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Perioperative Risk Assessment and Management of Cirrhotic Patients

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Abstract

Liver cirrhosis is an important risk factor for morbidity and mortality in any type of surgical procedure. For these patients, a distinct and tailored patient optimization approach prior to surgery is required in order to best risk mitigate towards avoiding decompensation and related complications, especially with the chronicity of this disease. This review is to enhance understanding of surgical risks in these patients in selecting patients for elective surgery, or managing those following emergency surgery.

Keywords: Liver cirrhosis; Surgery; Risk assessment; Risk evaluation; Risk management

Introduction

Surgery is common in patients with chronic advanced liver disease, particularly in the final 2 years of life [1]. Despite the high prevalence of liver cirrhosis (LC) and the related complications, which may have significant effect on surgical morbidity and mortality, there exists a paucity of current literature as to how best assess these patients and direct best practice strategies for risk mitigation.

This review will focus on patient assessment and management of cirrhotic patients in the perioperative period to best guide clinicians who deal with these complicated patients.

Epidemiology

In 2009, the Centers for Disease Control in the United States estimated cirrhosis/chronic liver failure was the 12th overall leading cause of death and 5th between the ages of 45-54 [2]. Total ICU costs in a 2012 British study [3] averaged 14,000 Euros with an average 12 day length of stay. Using data from the National Health and Nutrition Examination Survey 1999-2010, LC prevalence in the general U.S. population was 0.27%, or 633,323 adults, of whom 69% were unaware of the diagnosis. A bimodal age distribution emerged, peaking in the fourth/fifth decade and after 75, with a higher prevalence in Non-Hispanic Blacks and Mexican Americans, patients with <12th grade education level, and those living below the poverty level. Of note, with the homeless, illegal immigrants, or incarcerated not included, the authors concluded the prevalence was underestimated [2].

Etiology

The etiology of LC ranges widely from hereditary conditions to infective agents, with Non-Alcoholic Fatty Liver Disease (NAFLD) as the fastest growing cause (Figure 1). Undiagnosed LC incidence is 6-34% in asymptomatic patients with abnormal liver function tests (LFTs) [1], with 9.8% of adults having increased LFTs [4]. In the PCP setting NAFLD was the most common cause (26.4%) followed by alcohol (25.3%), with 7.6% achieving advanced liver fibrosis scoring at follow-up [5].

Hepatitis B and C viruses (HBV/HCV) can cause chronic viral hepatitis, possibly culminating in LC and hepatocellular carcinoma (HCC). HBV is a DNA virus with increased incidence in sub-Saharan Africa and Asia [6], while HCV is a RNA virus that chronically infects 80% of patients and further causes LC in 15% [7].

Alcoholic liver disease, unique due to complete prevention with hepatotoxin abstinence, globally results in 3.8% of deaths [8] and ranges from steatosis, LC, and HCC [9]. Non-cirrhotic liver damage and LC risk threshold is 30 g per day, increases with daily ingestion, non-mealtime alcohol intake, and multiple alcohol types [10]. Not to mention the withdrawal complications during the perioperative period [11].

LC signs can appear early or several years after cessation [6]. NAFLD, increasing in an almost parallel fashion with the increasing prevalence of obesity, has doubled between 1980 and 2014 [12]. Globally in 2014, 15% of women and 11% of men were considered obese (BMI >30 kg/m^2) [12].

NAFLD is thought to occur when too much fat is within the liver; using liver biopsy, the fat density correlates with steatosis classification: 5-33% (light), 34-66% (moderate), and >66% (severe).

NAFLD can progress to Non-Alcoholic Steatohepatitis (NASH), when fat deposits cause injury and NAFLD progresses to NASH, with 20% of NASH developing fibrosis and LC [13]; however, newer studies conclude the two as different conditions with separate processes [14].

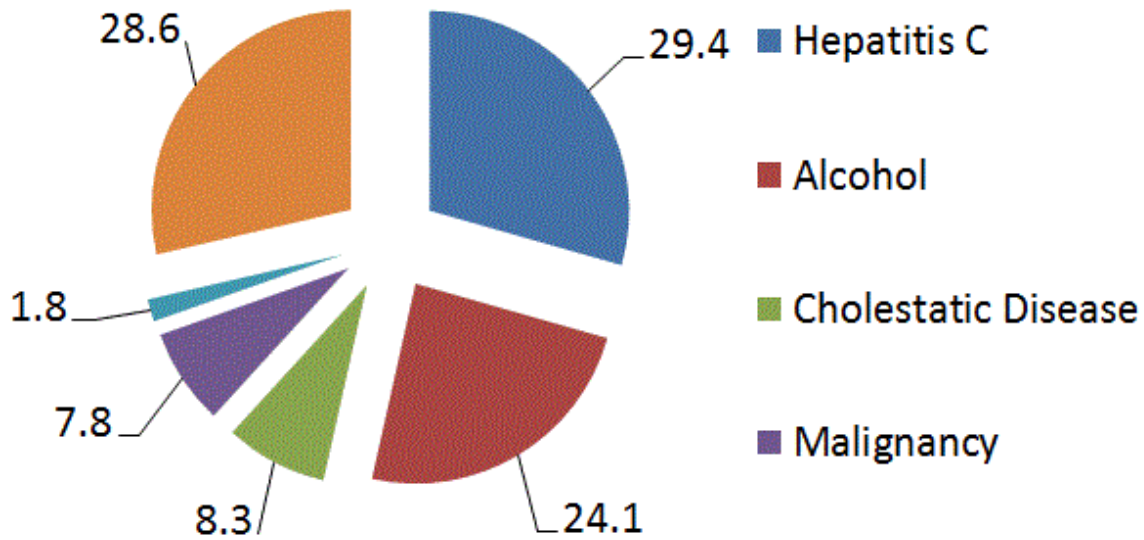

Figure 1: 2013 OPTN/SRTS Annual Liver Transplant Statistics on the Etiology of Cirrhosis (%). Cholestatic Disease includes Primary Biliary Sclerosis and Primary Sclerosing Cholangitis; other/unknown category includes NAFLD [102n].

