p = 0.01$) alone in this cohort. Using a cut off value 3.5, ADOPT-LC was strongly predictive of inpatient mortality (sensitivity 90.5%, specificity 69.7%). This study has shown promise for aiding clinicians for patients undergoing elective surgery but has not yet to our knowledge, been validated in multiple cohorts worldwide or in a prospective series.

5.6. Mayo postoperative mortality risk score

The MRS (Table 1), until recently, was the only surgery-specific risk assessment tool providing discrete postoperative short- and long-term mortality estimation in liver cirrhosis at 7-days, 30-days, 90-days, 1-year and up to 5-years [10]. The MRS has limitations, being formulated from a single center retrospective study spanning over 25 years which predated major advances in the field of surgery. It also does not account for surgery type or whether performed as an emergency. The MRS was validated in a Korean cohort with good risk prediction at 30- and 90-days but overestimating predicted 1-year mortality (22.6 ± 12.0%) compared to observed mortality (8.9 ± 1.4%, $p < 0.01$) [76]. Similar results were obtained in a cohort of 133 patients with MRS tending to overestimate mortality, especially at 1 year, but remaining a reasonable predictor of risk (30-day, cut off value 29.5, sensitivity 73.3%, specificity 73%; 90-day, cut off value 41.5, sensitivity 73%, specificity 75%; 1-year, cut off value 41, sensitivity 67.6%, specificity 69.7%) [71]. Compared with the Korean cohort, the severity of liver disease in this study population was more advanced (9% of patients CTP-A compared with 78% in Korean cohort), suggesting MRS remains a suitable risk tool for a range of cirrhotic patients. The score is recommended by the recent AGA guidelines as a validated method to determine operative risk [52], and can be calculated using an online tool on the Mayo Clinic website (https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/post-operative-mortality-risk-in-patients-with-cirrhosis/itt-20434721) [10].

5.7. VOCAL-penn model

The CTP and MELD, although frequently used, lack surgical specific parameters [8,9]. Until recently, only the MRS was a surgical specific tool but did not account for the type of surgery and was derived from single-center data [10,52]. Mahmud et al [11] recently provided external validation for the MRS and proposed a new risk prediction tool using population-level data. The group conducted a retrospective study from the VOCAL and VASQIP cohorts. This multi-center study included 4712 procedures from 3785 patients with cirrhosis. The study initially demonstrated that the MRS score lacked calibration over time, with both 30- and 90-day postoperative mortality demonstrating a statistically significant difference between predicted and observed mortality ($p < 0.001$). This finding was akin to the validation study in the Korean cohort which demonstrated over-estimation of predicted 1-year mortality by the MRS [76]. Following further analysis, the authors identified a number of components predictive of mortality (Table 1). The VOCAL-Penn model demonstrated excellent discrimination with superior performance to MELD, MELD-Na, CTP and MRS at all time points (30-day C-statistic = 0.859 versus 0.766 for the MRS and 0.852 for MELD-Na ($p = 0.003$)). The VOCAL-Penn score has recently been validated in a study examining two further cohorts demonstrating higher C-statistic (0.82 vs. 0.79 for MRS, vs. 0.79 for MELD, vs. 0.78 for MELD-Na) for 90 days postoperative mortality [12]. The results of this study add to the potential for VOCAL-Penn score utility in surgical risk prediction and further external validation is awaited. This is available to be used online at www.vocalpennscore.com.

5.8. Hepatic venous pressure gradient

HVPG has been studied in the setting of cirrhosis patients and surgery in only one paper. In a multi-center prospective study, Reverter et al [13] evaluated the role of portal hypertension by directly quantifying HVPG in 140 patients with cirrhosis (CTP-A/B/C: 59/37/4%) undergoing elective extra-hepatic surgery (121 abdominal, 9 cardiovascular/thoracic, 10 orthopedic and others). ASA class, high-risk surgery (open abdominal, cardiovascular and thoracic), HVPG readings, intrinsic indocyanine green clearance, renin activity, albumin, CTP score and previous decompensation were variables associated with mortality/requirement for liver transplantation at 12 months. Only ASA class (Hazard Ratio (HR) III vs. II = 2.98, HR IV vs. II = 9.97, $p = 0.008$), high risk surgery (HR = 3.65, $p = 0.006$) and HVPG (HR = 1.14, $p = 0.003$) retained prognostic significance on multivariate analysis. HVPG measurements were further dichotomized demonstrating values >16 mmHg and ≥20 mmHg being classed as *high* and *very high* risk, respectively. HVPG measurement is an invasive, highly technical procedure with availability often limited to large specialist centers or used in research settings. However if time permits in the context of major surgery, HVPG measurements could be justified given the strong predictive value in a prospective cohort. AGA *do not recommend* its use in non-hepatic surgery due to paucity of data outside of primary hepatic resection, although it should be noted these guidelines were published prior to the paper presented by Reverter et al. [52]. Further studies are required in this specific field.

