The burden of chronic liver disease continues to grow dramatically in the United States, driven primarily by chronic viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease. These conditions are associated with substantial morbidity and mortality, as confirmed by recent data from 2013 State of U.S. Health Report demonstrating that liver cirrhosis now represents the eighth leading cause of death in the U.S. with a 43% increase between 1990 and 2010, and corresponding increase in liver cancer-related mortality of 118% during this same period of observation.1 Liver cirrhosis additionally contributes to substantial cost and economic burden, an estimated $1.64 billion USD as of 2002,2 and an additional $2.8 billion USD from chronic hepatitis C infection as of 2004.3 Patients with chronic liver disease often undergo surgery for indications other than liver transplantation, and may face increased perioperative risk due both to surgical and anesthesia-related complications.4 An estimated 10% of patients with advanced liver disease require a surgical procedure other than liver transplantation in their final two years of life,5 and, furthermore, individuals with unrecognized chronic liver disease may also undergo surgery with cirrhosis diagnosed only intra-operatively based on macroscopic assessment.6 Preoperative screening for liver disease and assessment of surgical risk in patients with liver disease is essential to guiding patients in reaching treatment decisions with consideration of benefit and risk, and for optimizing pre-operative and post-operative management. In this lecture, we will review basic principles of pre-operative assessment of patients with chronic liver disease undergoing surgery, estimation of surgical mortality using the Child-Pugh-Turcotte (CPT) and Model for End-Stage Liver Disease (MELD) scores, and strategies to optimize pre-operative management.

Pre-operative Screening for Liver Disease

The primary objective of pre-operative screening is to identify undiagnosed chronic liver disease in otherwise asymptomatic individuals undergoing surgery. This requires a careful history and physical examination that will elicit clues that signal the need for further testing. As overt clinical symptoms may be lacking or are related directly to the indication for surgery (e.g., abdominal pain, jaundice, pruritus), thorough investigation of risk factors for liver disease is necessary, including alcohol consumption, use of potentially hepatotoxic medications or supplements, exposure to viral hepatitis (through intravenous or intranasal drugs, tattoos or body piercings, blood transfusions or exposure to blood products before 1992, high risk sexual contacts, etc.), and co-factors for fatty liver (e.g., obesity, diabetes mellitus type 2, hypertension, dyslipidemia). The family history should be queried to identify other family members with chronic liver disease or prior adverse reaction to anesthesia. The physical examination should include focused evaluation for signs of chronic liver disease, including scleral icterus, gynecomastia, palmar erythema, spider nevi, temporal wasting, ascites, and splenomegaly.

The role for routine laboratory screening for liver disease in asymptomatic individuals undergoing surgery remains controversial, and is not currently recommended. Routine evaluation of liver function tests including total bilirubin, alkaline phosphatase, AST, and ALT have not demonstrated predictive value in this context, and unlike the prothrombin time and serum albumin, do not reflect hepatic synthetic function. As such, directed liver testing should be reserved for individuals for whom there exists a clinical concern for liver disease. In context of recent recommendations by the U.S. Centers for Disease Control and Prevention (CDC) and U.S. Preventive Services Task Force (USPSTF) regarding screening for viral hepatitis, consideration may be given for screening for hepatitis B in asymptomatic individuals born in geographical regions with high endemicity,7 and for hepatitis C in asymptomatic individuals born between 1945-1965 or with other risk factors for transmission.8-10 Among individuals in whom abnormal liver enzymes or a new liver diagnosis is identified, surgery may require deferral until further examination of acuity and severity can be made, although most procedures can proceed as planned unless there is evidence for liver cirrhosis or portal hypertension.

Estimation of Surgical Risk

Although the literature is clear that patients with liver cirrhosis bear increased risk of complications and mortality when undergoing surgical operations, obtaining accurate preoperative risk estimates remains challenging. Current estimates of mortality risk in patients with liver disease undergoing surgical operations have been largely based on small, retrospective, single-center studies which are commonly limited by selection bias, and predominant inclusion of healthier Child-Turcotte-Pugh (CTP) Class A patients, and therefore are likely underpowered to provide more accurate estimates in patients with CTP Class B or C decompensated disease.