Pathophysiology and Management

Immunological and hematological

LC increases the risk for systemic inflammation and infection, especially if decompensated (Table 1) [15]. This is related to translocation of bacterial products from the intestinal lumen to systemic circulation [15,16]. The liver regulates immune system homeostasis through blood-borne pathogen surveillance via C3b receptors and soluble immune response molecule synthesis [17]. Systemic inflammation is due to persistent immune cell stimulation, pathogen or damage-associated molecular patterns (P/DAMPs) from a leaky gut and damaged liver, as well as increased pro-inflammatory cytokines and upregulated cell activation markers [18,19].

Additionally, immunodeficiency results from local hepatic surveillance and cell function damage and reduced protein synthesis [17]. LC leads to damage of the hepatic reticulo-endothelial system leads to portal-systemic shunting, damage to Kupffer cells, and sinusoidal capillarization [19], resulting in decreased pathogen clearing [17]. Hepatic protein synthesis defects lead to decreased complement, soluble recognition receptors, and acute phase proteins, resulting in decreased opsonization, impaired innate immunity, vaccine response, and antigen T-cell dependent response [17-19].

Organ System and Cirrhosis Effects	Potential Management Options
Immunology/Hematology	
Systemic Inflammation and Immunodeficiency [15,17-19] Persistent immune cell stimulation and ↑ pro-inflammatory cytokines and cell activation markers Translocation of bacterial products by across epithelium and M-cells by transcytosis and active dendritic sampling Destruction of local hepatic surveillance → ↓ pathogen clearance ↓ liver synthesis of soluble proteins including complement, receptors, and acute phase proteins → ↓ innate immunity and vaccine response	Preop steroid use may ↓IL-6 and Bilirubin, but mortality effects are questionable [158] ABX treatment for infections (e.g. SBP) [48,73] IV 3rd generation cephalosporin (ceftriaxone/cefotaxime 2 g q8) IV or po fluoroquinolone (norfloxacin/ofloxacin 400 mg q12) SBP prophylaxis for 7d if: [73] Upper GI bleed Ascitic fluid protein <1.5 g/dL Impaired renal/hepatic function
Thrombocytopenia [20-22] Not due to hypersplenism from PHTN ↓thrombopoietin release by liver Bone marrow suppression ↑ destruction ↑ anti-PLT-Ab with HCV-induced LC	Platelet transfusion if <100,000 [159] Interventional partial splenic embolization Surgical splenectomy DDAVP is not effective in increasing functional vWF [23]

Coagulopathy: Antihemostatic Drivers [25,26,30] ↓ PLT, fibrinogen, factors II, V, VII, IX, X, XI, thrombin-activatable fibrinolysis inhibitor, and plasmin inhibitor ↑ t-PA Keep in mind effects of PHTN, endothelial dysfunction, bacterial infection, and renal failure as causes	Vit. K 1-5 mg po depending on bleed Blood products: [160] RBC transfusion Cryoprecipitate >> FFP Depends on volume status Maintain Fibrinogen >120
Coagulopathy: Prohemostatic Drivers [25,29,30] ↑ levels of vWF, factor VIII, plasminogen activating factor inhibitor ↓ ADAMTS-13, antithrombin, protein-C, plasminogen Thrombomodulin resistance PVT allows chronic portosystemic collateral development → decreased risk for variceal bleeding and PHTN	Anticoagulation [161] Bleeding risk is not dependent on anticoagulation, rather organ dysfunction [26] PVT Recanalization methods [162] LMWH ~ 33-45% success 1.0 mg/kg q12 [163] Vit. K antagonists ~ 15-35% success Transjugular Intrahepatic Portosystemic Shunting (TIPS) [161] Splenic approach →? ↑LT candidacy [98,99]
Cardiopulmonary	
Hepatopulmonary Syndrome [35,36,38,45] Intrapulmonary vascular dilation Dilated precapillary/capillary vessels and shunt formation Gas exchange impairment Linear correlation with liver failure severity ↑ vWF-Ag → possible screening method HPS Evaluation: [50-52] Contrast echocardiography for intrapulmonary shunting	Liver transplant [36,47,48] Post-op death predictors: [46-48,54] PO2 <50 mmHg Large intrapulmonary shunts Oxygen administration and supplemental care
Portopulmonary Hypertension [35-37] ↑ pulmonary vascular resistance, similar to PAH PHTN of 15 mmHg, or portocaval gradient > 5 mmHg mPAP > 25 mmHg and mPAOP < 15 mmHg mPAP - mPAOP (transpulmonary gradient) > 10 mmHg Endothelial/smooth-muscle proliferation and fibrosis of small pulmonary arteries → obstruction Hemodynamic failure No correlation with liver failure severity POPH Evaluation: [46] Transthoracic echocardiography Right heart catheterization	Diuretics for volume overload (spironolactone/furosemide at ascites dosing below) [48] Endothelin receptor antagonists [36,48,54,164] Bosentan 62.5 mg po BID 4 wks → 125 mg po BID maintenance (↑ risk liver damage) Ambrisentan 2.5-5 mg po qd Macitentan 10 mg po qd Prostanoids [36,48,54] Epoprostenol 2 ng/kg/min IV infusion over 24 hrs → ↑1-2 ng/kg/min q15 until effect Treprostinil 1.25 ng/kg/min IV infusion → ↑1.25 ng/kg/min qweek Iloprost 2.5 mcg → 5 mcg q6-9x/d Phosphodiesterase Inhibitors [36,48,54] Sildenafil 5-20 mg po TID Tadalafil 40 mg po qd Liver transplant [36,47,48]
Cirrhotic Cardiomyopathy [41,44,50-52] Abnormal stress response - normal/↑ LV systolic contractility at rest Attenuated systolic contraction or diastolic relaxation due to stress* Three electrophysiological abnormalities: QT prolongation: abnormal myocardial repolarization; higher risk of TdP Chronotropic incompetence: inability to provide appropriate tachycardiac response under stimuli Electromechanical dyssynchrony: disconnection between heart excitation-contraction coupling Cirrhotic Cardiomyopathy Mechanism: [41-44,49]	Diagnosis: [50-52] Cardiac MRI Echocardiography Tissue Doppler NT-proANP/BNP Management: [50-52,103]* Aldosterone receptor antagonists Spironolactone 25-100 mg qd Eplerenone 25 mg po qd Maintain Albumin