6. Surgery-specific outcomes in patients with liver cirrhosis and portal hypertension

The outcomes of patients undergoing surgery are highly variable [5]. Studies are often retrospective, single-center and lack appropriate quality and controls [2,75,77–79]. In addition to this, details regarding severity of liver disease are frequently omitted and there remains limited data in those patients with severe end-stage liver disease. Degree of decompensation coupled with type and nature of surgery appear to be strong determinants of outcome [4,5,80]. In this regard, it is universally observed that patients with more advanced liver disease experience disproportionately high morbidity and mortality across the spectrum of surgical specialties [2,77,79,81,82]. A systematic review by De Goede et al [2] included 46 studies for a range of procedures. For general surgical risk, patients with cirrhosis experienced an overall 30.1% morbidity and 11.6% 30-day mortality for any type of surgery. Patients undergoing cholecystectomy, colectomy, coronary artery bypass graft (CABG) or abdominal aortic aneurysm repair (AAA) had a 3.4-fold, 3.7-fold, 8.0-fold and a 5.0-fold higher risk of mortality respectively when compared to patients without cirrhosis. The presence of portal hypertension conferred an even higher risk of mortality for the same procedures with a 12.3-fold, 14.3-fold, 22.7-fold and 7.8-fold increase in risk respectively [2]. More recently in a study by De Stefano et al [83], the impact of portal hypertension on surgical risk was assessed for 192,296 patients undergoing a range of gastro-intestinal surgery (esophageal surgery, gastrectomy, hepatectomy, colectomy, appendectomy, small bowel resection, pancreaticoduodenectomy, distal pancreatectomy, hepatico-jejunostomy and cholecystectomy). In this study 379 patients (0.2%) had portal hypertension. Regression analyses revealed that patients with portal hypertension had a 3-fold increase in morbidity (95% CI 2.5–3.7), a 6-fold increase in 30-day mortality (95% CI 4.6–7.9), a 3.2-fold increase in critical care complications (95% CI 2.6–3.9), and an additional increase in-hospital length of stay (LOS) of 6.5-days (95% CI 5.1–7.8). Despite propensity score matching, the impact of portal hypertension on surgical outcomes remained unchanged irrespective of whether the surgical procedures were emergency or elective. Generally, major hepatic resection carries the highest risk, followed by abdominal and thoracic surgery [52]. It is unclear whether this is through violation of the cavity itself as a specific risk factor or if these procedures are generally more invasive and disruptive to the splanchnic vasculature. It is suggested that laparotomy causes a greater reduction in hepatic blood inflow and is associated with greater risk of

Table 3. Studies with mortality and morbidity data in relation to non-hepatic surgery in liver cirrhosis and portal hypertension, categorized by type of surgery.

Type of Surgery	Type and details of study	Ref	Salient findings
Cholecystectomy	Meta-analysis including 25 publications (400 cirrhosis patients undergoing laparoscopic cholecystectomy)	[101]	• Patients with cirrhosis had higher conversion rates to open cholecystectomy (7% v 3.6%; $p = 0.024$), operative times (98 minutes vs 70 minutes; $p = 0.005$), bleeding complications 26.4% v 3.1%; $p < 0.001$) and overall morbidity (20.9% v 7.9% $p < 0.001$) • When compared with the open approach, laparoscopic cholecystectomy is associated with less operative blood loss (113 ml v 425 ml; $p = 0.015$), operative time 123.3 minutes v 150.2 minutes; $p = 0.04$) and length of hospital stay (6 v 12 days; $p < 0.001$).
	Randomized controlled trial 110 cirrhosis patients with symptomatic gallstones were randomized 1:1 from October 2002 to December 2006	[102]	• No operative mortality. • Four patients required conversion to open cholecystectomy. • Laparoscopic cholecystectomy offered lower morbidity, shorter operative times, earlier feeding resumption, less need for blood transfusion and reduced hospital stay compared with open cholecystectomy
	Retrospective analysis of 49,030 patients with cirrhosis presenting with acute cholecystitis	[85]	• Laparoscopic cholecystectomy had lower mortality rates and fewer complications compared with non-operative management or open cholecystectomy ($p < 0.05$). • Open cholecystectomy was associated with higher mortality, increased hospital stay, total cost and post-operative complications, independent of the presence or severity of cirrhosis.
Colorectal surgery	Retrospective analysis of national database between 1998–2005; 22,569 patients with cirrhosis (of whom 4214 had portal hypertension)	[78]	• Higher mortality for patients undergoing colectomy compared to controls (HR 3.7, 95% CI: 2.6–5.2) • Presence of portal hypertension conferred even higher risk (HR 14.3, 95% CI: 9.7–21.0)
	Population based study (1998–2005) identifying 4042 patients	[118]	• Patients with cirrhosis and cirrhosis with PHTN had higher in-hospital mortality compared to patients with no cirrhosis (14% and 29% v 5%, respectively, $p < 0.0001$) • Approximately 4-fold higher rate of in-hospital mortality for emergent and urgent procedures in comparison to elective procedures in liver cirrhosis patients • Higher mortality rate of cirrhotic patients with portal hypertension undergoing surgery (HR: 5.8; 95% CI: 4.9–7.6). • Independent risk factors for mortality were cirrhosis, P HTN, old age, colectomy and co-morbidities which included cardiovascular disease, chronic kidney disease, paraplegia and malnutrition.
	Prospective, clinical database between 2005–2007 identifying 1565 patients with chronic liver disease undergoing colorectal resections	[77]	• Chronic liver disease patients were identified using clinical characteristic: ascites, esophageal varices, or total bilirubin >2 mg/dL. • 6.5-fold increased risk of mortality following colorectal operations in chronic liver disease patients. • MELD score >15 was associated with higher rates of mortality and complications (Ascites, infection, bleeding anastomotic leaks and stoma issues including leaks, difficulty closing and peristomal variceal bleeding).
	Population based study between 1996–2009 identifying 39,840 patients undergoing colorectal surgery with 158 (0.4%) having liver cirrhosis	[86]	• Higher 30-day mortality (24.1%) corresponding to adjusted RR of 2.59 (95% CI: 1.86–3.61)
	Retrospective analysis of 161 liver cirrhosis patient undergoing surgery for colorectal cancer	[119]	• MELD score above 8 influenced overall survival ($p < 0.001$)
	Retrospective, observational, population-based study between 2005–2014 identifying outcomes for patients with cirrhosis undergoing surgery for colorectal cancer	[87]	• Increased risk of in-hospital mortality (adjusted OR 2.05, $p < 0.001$) • No significant increase in postoperative complications (adjusted OR 0.91, $p = 0.192$)
	Meta-analysis identifying 2485 patients from 5 studies	[117]	• Cirrhotic group experienced more major complications (OR 5.15; $p = 0.005$), higher rates of return to theater (OR: 2.04; $p = 0.03$), higher short-term mortality (OR: 2.8; $p < 0.00001$) and shorter survival (HR 2.96, $p < 0.00001$)
Peptic ulcer disease	Retrospective analysis (1972–1991), 69 patients undergoing surgery (90% – emergency) for gastroduodenal disease	[120]	• Overall mortality – 54% with bleeding and multiorgan failure being leading causes of death (70%).