Increased surgical mortality in cirrhotic patients have been estimated at 11-25% overall versus 1.1% in non-cirrhotic patients, with traditional figures for 30-day mortality stratified...
Based on these early studies, conventional wisdom in the gastroenterology consultation for preoperative assessment in patients with liver disease has been to recommend elective surgery without reservation in patients with CTP-A cirrhosis or non-cirrhotic chronic liver disease, consideration for elective surgery with preoperative preparation in patients with CTP-B cirrhosis except in higher risk operations, and that surgery is contraindicated in patients with CTP-C cirrhosis.

More recent literature provide stronger guidance on surgical risk stratification based on major factors influencing clinical outcomes, including: type of surgery; acuity, nature, and severity of liver disease; surgical and anesthesia expertise; and quality of intensive care unit (ICU) care within a center experienced in the care of patients with liver disease.

The nature and acuity of liver disease appears to remain an important factor in predicting operative risk, and specifically in cases of acute or fulminant hepatitis, and acute alcoholic hepatitis, operative mortality rates have been prohibitively high, estimated at 10-13% and 55-100%, respectively. On this basis, elective surgery in this context should be contraindicated, and should be deferred until the acute hepatitis episode has resolved with clinical and histological improvement.

The severity of liver disease likely represents one of the most important contributors to operative risk, and is not adequately reflected in the standard American Society of Anesthesiologists (ASA) physical classification which is typically used for pre-operative risk assessment (Table 1).

Table 1: American Society of Anesthesiologists (ASA) Classification of Preoperative Risk 2010

<table>
<thead>
<tr>
<th>ASA Class</th>
<th>Systemic Disturbance</th>
<th>Mortality (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Healthy patient with no disease outside of the surgical process (a normal healthy patient)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate systemic disease caused by the surgical condition or by other pathological processes, medically well-controlled (a patient with mild systemic disease)</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>Severe disease process which limits activity but is not incapacitating (a patient with severe systemic disease)</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>Severe incapacitating disease process that is a constant threat to life (a patient with severe systemic disease that is a constant threat to life)</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Moribund patient not expected to survive 24 hours with or without an operation (a moribund patient who is not expected to survive without the operation)</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>Declared brain dead patient whose organs are being removed for donor purposes</td>
<td>n/a</td>
</tr>
<tr>
<td>E</td>
<td>Suffix to indicate emergency surgery for any class</td>
<td>Increased</td>
</tr>
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Table 2: Child-Turcotte-Pugh Score (CPT)

<table>
<thead>
<tr>
<th>Component</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
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<tr>
<td>Total bilirubin</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.5</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight-moderate</td>
<td>Tense</td>
</tr>
<tr>
<td>Class A (score 5-6)</td>
<td>Class B (score 7-9)</td>
<td>Class C (score 10-15)</td>
<td></td>
</tr>
</tbody>
</table>
The MELD score incorporates weighted scoring based on objective laboratory measures including total serum bilirubin, international normalized ratio (INR), and creatinine, and has been confirmed to provide accurate risk estimation for 30-day post-operative mortality. Early studies evaluating the predictive value of MELD in predicting nontransplant surgical mortality demonstrated significant differences in MELD in patients who survived or died within 30 days, with a corresponding rise in mortality of 1% below a MELD score of 20, and 2% for MELD scores 20 and above. Further studies confirmed the superiority of MELD over CPT score in evaluating operative risk, and reinforced a threshold of MELD score 14 or higher as a threshold for increased mortality risk in patients undergoing major abdominal surgery.

One of the largest studies evaluating post-operative mortality in cirrhotic patients by Teh et al. reviewed short and long-term survival in 772 patients with cirrhosis undergoing surgery and reaffirmed the predictive value of MELD score; 30 day mortality ranged from 5.7% in patients with low MELD (< 8) to greater than 50% in patients with the highest MELD > 20, with MELD remaining predictive of mortality at 90 days, one year, and long-term throughout the 20-year postoperative period.