↑ Endotoxin release, vWF-Ag, systemic inflammatory mediators → damage pulmonary endothelium → increased NO production → hyperdynamic circulatory syndrome Arterial splanchnic vasodilation, ↓ TPR and arterial pressure → secondary ↑in CO Impaired β-adrenergic pathways, cardiomyocyte plasma membrane function, and humoral factors (NO/endocannabinoids)	↑ plasma volume Maintains endothelium glycocalyax Binds pro-inflammatory mediators Beta blockers Carvedilol 3.125-6.25 mg po BID Metoprolol succ. 25 mg po qd Propranolol 10-60 mg po q8 Nadolol 40-160 mg po qd Loop and Thiazide Diuretics - careful prn Furosemide 40-80 mg po q8 Chlorthalidone 12.5-25 mg po qd ACE inhibitors/ARBs Generally avoid due to ↓ systemic vascular resistance despite ↓ PHTN *(Recommendations based on non-LC induced heart failure guidelines due to lack of LC clinical trials)
Increased risk for Atherosclerosis [55,56]	Low-dose high-intensity statin [57,58] Atorvastatin 10-20 mg qd
Ascites Formation [27,93] ↑ risk if HVPG ≥10 → 8%/yr; 5-15% bleed/yr ↓ HVPG 20% → ↓risk hemorrhage, ascites, death ↑HVPG 1 mmHg ≥10 → additive ↑11% Transjugular Intrahepatic Portosystemic Shunt [73,96-100] Indication: unresponsive tense ascites without HE, if require LVP ≤2 weeks Contraindication: EF <60%, diastolic dysfunction, renal disease, PHTN ↓ Ascites at 1 yr (OR 6.07), but ↑ HE (OR 2.95) No change in mortality	Sodium restrict diet ≤ 2000 mg/day [73] Poor taste and ↓po → 5-6 g/d [71] Spironolactone 100 mg/d (400 mg/d max) +/- furosemide 40 mg/d (160 mg/d max) [1,73] Midodrine 7.5 mg q8 if refractory [48,73] LVP + albumin 6-8 g/L-removed if ≥5 L [73] SBP prophylaxis if appropriate (above) Decompressive TIPS → ↑ Surgery candidacy [73,96-100] Maintain Albumin ≥2.5 [78,102] Albumin 1 g/kg/d for 2 d trial [72] Unaffected by PPI administration [95]
Endocrine	
Adrenal Failure [59-62] Impaired liver synthesis of APO-A1 → ↓ HDL → ↓ cholesterol precursor → impaired cortisol synthesis ↑ TNF-α, IL-1β, IL-6, and endotoxin → ↓ synthesis/release of apoA-1, ↑ tissue cortisol resistance	Potential use for supplementary hydrocortisone and fludricortisone treatment during sepsis/septic shock [165]
Renal	
Hepatorenal Syndrome [69] HRS type 1: Doubling of Cr (above 2.5 mg/dL) and ↓ CrCl by 50% (or >20 mL/min) in less than 2 weeks 1 month mortality exceeds 50%. HRS type 2: ↑ Cr >1.5 mg/dL (or CrCl < 40 mL/min) and a urine sodium level < 10 mmol/L. Less progressive course, but still has a 6-month mortality of 50% HRS Mechanism: [64-69] PHTN → splanchnic arterial vasodilation → ↑ portal venous flow/PHTN Sodium retention with water and ascites develop → ↑ endogenous natriuretic hormones ↑ sodium retention → ↑ plasma renin activity and NE levels Extra-splanchnic organ vasoconstriction compensates splanchnic arterial vasodilation → ↓renal/cerebral/muscular flow ↑ plasma renin and NE, ↓ renal perfusion and GFR → ↑ADH and ↓ free water clearance	HRS Prevention: [48,72,166] During SBP: Albumin 20 g weekly If CrCl 41-80 ml/min: Pentoxifyllin 1.2 g/d Hyponatremia: [48] Vaptans Conivaptan 10 mg IV 30-min infusion → 10 mg qd infusion Fluid restriction <1 L/d if severe HRS Management: [32,48,70,71,74] Avoid excess fluid administration Avoid NSAIDS due to: 1) renal perfusion becoming dependent on prostaglandin synthesis, and 2) prostaglandins inhibit ADH-induced dilutional hyponatremia (Na <130 mEq/L) Albumin 1 g/kg 1st day → 20-40 g qd and: Midodrine 7.5 mg-12.5 mg TID Octreotide 100-200 mcg TID, or 50 mcg/h gtt