(*Continued*)

Table 3. (Continued).

Type of Surgery	Type and details of study	Ref	Salient findings
Gastric cancer surgery	Retrospective analysis of 39 patients with liver cirrhosis undergoing curative surgery for gastric cancer between 1978–1994	[121]	• Post-operative complications were observed in 10 (25.6%) patients with 4(10.3%) hospital deaths.
	Retrospective analysis of 58 patients with liver cirrhosis undergoing radical gastrectomy between 2001–2012.	[122]	• Forty-four patients received subtotal gastrectomy and 14 received total gastrectomy accompanied by D1 (26 patients) or D2 (32 patients) lymphadenectomy. • Severe postoperative complications occurred in 58.6% of patients and occurred more frequently in CTP-B ($p = 0.03$) or if underwent D2 lymphadenectomy ($p = 0.015$). • Postoperative mortality occurred more frequently in CTP-B patients ($p = 0.033$). • 100% mortality was experienced in CTP-C.
Esophageal surgery	Retrospective analysis of esophageal cancer database identifying 3445 esophageal cancer patients, 73 with cirrhosis undergoing esophagectomy	[124]	• Cirrhosis patients experiencing more respiratory events ($p = 0.013$), infections ($p = 0.005$) and more severe anastomotic complications ($p = 0.046$) • MELD >9 associated with reduced 5-year survival ($p = 0.004$) and MELD score or 9 or lower showed outcomes similar to that of non-cirrhotic patients.
	Retrospective, propensity-matched study (Liver cirrhosis and no liver cirrhosis patients 50 and 100, respectively)	[88]	• Patients with cirrhosis experience higher rates of postoperative complications with postoperative pneumonia (22 vs. 9%, $p = 0.027$), pleural effusion (38 vs. 20%, $p = 0.018$), chylothorax (10 vs. 1%, $p = 0.016$) and had longer intensive care unit stay (mean: 6.10 vs. 2.58 days, $p = 0.002$) compared with controls
	Meta-analysis of 12 observational studies including 1938 patients (238 with cirrhosis)	[123]	• 30-day mortality higher in cirrhosis (OR 3.04, 95% CI 1.71–5.39) although this was not observed at 90-days (OR 2.84, 95% CI 0.94–8.93) or long-term (mean 24 month follow up) (OR 1.70, 95% CI 0.53–5.51). • Anastomotic leak occurred at a higher rate in patients with cirrhosis (OR 2.81, 95% CI 1.05–7.49). • CTP-A patients were associated with a significantly lower 30-day mortality compared with CTP-B (OR 0.14, 95% CI 0.04–0.54).
Bariatric surgery	Retrospective, 1:1 propensity-matched case control study of 957 patients with and without cirrhosis undergoing bariatric surgery.	[126]	• No difference in mortality (OR 1.73; $p = 0.33$) • Comparing decompensated ($n = 117$) and compensated ($n = 957$) cirrhosis, increased mortality was observed (7.69 vs. 0.94%, $p < 0.001$).
	Retrospective study of 20,096 chronic liver disease (using ICD coding) patients undergoing bariatric surgery	[89]	• Chronic liver disease patients experience high inpatient mortality (adjusted OR 1.47, 95% CI 1.24–1.73) but significantly less surgical revision, improper wound healing and postoperative infection following bariatric surgery compared with non-matched controls without liver disease.
	Systematic review and meta-analysis including 18 studies and 471 patients with obesity and liver cirrhosis undergoing bariatric surgery (mainly LSG and RYGB)	[90]	• 397/423 patients with defined CTP class were CTP-A • The weighted pooled proportion of overall complications was 22.14% and all-cause 90-day mortality was 0%. • Significant increase in postoperative complications ($p < 0.001$) but no difference in all-cause 90-day mortality ($p = 0.1165$) compared to non-cirrhotic controls.
Appendectomy	Meta-analysis of 923 patients with cirrhosis undergoing appendectomy	[91]	• Pooled mortality (inpatient and 30-day) was 1.76 vs 0.37% in cirrhotic and non-cirrhotic patients respectively (OR 9.92, 95% CI 4.67 to 21.06). • Laparoscopic appendectomy appeared safer with a mortality of 0.5% in comparison to open appendectomy with mortality of 3.2%).