The type of surgery performed represents a critical consideration in the preoperative assessment of risk in patients with liver disease. Although most studies evaluating operative mortality in cirrhotic patients have focused on major abdominal, hepatic, or cardiac surgeries, stratification of risk into low, moderate, and high risk groups may be useful in counseling patients and surgeons on the advisability of pursuing elective operations, and informing preoperative management. One proposed stratification by Millwala et al. is summarized in modified format in Table 4. In addition to emergency abdominal and trauma surgeries, which have been well-established as bearing significantly increased mortality risk, major cardiac and open abdominal surgeries, gastric resection, colectomy, and hepatic resection have been identified as high risk operations. A systematic review of 46 studies by de Goede et al. evaluated morbidity and mortality following non-hepatic surgery in patients with cirrhosis, and confirmed that emergency surgery, trauma surgery, and major abdominal (e.g., pancreatic) and cardiac surgeries correlated with the highest morbidity and mortality, whereas laparoscopic cholecystectomy and umbilical and inguinal hernia correction surgeries were associated with the lowest morbidity and mortality.

Major abdominal surgeries remain a high risk operation for patients with cirrhosis, but recent literature have provided stronger evidence for specific subgroups and variables which are more strongly associated with mortality risk. Prior studies identified risk factors for poor surgical outcomes, including emergency surgery, pre-operative hypoalbuminemia, prolonged prothrombin time, ascites, and GI bleeding, in addition to CTP and MELD scores, although more recent studies suggested a specific threshold of MELD > 14 was a stronger predictor of poor surgical outcome (death, liver transplant within 90 days, or hospitalization longer than 21 days) than CTP Class C. Furthermore, poor outcomes (25%) and death (17%) remained common despite specialized liver care, and anemia (hemoglobin levels < 10 g/dL) appeared to represent an independent negative prognostic marker, suggesting that corrective blood transfusion prior to abdominal surgery may be advisable. However, a more recent study evaluating 100 cirrhotic patients undergoing major abdominal surgery at a highly experienced liver transplant center in New York City suggested 30 day post-operative mortality appears to be quite low (7%), even in CTP-A (2%), CTP-B (12%), and CTP-C (12%) patients, although MELD score ≥ 15 was as-
associated with increased mortality (29%). This report additionally highlighted that serum albumin further stratified high MELD patients by risk, with higher mortality if albumin \( \leq 2.5 \text{ g/dL} \) (60%) than individuals with higher albumin \( > 2.5 \text{ g/dL} \) (14%); other independent risk factors on multivariate analysis included intraoperative blood transfusion, ASA score > 3, total bilirubin > 1.5 mg/dL, emergency surgery, presence of ascites, and blood loss > 150 mL. With specific consideration of cholecystectomy, emerging data confirm that laparoscopic approach is preferred over an open approach in patients with cirrhosis. Two independent meta-analyses which evaluated randomized controlled trials of at least level 2b Oxford Level of Evidence, and were performed according to PRISMA guidelines, concluded that laparoscopic cholecystectomy was associated with no post-operative deaths, fewer post-operative complications, faster return to normal diet, and decreased length of hospitalization among patients with CTP-A or CTP-B cirrhosis, although the differences in frequency of post-operative hepatic insufficiency did not reach statistical significance (7.7% laparoscopic vs. 18.1% open, p=NS).32-33

Major cardiac surgeries also present significant operative risk in patients with cirrhosis, believed secondary to exacerbation of severe cardiac alterations of diastolic and systolic function, impaired myocardial contractility, and electrical abnormalities such as QT prolongation, particularly in individuals undergoing cardiopulmonary bypass. Multiple studies have reported poor outcomes in patients with decompensated liver cirrhosis, including post-operative mortality rates of 0-25% in CTP-A patients, but unacceptably high rates of up to 80% in CTP-B patients, and up to 100% in CTP-C patients.34-38 A meta-analysis reported pooled estimates of post-operative mortality of 5.2%, 35.4%, and 70% in CTP-A, B, and C patients, respectively, and that MELD score > 13 represented a strong predictor.39 A recent study focusing on outcomes in cirrhotic patients undergoing major cardiac surgery requiring cardiopulmonary bypass concluded that patients with compensated cirrhosis (CTP < 8) had a 97% negative predictive value for mortality, and that their risk (4.6% mortality) was identical to a propensity score matched cohort of noncirrhotic patients, again confirming that CTP-A patients may proceed directly to surgery, whereas CTP-B individuals require individualized consideration for surgery.40 Individuals with CTP-C end-stage liver disease are contraindicated from elective cardiac surgery and consideration should be given for combined liver transplantation and cardiac surgery.41

**Preoperative Management**

Patients who are determined to have non-cirrhotic chronic liver disease or CTP-A cirrhosis without prior decompensation may proceed directly to elective surgery, whereas patients with CTP-B or CTP-C disease require careful consideration and individualized assessment of surgical risk. Risk stratification based on the elements outlined above should be pursued, and communicated clearly with the surgeon, anesthesiologist, and patient. Special efforts should be made in patients with hepatic decompensation to optimize liver care prior to elective surgery, with particular attention to the management of ascites, coagulopathy, infection, renal dysfunction, hepatic encephalopathy, GI bleeding, and malnutrition.