	Terlipressin 3-12.5 mg gtt qd Liver transplantation
Acute Kidney Injury [77-80] ↑ Cr ≥ 0.3 mg/dL in less than 48 hrs, or Cr ↑ ≥50% from baseline within 6 mo 67% mortality with renal dysfunction, vs. 11% without	Treat/discontinue precipitating factor - diuretics, lactulose, vasodilators, nephrotoxins, bacterial infections [80,81] Volume repletion HRS-1/2 treatment If ATN present: Dialysis [67]
Central Nervous System	
Hepatic encephalopathy [82] Psychomotor, cognitive, emotional, behavioral, and motor skill dysfunction HE mechanism: [68,83-86] Dilutional hyponatremia depletes brain osmolytes → ↑risk of brain edema and HE → poor outcomes ↑ systemic ammonia due to ↓ liver function and ↑ portosystemic shunts (including TIPS) Innate compensation: [82,84,85] SKM and kidneys → activate inactivated glutamine synthetase and glutaminase → detoxify circulating ammonia Astrocytes → convert ammonia to glutamine → osmotic disbalance and edema	Avoid protein restriction [48,70,87,88] 0.8-1.2 g proteins/kg/day [61] Laxatives – titrated to 3-4 stools/day [48] Lactulose 20-30 g po q6 Rifaximin 550 mg po BID Neomycin 4-12 g/d po q6 for 5 d [32,48] Avoid in renal dysfunction Use for <6 mo Correct hyponatremia [86]
Preop: Preoperative; → leads to/for; ↑: Increase; ↓: Decrease; ABX: Antibiotic; IV: Intravenous; PAMPS: Pathogen-Associated Molecular Patterns; DAMPS: Damage-Associated Molecular Patterns; PLT: Platelet; vWF: Adhesive Protein von Willebrand Factor; LMWH: Low Molecular Weight Heparin; ?: Questionable/Possible; TPR: Total Peripheral Resistance; PAH: Pulmonary Artery Hypertension; mPAP: Mean Pulmonary Artery Pressure; mPAOP: Mean Pulmonary Artery Occlusion Pressure; PVR: Pulmonary Vascular Resistance; CO: Cardiac Output; *stress: Eating, Valsalva maneuver, and mental stress; TdP: Torsade de Points; AKI: Acute Kidney Injury; HRS: Hepatorenal Syndrome; Cr: Creatinine; CrCl: Creatinine Clearance; NE: Norepinephrine; ADH: Anti-Diuretic hormone; TIPS: Transjugular Intrahepatic Portosystemic Shunt; SKM: Skeletal Muscle.	

Table 1: Pathophysiology, mechanisms, and perioperative management options of liver cirrhosis.

Coagulopathy

Thombocytopenia, historically [20,21] believed due to platelet (PLT) sequestration by the spleen secondary to portal hypertension (PHTN) despite no clear correlation, is however a multifactorial process (Table 1) [21,22]. Thrombopoietin, the primary platelet stimulating factor normally produced by the liver, production is impaired [21]. Some HCV-induced LC has increased anti-PLT antibody level prevalence [22]. Platelet infusion is not recommended until counts fall below 100,000 [1]. Although DDAVP is often used to correct prolonged bleeding times, recent data [23] suggests it is not effective and does not increase functional von-willebrand factor (vWF) in cirrhotics.

The coagulopathy of LC is a delicate balance between hyper/hypo-coagulability (Table 1) [24]. Malnutrition, poor absorption due to cholestasis, and diminished liver function comprise only some of the mechanisms, making preoperative management all-encompassing. Antihemostatic drivers result in increased bleeding risk, especially in the gastrointestinal tract [25,26]. However, when assessed by global tests, a 2011 review did not show hypocoagulability [25], rather underlying conditions of PHTN, endothelial dysfunction, bacterial infection, and renal failure be emphasized [27,28]. Combined with prohemostatic driver shifts, cirrhotics are not protected from arterial or venous thrombosis [25]. This paradox is due to an imbalance inducing resistance to thrombomodulin [25,29,30]. Akamatsu et al. found low pre-liver transplant (LT) fibrinogen was associated with postoperative hemorrhage, and low protein-C with postoperative thrombosis [31]. While hepatic coagulation factor synthesis may be impaired, intramuscular vitamin K should be administered if significant malnutrition or malabsorption exists [32]. INR correction with fresh frozen plasma (FFP) is often used, but with severe coagulopathy, FFP volume presents a large fluid load [33] and as such cryoprecipitate should be used as it also repletes fibrinogen and vWF [1,33].

Portal vein thrombosis (PVT) occurs in 1-16% of cirrhotics [20,34]. A cohort study by Berry, et al. concluded PVT does not increase mortality in LC, rather it was associated with decreased mortality [20] due to significant collaterals developing slowly, decreasing catastrophic variceal bleeding risk and other PHTN complications [34].

Cardiopulmonary

Pulmonary manifestations in LC are common, two of which include hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) (Table 1) [35,36]. Both result from abnormal pulmonary microvascular angiogenesis due to chronic liver disease and/or PHTN [37], however HPS has vascular dilations, hyperplastic capillaries, arteriovenous shunts distally resulting in gas exchange impairment [35,38], while POPH has elevated pulmonary vascular resistance and obstruction similar to PAH resulting in hemodynamic failure [35,37]. While HPS severity correlates equally with liver failure, no such relationship exists with POPH [35]. Increased inflammatory mediators and damaged pulmonary endothelium induce macrophage recruitment [39], a key HPS pathogenesis concept [35,40]. Nitric oxide (NO) and endocannabinoids, major vasodilators of systemic and pulmonary circulation, lead to hyperdynamic circulatory syndrome in LC and/or PHTN [41-44], by upregulation of NO synthases [35,37]. Furthermore, endothelial vWF-antigen, often elevated in LC, may be useful in early HPS screening [45].