(*Continued*)

Table 3. (Continued).

Type of Surgery	Type and details of study	Ref	Salient findings
Umbilical hernia	Systematic review of 13 prospective, 10 retrospective studies including 3229 patients	[107]	• Evidence was graded as very low quality for all outcomes. • Mortality quoted to be 6% (n = 191). • Patients with cirrhosis are eight times more like to die after surgery compared with patients without cirrhosis
	Randomized controlled trial (CRUCIAL trial) with 2 years of follow up recruiting 34 patients compensated cirrhosis.	[92]	• Randomized controlled trial (16 – elective repair, 18 – conservative management) • After 24 months there was no significant difference in morbidity (either complications of repair or the hernia itself) – Eight (50%) patients assigned to elective repair compared with 14 (77.8%) assigned to conservative treatment.
	Retrospective analysis of 1421 cases, 127(8.9%) cirrhotics	[108]	• Elective repair in cirrhotics was associated with similar outcomes in patients without cirrhosis. • Cirrhotics were more likely to undergo emergency repair (26% vs 4.8%; $p < 0.0001$), concomitant bowel resection (8.8% vs 0.8%; $p < 0.0001$), return to theater (7.9% vs 2.5%, $p = 0.0006$) and increased length of stay (4 vs 2 days; $p = 0.01$)
	Prospective study	[93]	• In total, 30 patients (6 CTP-A, 19 CTP-B and 5 CTP-C) with a median MELD score was 12 (IQR 8–16). • Elective umbilical hernia repair is safe with no post-operative intensive care admissions and only 2 of 30 patients died; neither of deaths were attributable to umbilical hernia repair.
	Nationwide retrospective cohort study 32,033 patients (30,836 non-cirrhotic and 1197 cirrhotics)	[94]	• Cirrhotics had a higher age distribution ($P < 0.0001$) underwent ICU admission more commonly (15.9% vs. 6%; $P < 0.0001$), longer length of stay (5.4 vs. 3.7 days), and higher morbidity (16.5% vs. 13.8%; $P = 0.008$), and mortality (2.5% vs. 0.2%; $P < 0.0001$) compared to non-cirrhotics. • Mortality was 7-fold higher in patients undergoing emergency repair (3.8% vs 0.5%; $P < 0.0001$)
	Prospective cohort study 246 patients with cirrhosis	[95]	• A total of 246 patients (57 underwent elective hernia repair and 189 who opted for 'wait and see' approach) were including in the study. Of the latter, 43 (22.7%) patients required emergency hernia repair due to complications such as ascites leakage due to skin rupture in hernia site (n = 28), incarceration (n = 7), small bowel strangulation (n = 5), and extensive skin necrosis or ulceration (n = 3). • MELD score>11 (HR 7.8; $p = 0.011$) and emergency hernia repair (HR 5.35; $p = 0.005$) were identified as risk factors for 30-day mortality.
Inguinal hernia	Retrospective study over 10-year period 780 patients having inguinal hernia repair. 129 patients with cirrhosis	[109]	• Morbidity (9.1–16.7%) was not significantly higher than patients without cirrhosis • Overall mortality ranging from <1-2.7% • Cumulative recurrence rates were not significantly different between cirrhosis and non-cirrhosis group ($p = 0.87$)
	Prospective evaluation of QOL by questionnaire including 32 patients.	[110]	• Inguinal hernioplasty in patients with cirrhosis was a safe procedure and improved quality of life.
Cardiovascular	Systematic review (19 studies) of short-term and overall mortality in patients with liver cirrhosis classified by CTP score undergoing cardiac surgery.	[79]	• CTP score reporting 30-day mortality noted to be 9%, 37% and 52% for CTP class A, B and C respectively. • One-year mortality was reported to be 27.2%, 66.2% and 78.9% respectively per Child class, respectively.
	Nationwide, population-based study from Taiwan between 1997–2001 including 1030 Liver patients and 1040 matched controls without LC.	[96]	• 1 year survival was 68 vs. 81% ($p < 0.001$) in cirrhosis for CABG and valve surgery
	Retrospective study between 1989–2003 of 18 patients with cirrhosis undergoing cardiac operations	[131]	• Overall postoperative mortality – 17% • CTP-A – no increased mortality when undergoing elective cardiac surgery • CTP-B and C – mortality rate 50–100% after cardiopulmonary bypass
	Retrospective, propensity-matched, case-control study of 1197 patients with liver dysfunction undergoing cardiac surgery (n = 755 CABG, n = 442 valve surgery)	[129]	• Increased mortality was observed for both CABG (OR 5.19, $p < 0.0001$) and valve surgery (OR 7.49, $p < 0.0001$) in comparison to controls. without liver cirrhosis. • Higher rates of complications (bleeding, respiratory, renal, infections) in patients with liver dysfunction and CABG.