**Ascites**

Intraoperative ascites may worsen surgical outcomes due to abdominal wound dehiscence, abdominal wall herniation, or respiratory compromise, and therefore ascites should be aggressively treated pre-operatively with a combination of dietary sodium restriction (< 2 g/day), oral diuretics with furosemide and spironolactone with careful monitoring of electrolytes and renal function, as well as large volume therapeutic paracentesis as needed with albumin resuscitation.42-43 If paracentesis is performed, spontaneous bacterial peritonitis (SBP) should be excluded by peritoneal fluid analysis for which antibiotics may be indicated if ascitic polymorphonuclear neutrophil (PMN) count exceeds 250/mL. Although several small studies have suggested that pre-operative transjugular intrahepatic portosystemic shunt (TIPS) placement may improve outcomes in patients with refractory ascites, current evidence is inadequate to support recommendation of its routine use prior to elective surgery.44-45

**Coagulopathy**

Impairment of coagulation function is common in patients with cirrhosis, and likely stems from several factors including primary hepatic synthetic dysfunction in the production of clotting factors, as well as malnutrition and cholestasis contributing to vitamin K deficiency. Although a prolonged prothrombin time may be corrected by vitamin K or fresh frozen plasma (FFP) administration, fibrogen and von Willebrand factor-rich cryoprecipitate may be useful and is associated with significantly less fluid volume load when compared with FFP. In refractory cases, consideration may be given for the use of DDAVP, factor VIIa infusion, or plasma exchange, although the limited literature does not suggest decreased blood transfusion requirements using these strategies.46 Furthermore, platelet transfusions are frequently considered in cases of severe baseline thrombocytopenia with target platelet goals ranging from 50,000/mm3 to 100,000/mm3.

**Renal Dysfunction**

Patients with cirrhosis and portal hypertension are vulnerable to acute kidney injury in context of extreme splanchnic vasodilatation and associated renal hypoperfusion and renal vasoconstriction despite compensation by local renal vaso dilators, which may be exacerbated by volume depletion, systemic infections, nephrotoxins such as NSAIDs, gastrointestinal bleeding, or hepatorenal syndrome. Excess removal
of peritoneal fluid should be avoided by LVP and should be accompanied by corresponding albumin resuscitation.

Hepatic Encephalopathy
Portosystemic hepatic encephalopathy (HE) is a common complication of cirrhotic portal hypertension that is often precipitated by environmental triggers that result in covert subclinical, as well overt changes in mental status; these include volume depletion, infection, GI bleeding, medications (e.g., sedatives, narcotic analgesics), renal failure, etc. Management should be targeted at early detection and adequate medical therapy with lactulose with or without rifaximin, or alternatively older antibiotics such as neomycin or metronidazole. Although dietary protein restriction has been used in some patients to reduce ammonia load in patients with chronic HE, this is not supported by evidence and should be avoided to prevent worsening of baseline malnutrition frequently seen in patients with cirrhosis.

Conclusion
Elective surgeries are commonly indicated in patients with cirrhosis, who face increased risk of morbidity and mortality. Preoperative screening for liver disease, careful history and physical examination, as well as an individualized risk stratification using CTP and MELD score based on type of surgery and acuity and severity of liver disease may help guide surgeons and consultants in providing patients with accurate estimates of operative risk. Whereas most surgeries may be performed without reservation in patients with non-cirrhotic chronic liver disease or compensated CTP-A cirrhosis, elective surgeries may require closer examination based on individual risk factors among patients with CTP-B or CTP-C decompensated cirrhosis in whom preoperative management steps to optimize liver status may help optimize perioperative outcomes. Further investigation is needed to clarify many ongoing clinical questions and deficits in evidence to guide management for this clinically important issue.

REFERENCES