When HPS is suspected, evaluation includes contrast echocardiography for intrapulmonary shunting [46]. The strongest predictor of postoperative death was PO2<50 mmHg or large intrapulmonary shunts. Current HPS management options are dismal [46], restricted to oxygen administration, supplemental care, and LT with 75% 5-yr survival of HPS post-LT vs. 23% without [47]. When POPH is suspected, transthoracic echocardiography is the best noninvasive test (100% Sn, 88% Sp), while right heart catheterization is the gold standard evaluating PAP ≥50 mmHg [46]. POPH management options include prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, while the most effective long term solution is LT [47,48].

The cardiac complications of LC are complex. Disturbed arterial splanchnic vasodilation, reduced total peripheral resistance and arterial pressure, impaired β-adrenergic pathways and cardiomyocyte plasma membrane function, result in secondary cardiac output increase and reduced function [41,44,49] known as cirrhotic cardiomyopathy (CC) (Table 1) [50-52]. This can be diagnosed by cardiac MRI, EKG, or echocardiography, despite the lack of CC specific trials [50-52], preoperative management includes aldosterone antagonists, maintaining albumin, and ACEi caution due to decreased systemic vascular resistance (Table 1) [50-54].

Additionally, LC also has higher prevalence of atherosclerosis [55]. NASH-related LC, ≥50% linked with metabolic syndrome including obesity, hypertension, diabetes and high serum triglycerides, puts patients at increased risk for carotid and coronary atherosclerotic plaque formation [55-58].

Endocrine

Patients with liver failure and post-LT have a high incidence of adrenal failure, likely due to impaired cortisol biosynthesis (Table 1) [59], as adrenal glands do not store cortisol, rather production and secretion are increased by adrenocorticotropic hormone (ACTH) [59]. Impaired liver apolipoprotein A-1 (APO-A1) synthesis [59], a lipoprotein in high-density lipoprotein (HDL) [60], reduces HDL's ability to transport the precursor cholesterol, resulting in reduced cortisol synthesis and thus adrenal insufficiency [59]. TNF-α, IL-1β, IL-6, and endotoxin decrease the synthesis and release of apoA-1, and increase both cortisol's tissue resistance and synthesis inhibition in a dose dependent manner in LC [59,61,62]. This may be worsened by certain medications, including etomidate, by inhibition of CYP-11B2 aldolase [63].

Renal

Acute renal failure occurs in 20% of hospitalized cirrhotics, and is associated a poor prognosis and high mortality rate [64]. Death increases 7-fold in LC with renal dysfunction; 50% die within one month of the onset [65]. While only 15-20% of cirrhotics present with the classic form of hepatorenal syndrome (HRS), most display superimposed infection [66] or inflammation (Table 1) [67]. The most common renal effects include sodium retention from impaired free water excretion and glomerular filtration rate reduction, which quickly leads to HRS [68]. HRS, secondary to intense renal vasoconstriction, is due to severely impaired circulatory function and overactive endogenous vasoconstriction; both overpower intrarenal vasodilatory mechanisms [68,69]. Care should be taken to limit certain medications (ACEi/ARBs, NSAIDs, intravenous dyes, aminoglycosides). Other factors such as large volume paracentesis (LVP), infections (SBP and UTI), and gastrointestinal bleeding can precipitate renal failure [32,48,70,71]. During surgery, hemorrhage and anesthetic effects may precipitate a reversible HRS [32]. HRS-1/2 should be referred for LT, and managed with albumin 1 g/kg/d increasing to 100 g loading dose followed by 20-40 g/d [72] combined with vasconstrictor treatment [65,73]. Although not available in the U.S., terlipressin plus albumin maintains better MAP [72] with a higher rate of renal recovery at 70% compared to midodrine and octreotide plus albumin in the treatment of HRS at 28.6% [74], despite higher rates of cardiovascular side effects [75]. However, there tends to be a 50% recurrence rate after cessation of therapy [75].

As LC advances, serum creatinine (Cr) is often an inaccurate assessment of renal function, especially in the setting of muscle wasting [76]. Recent data clearly demonstrates even mild renal injury in LC portends a poor prognosis [77], and the stringent HRS or acute kidney injury (AKI) criteria often missed a significant portion of renal injury (Table 1) [78]. Renal dysfunction, the most important independent predictor of death in SBP, has 67% mortality, similar to HRS patients [79]. However, Wong et al. noted previous studies used Cr ≥1.5 mg/dL defining renal failure [80], and thus redefined acute kidney injury in LC (Table 1). With the most common AKI precipitants of urinary tract infection (UTI), spontaneous bacterial peritonitis (SBP), and skin infections, 49% developed AKI, higher percentages of AKI patients either died within 30 days of hospitalization (34% vs. 7%), transferred to the ICU (46% vs. 20%), required ventilation (27% vs. 6%), or went into shock (31% vs. 8%) [78]. Mortality was highest among those who never recovered (80%), vs. a partial (40%) or full (15%) recovery [80]. Notably, more than half of the patients had minor Cr increases between 0.3-0.5 mg/dL, which would not have qualified as HRS, therefore these criteria appear to be more Sn. Treatment is still the same as HRS, however at an earlier stage of renal dysfunction [67,80,81].