(*Continued*)

Table 3. (Continued).

Type of Surgery	Type and details of study	Ref	Salient findings
	Meta-analysis (22 studies, 939 patients -CABG, valve surgery and cardiopulmonary bypass)	[132]	• Nineteen of the studies evaluated mortality with 354 patients in CTP-A, 205 in CTP-Band 33 in CTP-C. • Mean mortality rates were 20.58%, 43.58% and 56.48% for patients in class A, B and C respectively ($p < 0.01$ for comparisons between each class). • Major postoperative morbidity with rates up to 60%, 100% and 100% for CTP-A, B and C, respectively.
	Retrospective, propensity-matched study between 1998–2011 identifying 2769 patients with cirrhosis undergoing surgical aortic valve replacement	[97]	• Aortic valve surgery in-hospital mortality was 16 vs. 5% in controls (OR 3.6, $p < 0.0001$) and greater rate of complications (55% vs 45% for controls). • Risk factors of mortality included congestive cardiac failure, fluid and electrolyte disturbances, pulmonary circulation disorder and weight loss.
AAA repair	Retrospective, single center study between 2001–2006 identifying 24 patients with Liver cirrhosis undergoing elective open repair of infrarenal AAA.	[138]	• CTP-B and MELD≥10 – associated with reduced survival • Significant difference in 2-year survival (77.4% vs 97.8%; $p = 0.03$)
Elective hip and knee arthroplasty	Retrospective analysis of outcomes of primary total hip arthroplasty and total knee arthroplasty in cirrhotic patients.	[139]	• Complication rates, decompensation and/or death in up to 80% of cirrhosis patients after emergency THA due to a fracture. • Primary THA or TKA can be safely performed electively in CTP-A and CTP-B patients
	Retrospective study identifying 18,129 cirrhotic patients undergoing TKA and compared to control of 1,716,439 TKA patients.	[140]	• Cirrhosis was associated with increased rate of major complications (3.7% v 2.3%; OR 1.23, 95% CI: 1.13–1.33; $p < 0.001$). Higher risk of periprosthetic joint infection compared to controls, minor medical complications (13.5% vs 7.4%; OR 1.52, 95% CI 1.45–1.59, $p < .001$), transfusion (2.8% vs 1.4%; OR 1.66, 95% CI 1.51–1.81, $p < .001$), encephalopathy (1.0% vs 0.2%; OR 3.00, 95% CI 2.55–3.51, $p < .001$), DIC (< .001) within 90 days • Alcohol and viral etiologies were associated with increased rate of major complications.
	Systematic review identifying eight studies on 28,514 THAs	[141]	• Increased post-operative infection rates of 0.5% ($p < 0.001$) and perioperative mortality of 4.1% ($p < 0.001$) compared to non-cirrhotic controls. • Frequent need for revision surgery at 4% ($p < 0.001$). • Etiology of need for revision surgery included periprosthetic infection (70%), aseptic loosening (13%), instability (13%), periprosthetic fracture (2%) and linear wear (2%).

Abbreviations: AAA: abdominal aortic aneurysm; CABG: coronary artery bypass grafting; CTP: Child-Turcotte-Pugh; HR: Hazard ratio; IQR: interquartile range; LC: laparoscopic cholecystectomy; MELD: model for end stage liver disease OC: open cholecystectomy; OR: odds ratio; RR: relative risk; THA: total hip arthroplasty; TKA: total knee arthroplasty.

decompensation [84]. Table 3 summarizes mortality and morbidity data alongside type of surgery from various studies.

6.1. Emergency surgery

In patients with normal liver function, emergency surgery is higher risk than elective procedures with a greater rate of postoperative morbidity and mortality [4]. It has been demonstrated consistently that this rate is elevated in the setting of chronic liver disease with an estimated 4–10-fold higher postoperative mortality [59,61,62,78,98–100]. In abdominal surgery, 8193 patients with cirrhosis were compared to noncirrhotic controls to identify risk factors for postoperative mortality [98]. Compared with patients without cirrhosis, patients with cirrhosis had a 5-fold higher 30-day mortality for emergency surgery (adjusted OR 5.11, 95% CI 3.08–8.47). For patients with cirrhosis, postoperative mortality was almost 6-fold higher for emergency surgery compared to elective procedures (17.2 vs. 2.1%, adjusted OR 5.82, 95% CI 4.66–7.27). In a retrospective study from Demetriades et al [99] of a level 1 trauma registry, overall hospital mortality for patients with cirrhosis undergoing laparotomy after trauma was significantly higher than matched controls (45 vs. 24% $p = 0.021$). Recently Adiamah et al [100] reviewed 248 patients with cirrhosis (70% compensated) as part of a 36,380 patient cohort undergoing colectomy. Of the patients with cirrhosis 111 underwent colectomy in the emergency setting. For compensated cirrhosis, there was a significant increase in 90-day mortality (adjusted HR 2.57, 95% CI 1.75–3.76) which was not observed in the elective group. In a retrospective study of 138 patients with cirrhosis undergoing abdominal surgery (40% various GI tract procedures, 28% hernia repair, 15% perforation, 9% bleeding and 8% cholecystectomy), mortality was 9% and 47% for elective and emergency respectively ($p < 0.0001$) [75].