Encephalopathy

Patients with hepatic encephalopathy (HE) exhibit psychomotor, cognitive, emotional, behavioral, and motor skill dysfunction (Table 1) [82]. Ammonia, a neurotoxin [83] that impairs nutrient transport into neurons and astrocytes, metabolism of amino acids, brain energy consumption, and nerve potential transmission, is produced by intestinal bacteria metabolic effect on proteins, purines, and urea [84]. The liver, a major ammonia metabolizer, converts this into urea and glutamine through the urea cycle and glutamine synthetase, respectively [84]. In LC, due to portosystemic shunts formation and decreased liver function, circulating ammonia triggers secondary organ detoxification mechanisms in the brain, skeletal muscles, and kidneys [84]. The latter two activate normally inactivated enzymes, including glutamine synthetase and glutaminase [85], while the only CNS cells capable of detoxification, astrocytes, produce high amounts of the osmotic regulator glutamine resulting in edema [82,86]. When these mechanisms fail or become saturated, ammonia reaches toxic levels resulting in HE [68,82], often precipitated or worsened by surgery and anesthesia [1,32]. HE can be complicated by unnecessary workup and sub-optimal recovery including immobility, inability to comply with physical therapy, and aspiration [32]. Protein intake recommendations most notably include a well-balanced diet, in contrast to prior conventional teachings of protein restriction [48,70,87,88]. Treatment includes either titrated oral lactulose or rifaximine, due to less adverse effects [1,87]. A Cochrane analysis found both oral lactulose and antibiotics effective, however oral antibiotics appeared more effective at controlling HE, despite lacking

strong studies [89]. Of note, neomycin should be avoided in renal dysfunction patients and given for <6 mo [32].

Overall Prognosis of Cirrhosis in the Perioperative Setting

Overtime, chronic damage progresses to fibrosis and LC with type 1 and 3 cross-linked collagen only sensitive to matrix metalloproteinases [90]. Injury source withdrawal may lead to biopsy-proven extracellular membrane reduction, depending on initial LC grade [90,91]. However, HCC risk remains despite treatment [90,92]. LC is often classified based on clinical status as decompensated [90] with a median two year survival, compared to 12 years with compensated [93]. Decompensated LC exhibits features of PHTN and/or liver insufficiency, including jaundice, ascites, HE, or variceal hemorrhage [90]. PHTN is often indirectly evaluated by measuring the hepatic venous pressure gradient (HVPG) (Table 1). A normal HVPG is 3-5 mmHg, with a HVPG ≥6 defining PHTN. As HVPG rises ≥10, the rate of variceal development is 8% per year; bleeding rate is 5-15%/year, with the most important prognostic indicator being the size of the varix [27]. A HVPG decrease by 20% from baseline significantly lowers the risk of hemorrhage, ascites, SBP, and death [27]. In two studies, HVPG ≤10 mmHg demonstrated a 90% probability of not developing clinical decompensation within 4 years, and every 1 mmHg ≥10, there was an additive 11% increased risk of developing decompensated cirrhosis at equivalent MELD and albumin values, along with a six-fold increase in HCC development risk [93].

The presence of ascites (Table 1) requires aggressive preoperative management, as complications include respiratory compromise, postoperative wound dehiscence, and peritonitis [1,32]. Preoperative maintenance includes current sodium restricted diet and appropriate use of diuretics [1,48,73]. If moderate to severe or tense ascites exists, LVP or laparotomy ascites removal are rapid treatment options [73]. LVP alone has a 6.5% in-hospital mortality vs. 8.5% who did not (OR 0.55) [94]. Maintenance of a low threshold for primary or secondary bacterial peritonitis, especially in the surgical setting and is unaffected by PPI administration [95], is critical and requires quick treatment [32,73]. Despite no change in mortality if used for ascites [96], preoperative TIPS may allow safe portal vein recanalization to treat PVT, possibly negating further anticoagulation needs, and improve not only LT but general surgery candidacy if done 2-4 weeks prior to surgery [97-100].

Historically, postoperative complication rates were 40%, with 23% ascites, 13% infection, 8% pulmonary, and 8% renal failure [101]. Of interest, Kao et al. found postop hypoalbuminemia ≤2.7 g/dL associated with surgical complications [78,102]. Albumin, a recurring therapy in LC, appears to restore endothelial glycocaylax and bind pro-inflammatory mediators [103]. If ICU admission is required, several scoring systems exist as independent 6 month mortality predictors [49], including the Acute Physiology and Chronic Health Evaluation III and Chronic Liver Failure - Sequential Organ Failure Assessment score. The latter was found to have the best discriminatory power with a cutoff value of 11, due to taking into account end-stage liver disease specific parameters.

Diagnosis of Cirrhosis

Liver biopsy, serum markers, and magnetic resonance imaging

Accurate diagnosis and evaluation of the liver disease stage prior to surgery is critical (Table 2). Despite liver biopsy remaining as the gold standard with a high Sn and Sp (80-100%) [104] for cirrhosis, biopsy is not required and generally would not be performed before the surgery at hand due to increasing near-future surgical risk, ongoing hospitalization (1-5%), and severe complications (0.57%) including mortality (0.009-0.12%) [104,105]. However if the surgery is elective and can be postponed until an appropriate recovery period has elapsed, management and optimization of the LC may become more specific if underlying etiology is uncertain. If undertaken, the average biopsy size is small, with significant sampling and histologic assessment variability between two pathologists or even by the same who are highly specialized [106-108]. Classical staging systems include LC as one broad category, while modified Laennec system splits LC into three subcategories (4a, 4b, 4c) to potentially capture the progressive nature of mild, moderate, and severe LC; it is unknown at this time if this has any effect on surgical risk [90,109].