6.2. Laparoscopic vs. open surgery

Cirrhosis was initially seen as a relative contraindication to laparoscopic surgery due to theoretical risk of rupturing abdominal wall varices during port placement, technical ability to control massive hemorrhage and effects of pneumoperitoneum on compromising hepatic blood flow [4]. As minimally invasive surgical techniques have improved, several studies have since challenged these views and demonstrated safety and benefits with favorable outcomes for laparoscopic surgery in a range of procedures [101–105]. Laparoscopic techniques (irrespective of cirrhosis) have established benefits on reduced pain, blood loss, complications related to large wounds, rehabilitation and length of stay for patients. Access to the abdomen, particularly for open surgery, as opposed to minimally invasive surgery may be challenging when shunts are present in the anterior abdominal wall. In the context of cirrhosis, laparoscopic cholecystectomy is the most common procedure examined. In a meta-analysis of randomized controlled trials comparing laparoscopic and open cholecystectomy ($n = 234$ patients (97% CTP-A or B)) there were no postoperative deaths and laparoscopic approach was associated with fewer postoperative complications ($p = 0.03$), shorter hospital stay ($p < 0.001$) and quicker resumption of normal diet ($p < 0.001$) [103]. Laparoscopic inguinal hernia repair can be performed safely [104] and there are also favorable outcomes when comparing laparoscopic to open appendectomy [105]. In more complex procedures, the laparoscopic approach remains a safe option. Sixty-two patients underwent laparoscopic radical resection for colon cancer (majority CTP-A) with no difference in postoperative morbidity ($p = 0.133$) and no difference in 5-year overall or disease-free survival ($p = 0.269$ and $p = 0.695$ respectively) compared to open approach [106]. There was significantly reduced bleeding ($p = 0.015$), shorter time to first oral intake ($p = 0.033$) and faster time to first flatus ($p = 0.002$) in the laparoscopic group. This did not, however, translate into reduced operating time ($p = 0.856$) or length of stay ($p = 0.17$).

6.3. Hernia repair

The incidence of abdominal wall hernia in patients with cirrhosis is 16%, which rises to 24% in patients with ascites [70]. Half of these are umbilical and 60% of patients experience recurrence following repair [70]. Mortality is quoted to be around 6% for umbilical hernia repair [107]. Elective hernia repair in cirrhotic patients is considered safe and is associated with similar outcomes in patients without cirrhosis [108]. Cirrhotic patients are more likely to undergo emergency repair, concomitant bowel resection and return to theater [108]. Whilst a conservative management strategy may appear favorable, poor quality of life and risks such as strangulation, rupture of overlying skin and the added risk of emergency surgery may promote addressing hernias surgically where deemed appropriate. Inguinal hernia repair is generally well tolerated in patients with compensated cirrhosis [109,110].

The timing of intervention for a patient with an abdominal hernia should be assessed on a case-by-case basis determined by severity of liver disease (per risk scores), patient preference, symptomology and whether patient is a transplant candidate. If a patient is a candidate for liver transplantation, repair of umbilical hernia is usually deferred till time of transplantation. Several studies have looked at the commonly used scoring systems to predict mortality following umbilical hernia repair with reasonable correlation for MELD (MELD >15 predictive of 30-day mortality, $p < 0.001$) [81]; ASA+CTP (ASA Risk Ratio (RR) 3.2, $p = 0.038$; CTP RR 2.4, $p = 0.025$) [75]; and MELD-Na (30-day mortality logistic regression area under curve 0.82) [111]. Similar to other procedures, MELD scores >15 were associated with significantly higher mortality (11.1 vs. 1.3%, $p = 0.002$) [81].