Diagnostic Method	**Evaluation Statistical Parameters**	
Liver Biopsy [104]	Sn and Sp (0.80-1.0)	
Ultrasound [110]	Sn (0.67); Sp (0.87); PPV (0.64); NPV (0.88)	
Transient Elastography [117,118] (normal reference=~5 kPa)	F1 cirrhosis (5.9 kPa): F2 cirrhosis (7.5 kPa): F3 cirrhosis (9.5 kPa): F4 cirrhosis (12.5 kPa):	Sn (0.83); Sp (0.88) Sn (0.94); Sp (0.89); +LR (8.2); -LR (0.07) Sn (0.92); Sp (0.70); +LR (3.10); -LR (0.11) Sn (0.95); Sp (0.71); +LR (3.30); -LR (0.07)
Magnetic Resonance [114,115]	F1 cirrhosis: F2 cirrhosis: F3 cirrhosis: F4 cirrhosis:	Sn (0.91); Sp (0.87) Sn (0.87); Sp (0.91) Sn (0.80); Sp (0.89) Sn (0.81); Sp (0.85)
Serum Markers Overall [110]	PPV (0.40-0.52); NPV (≥0.80)	
AST/ALT ratio > 1 [167]	Sn (0.24); Sp (0.87)	

APRI > 0.80 [167]	Sn (0.61); Sp (0.83); PPV (0.62); NPV (0.82); Accuracy (0.70)		
FibroTest© [104,111]	Sn (0.71); Sp 0.87); +LR (5.49); -LR (0.33); OR (16.77)		
Hyaluronic Acid [112]	Sn (0.68); Sp (0.71)		
Evaluation Method	Mortality Statistical Parameters		
MELD Mortality 30 d (L) vs. 90 d (R)[%] [122]	MELD 6-9 MELD 10-14 MELD 15-19 MELD 20-24 MELD ≥25	1.9 3.6 3.6 12.5 36.4	3.5 8.9 14.3 12.5 63.6
MELD Conclusion	Cutoff score for MELD ≥10=best Sn (30-ds: 61.0%, 90-days: 66.0%) Cutoff score for MELD ≥25=best Sp (30-d: 99.0%, 90-days: 99.0%)		
MELDNa Mortality 30 d (L) vs. 90 d (R)[%] [123,131]	MELD 6-9 MELD 10-14 MELD 15-19 MELD 20-24 MELD ≥25	1.2 3.9 1.9 11.8 31.3	1.9 6.2 13.2 20.6 50
MELDNa Conclusion	Cutoff score for MELDNa ≥10=best Sn (30-d: 83.0%, 90-d: 86.0%) Cutoff score for MELD ≥25=best Sp (30-d: 98.0%, 90-days: 98.0%) Median MELD-Na scores (mortality vs. non-mortality)=12.5 vs. 10 (P=0.028)		
CTP Class [%] [123]	CTP-A (H. 10%) CTP-B (H. 30-31%) CTP-C (H. 73-82%)	1.0 9.5 22.1	2.1 22.1 54.5
30-d MELD + Albumin + HCT vs. Traditional MELD (Sn/Sp/PPV/NPV) [%] [121]	Combination Method MELD ≥10: 63/90/31/97 MELD ≥15: 38/97/50/95 MELD ≥20: 38/100/100/95	Traditional Method 67/61/13/96 44/88/24/95 33/95/38/95	
30-d CTP + Albumin + HCT vs. Traditional CTP (Sn/Sp/PPV/NPV) [%] [121]	CTP-A: 80/82/29/98 CTP-B: 60/91/38/97	67/44/11/93 50/80/20/94	

Sensitivity (Sn); Specificity (Sp); Positive Predictive Value (PPV); Negative Predictive Value (NPV); Positive Likelihood Ratio (+LR); Negative Likelihood Ratio (-LR); Odds Radio (OR); H: Historically; hematocrit (HCT).

Table 2: Comparison of liver cirrhosis diagnostic, evaluation, and mortality prediction methodologies with statistical parameters.

Many patients with chronic liver disease are monitored clinically with liver enzymes, platelet counts, and liver ultrasounds, invigorating the search and routine utilization for noninvasive diagnostic markers such as AST-Platelet Ratio Index (APRI), Fibrotest©, and Fibrosis-4 test (FIB-4) (Table 2) [110]. Martin et al. concluded despite the low positive predictive value (PPV) of noninvasive markers, the negative predictive value (NPV) of each marker exceeded 80%, however combining both noninvasive markers with radiological evidence did not increase the NPV [110]. Fibrotest©, a widely validated indirect serum marker panel, is calculated using total bilirubin, haptoglobin, gamma-glutamyl-transpeptidase, a2-macroglobulin and apolipoprotein-A. In a systematic review, it had an excellent discrimination for identifying LC, but a lesser ability to identify significant (≥F2) fibrosis [104,111]. Of the direct serum markers of fibrosis, only hyaluronic acid had a statistically significant relationship to LC (Table 2) [112]. These tests may assist LC evaluation if a previous diagnosis is nonexistent or classic stigmata are not apparent.

Similarly, magnetic resonance technology/elastography (MRE) with T1 mapping allows quantitative mapping of liver stiffness (LS) and fibrosis distribution over large regions, and differentiates all levels of fibrosis especially ≥F2 more accurately than a traditional contrast-enhancement index [113-115]. Even so, the major limitation of MRE are availability, cost, and time which many times is not available for the surgical patient [106].

Fibroscan

Due to the limitations of biopsy, alternative methods have been developed including advancements in ultrasound [110] and transient elastography (TE) using Fibro-Scan© (Table 2) [116]. TE is not yet validated for assessing dynamics of fibrosis or longitudinal evaluation

of regression [90]. The probe is separate from an ultrasound probe, and requires a vessel-free area for proper measurement [117]. A recent meta-analysis of TE use in alcoholic-related disease and LC diagnosis, TE could be useful in ruling out the presence of significant fibrosis, thus possibly avoiding a liver biopsy depending on clinical reasoning, and more applicable screening method to the surgical patient [118]. Defining specific different cut-off values of deviation from a normal LS of ~5 kPa for the diagnosis of LC have been proposed for various etiologies including NAFLD, HCV-induced LC, or alcoholic steatohepatitis [117], with its diagnostic utility gleaned from a 2015 metanalysis (Table 2) [118]. De Robertis et al. noted LS measurements should be postponed ≥3 months after stabilization of ALT levels due to an acute insult in order to restore reliability, and there is a need for cutoff adjustments due to inflammation-induced overestimation if performed earlier [117] which result in a wide change in Sp but small in Sn [118]. A possible improvement is the progression of TE to real-time strain elastography (RTE), allowing LS evaluation while performing an abdominal US exam, and according to De Robertis et al., RTE does not suffer from breathing artifacts, ascites, steatosis, BMI, or skin thickness [117]. Of note, according to Wong et al., Fibrotouch©, a 3rd generation TE unit, has the potential of overcoming obesity with a dynamic probe measurement based on subcutaneous fat [106]. These advancements may be of greater utility with respect to increased speed and applicability to the surgical patient. The combination of liver stiffness (LS) and Fibrotest© was found to have the best diagnostic performance compared to either test alone [104,106,111].