6.4. Cholecystectomy

The prevalence of gallstone disease in patients with cirrhosis ranges between 17–28% [70]. Historically, laparoscopic cholecystectomy in the context of liver cirrhosis was regarded as a relative contraindication because of bleeding complications and subsequent liver failure [112]. With improvement in surgical techniques laparoscopic cholecystectomy is now considered a safe management option and, in comparison to open cholecystectomy, is associated with less operative blood loss, lower operative times, and shorter length of stay in a meta-analysis [101] (Table 3). A randomized controlled trial of 110 cirrhotic patients with symptomatic gallstones were randomized (1:1) to either open or laparoscopic cholecystectomy by El-Awadi et al [102]. laparoscopic cholecystectomy was associated with lower morbidity, shorter operative times, earlier feeding resumption, lower need for blood transfusion and reduced hospital stay. Despite cholecystectomy being regarded as a safe procedure, there are a higher incidence of complications compared with non-cirrhotic controls [113]. For surgeons undertaking the procedure, consideration should be given to liver retraction, adequate exposure of the hilum, adhesions surrounding gallbladder and hemostasis. One group has advocated the use of a modified subtotal cholecystectomy in patients with symptomatic gallstones [114]. If a patient is being considered for liver transplantation, elective cholecystectomy should be delayed till transplant [52]. The CTP classification demonstrates good correlation and outcomes following laparoscopic cholecystectomy. CTP-A and CTP-B patients experience 5–10% morbidity and 0.1% mortality respectively [114,115]. Two hundred sixty-five patients with CTP-A/B cirrhosis underwent the procedure in a single center and experienced no mortality [114]. A meta-analysis was unable to draw conclusions regarding CTP-C patients due to insufficient data [101].

6.5. Colorectal

Colorectal surgery has unique risks in patients with cirrhosis. The advent of colonic surgery in patients with cirrhosis is often seen due to links of primary sclerosing cholangitis and inflammatory bowel disease. Risks include anastomotic and stoma-related issues [116] and extra-intestinal complications in patients with cirrhosis and portal hypertension. Altered hemodynamics, ascites and coagulopathy complicate matters and heighten the risks involved. Presence of ascites can lead to increased pulmonary and wound complications including dehiscence [5]. A meta-analysis ($n = 2485$, 5 studies) concluded cirrhotic patients experiencing more major complications, higher rates of return to theater, higher short-term mortality and shorter survival [117] (Table 3). Presence of portal hypertension further heightens the risk of complications and death [77,78,118]. Due to improvements in surgical techniques, perioperative care and cancer management, a more recent study by Lee et al. of 161 patients reported mortality to be 3.1% [119].

6.6. Upper gastrointestinal/bariatric

Upper gastrointestinal and bariatric surgery has variable outcomes in the setting of cirrhosis. Emergency surgery for complicated peptic ulcer disease (bleeding or perforation) is associated with a high mortality (23–64%) with a linear risk from presence of ascites and CTP [120]. In gastric cancer operations, a study in Japan demonstrated that surgical management in cirrhotic patients carried a morbidity 25.6% and mortality 10.3% [121]. Surgery carries acceptable risk for CTP-A and B patients but radical gastrectomy is fatal in CTP-C with mortality reported to be 100% [122]. Similar experiences in outcomes have been noted following esophagectomy in liver cirrhosis patients experiencing higher rates of complications. CTP-A patients have significantly lower mortality in comparison to CTP-B and CTP-C which remains a contraindication to esophagectomy [123]. As per MELD, a score >9 was associated with significantly worse 5-year survival ($p = 0.004$) and a score ≤9 was associated with similar outcomes to non-cirrhotic controls [124]. Nonalcoholic steatohepatitis (NASH) is rapidly becoming one of the most common cause for liver transplantation [125]. Given the link between NASH and obesity, there is increasing experience in bariatric surgical procedures for patients with cirrhosis including Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG) and gastric banding. In compensated patients without CSPH, bariatric surgery is generally considered safe to be undertaken in high volume centers, however surgical risk may be higher than that of the general population [52,126–128].

6.7. Cardiac/vascular

Cardiac surgery is often lifesaving and should always be considered on a case-by-case basis. Unique risks are posed by cardiac surgery including cardio-pulmonary bypass, hyperfibrinolysis, platelet activation and need for anticoagulation. In addition, there is increased rate of infectious, respiratory and renal complications alongside longer hospital stay and mortality. Perioperative management of coagulation, even in the presence of cirrhosis, can be guided by use of thromboelastography (TEG) [52,129]. Studies have observed increased mortality and morbidity in patients with cirrhosis undergoing cardiac surgery (Table 3) [130]. Evidence supports use of CTP or MELD scores to risk stratify these patient demonstrating advanced disease being accompanied by an increase in morbidity and mortality [79,131–133]. In patients undergoing cardiopulmonary bypass, mortality was reported to be 0%, 50% and 100% for CTP-A, B and C respectively [131]. A systematic review by Jacob et al [79] classified mortality by CTP score reporting 30-day mortality noted to be 9%, 37% and 52% for CTP class A, B and C respectively. One-year mortality was reported to be 27.2%, 66.2% and 78.9% respectively per Child class. It was concluded that short-term mortality is considerably increased in patient CTP-B and CTP-C cirrhosis, but overall mortality is significantly higher in all classes. Studies assessing MELD as a surgical risk prediction model have reported significantly higher mortality with increasing MELD score [133,134]. In general MELD >13.5 and CTP >7 are considered contraindications to CABG [135,136]. Surgical aortic valve replacement (SAVR) is associated with high mortality, hence, transcatheter aortic valve replacement (TAVR) has been explored as alternative management [137].

Studies examining patients with cirrhosis undergoing vascular procedures is limited. A retrospective analysis of 24 elective cirrhotic patients undergoing AAA repair for infrarenal aortic aneurysms, compared to matched controls showed equal 30-day mortality and complications, but 2-year survival differed significantly (77.4 vs. 97.8%, $p = 0.03$). In this study, a MELD score >10 corresponded to a higher mortality rate [138].

6.8. Orthopedic

There is limited data regarding orthopedic procedures in patients with cirrhosis, although adverse outcomes are reported for patients undergoing knee and hip arthroplasty [139–144]. Significant adverse outcomes are noted compared with matched controls and this is particularly evident in patients undergoing emergency arthroplasty following fracture [139]. In a systematic review of eight studies, including 28,514 total hip arthroplasties (THA) in patients with cirrhosis, postoperative infection rate was 0.5% (range 0.3–15.4%) compared with 0.15% in controls ($p < 0.001$) [141]. In the same review, five studies assessed mortality ($n = 1048$), observing a mean perioperative mortality rate of 4.1% compared with 0.2% in controls ($p < 0.001$). There is evidence to suggest that more advanced stages of liver cirrhosis are associated with less favorable outcomes [139,142,143]. There is also evidence to suggest that arthroplasty in patients with cirrhosis is associated with a greater likelihood in postoperative transfer to intensive care, a medical unit or readmission within 30 days [145].

7. Conclusion

With increasing prevalence of liver disease coupled with higher life expectancy due to improved treatment modalities, the numbers of patients with liver cirrhosis requiring surgery will continue to rise. The associated postoperative morbidity and mortality in these patients may be high. Utilization of prognostic scores allows time for preoperative planning and assessment of this 'at risk' cohort of patients along with optimization where possible. CTP and MELD as risk scores are often used independently to determine mortality risk but can be used complementary in the assessment of surgical risk for cirrhotic patients to translate liver disease severity to quantify a patient's surgical mortality predictions. Due to complexities highlighted in the review, there is a need for precision medicine delivering personalized care directed at each individual – pre-, peri- and postoperatively. Portal hypertension underpins principal surgical complications of patients with liver cirrhosis and is associated with increasing mortality and morbidity, especially in an emergency surgical setting. With surgery providing complex issues in patients with liver cirrhosis, high-risk patients are best managed in an MDT environment with surgeons, anesthetists and physicians experienced in treating liver disease.

8. Expert opinion

Liver disease is on a rise worldwide with patients living longer and likely to require surgery more often. With improvement in understanding and management of cirrhosis, enhanced pre-, intra- and postoperative care have expanded the surgical eligibility of patients with chronic liver disease. In 2022, these patients present within the everyday scope of a non-hepatic surgeon. The risk of surgery in this high acuity cohort is heightened resulting in increased morbidity and mortality. In compensated cirrhosis, patients with portal hypertension may exhibit a state of rebalanced homeostasis. For such patients, the physiological stresses posed by surgical intervention may risk precipitating hepatic decompensation from a position of equipoise. Perioperative changes in hepatic blood flow as a result of vasodilatory effects of anesthetic drugs and fluid losses during surgical trauma can disrupt this state. This is exacerbated in the setting of emergency surgery. Deranged hemostasis, altered drug pharmacokinetics and neurohormonal mediator imbalance, exacerbating sodium and fluid retention complicate perioperative surgical management. Malnutrition and progressive sarcopenia may compromise postoperative wound healing and rehabilitation.

Comprehensive preoperative assessment is fundamental to identifying patients at risk from higher rates of complication during surgery. Emergent nature of surgery, age and ASA class, severity of liver disease and type of surgery are significant contributing factors that can be identified in advance of most surgery, however most unable to be ameliorated. Literature relating to surgical outcomes is often single-center, heterogeneous, lacking controls and are retrospective in nature. Several contraindications to elective surgery exist, varying by institution, including acute or fulminant liver failure, acute viral or alcoholic hepatitis and ASA class V. Hepatic resection followed by open abdominal surgery and operations breaching the thoracic cavity are considered high-risk and warrant multidisciplinary discussion between surgeons, anesthetists, radiologists and hepatologists. New and bespoke prognostic scoring systems such as VOCAL-PENN score aid informed decision making. HVPG remains the gold standard in assessing portal hypertension pre-surgery although its availability remains an issue confined to specialist centers. If is HVPG high there remains a paucity of large volumes trials exploring preemptive TIPSS to decompress portal hypertension. The role of established liver scoring systems remains. Elective surgery in CTP-C, ASA class IV and V, MELD>15, HVPG ≥20 mmHg should be deferred and alternative should be considered. In patients with CTP-B, ASA class III, MELD 10–15 and HVPG >16 mmHg, a multidisciplinary discussion should convene to formulate a bespoke optimization strategy and counsel patients (with use of prognostic scoring systems predicting mortality). Exploration of TIPSS and transplant candidacy can be made with help from MDT with a hepatologist. Finally, patients considered very high risk for surgery should be considered for palliative care. With surgery providing complex issues in patients with liver cirrhosis, high-risk patients are best managed in an MDT environment with surgeons, anesthetists, hepatologists, hematologists, dieticians and physiotherapists experienced in treating liver disease.

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