Preoperative Evaluation of Known Cirrhosis

Model for end-stage liver disease score

Model for End-Stage Liver Disease (MELD), originally a prognostic tool in advanced liver disease, is now used by UNOS to prioritize organ allocation for LT [69]. Numerous attempted changes to increase the accuracy by adding LC complications including ascites, HE, variceal bleeding, and SBP, have not improved the accuracy [69]. Many recent studies have attempted to show the efficacy of MELD score in predicting operative mortality for cirrhotics undergoing cardiac and noncardiac surgery. A retrospective analysis by Teh et al., showed 772 cirrhotics who underwent major gastrointestinal, orthopedic, or cardiovascular surgery, MELD was a strong predictor of mortality at 30 and 90 days while persisting throughout a 20-year follow-up period [119]. MELD score 0-11 correlated with 5-10% 90-day mortality, 12-25 with 25-54% mortality rate, and ≥26 with a 90% postoperative mortality rate [120,121]. This was expanded by Cho et al.'s data of 490 pts from 2003-2008 showing better survival in patients with LC (Table 2) [122], resulting in a MELD ≥10 having better Sn while MELD ≥25 with better mortality Sp. This was attributed to several factors including more post-necrotic LC and less cardiovascular surgery cases, whereas Teh's study included more patients with alcoholic cirrhosis with a poorer short term survival, and possible ethnic differences medication tolerance [123]. According to Lau et al., problems with MELD include falsely elevated INR due to warfarin use, elevated creatinine from underlying AKI rather than HRS, and serum bilirubin elevation in cases of sepsis or hemolysis [69]. There is a notable "MELD exception", where patients with HCC and other diseases [69], compared to chronic liver disease, do not demonstrate the degree of hepatic dysfunction required to reach threshold MELD score to get LT priority. This led to the "Milan criteria" which assigns an initial MELD score of 22, with interval increases every 3 months on the LT wait-list, to reflect a corresponding increase in estimated 3-month mortality rate [69,124]. These etiologies are critical to understand and acknowledge in the surgical setting. Northup et al. noted in their study that an approximate 1% increase in mortality risk per MELD <20 compared to a 2% increase in mortality risk per MELD ≥20 [125].

MELD scoring variations: ΔMELD and MELDNa

There have been attempts by adding variables or monitoring changes in in MELD to improve its accuracy [69]. For example, a ΔMELD may have better mortality prognostic value compared to initial MELD and CTP scores at 6 and 12 month follow-up [126], and the magnitude and direction of MELD change is thought to be an independent mortality predictor [127].

Pre-operative hyponatremia is an independent predictor of mortality following LT [128]. In several studies with MELDNa vs. MELD, MELDNa had a higher prognostic indicator in patients with acute hepatitis [129], as well as minor superiority in predicting postoperative 90-day mortality in cirrhotics [123]. According to Cho et al., cirrhotics with high MELD tended to have lower serum sodium levels, and Lau concluded with this reverse correlation that MELDNa may be more meaningful in patients with low MELD score and low serum sodium level. Ninety-day mortality according to MELDNa (Table 2) revealed a cutoff score ≥10 had better Sn than ≥25 [123]. The loss of MELDNa superiority may be due to receiving intensive therapy to correct electrolyte imbalance before or during surgery [123]. However in Kim et al.'s more recent study, the median MELDNa in mortality vs. non-mortality cases were 12.5 and 10, respectively (P=0.028), concluding MELDNa neither correlated with operative or overall mortality, nor superiority over other models [130]. This is corroborated by Neef et al.'s 2014 study of emergency surgery mortality in cirrhotics, in which MELDNa did not predict early or late mortality [131].

Child-Turcotte-Pugh score

The Child-Turcotte-Pugh (CTP) score, originally developed in 1964 to stratify liver disease severity into class A, B, and C (5-6, 7-9, and 10-15 points, respectively) and determine the preoperative risk of portosystemic shunt surgery for patients with variceal bleeding. It takes into account five factors including ascites, HE, serum levels of bilirubin and albumin, and nutritional status later changed to prothrombin time in 1973 [69]. The major limiting factor is using the two highly subjective parameters of HE and ascites severity, according to Lau et al., with differing interpretations and both being subject to iatrogenic manipulation including lactulose, albumin, and diuretics, and the prognostic marker of renal function not being taken into account [69,132].

Historically following abdominal surgery, there is a 10% perioperative mortality risk for patients in CTP-A, 30-31% with CTP-B and 76%-82% with CTP-C, with elective surgery tolerated well in CTP-A, permissible with good preoperative preparation in class B, except for major hepatic resection or cardiac surgery, and contraindicated in CTP-C [133]. However, that data was referred from 1984 and 1997 and may no longer be accurate given the advancement in surgical and medical technology [123]. Cho et al.'s paper found 90 day mortality in patients with CTP-A, B, and C (Table 2) was 2.1, 22.1 and 54.5%, respectively. A recent systematic review [134], de Goede et al. found very few articles that included CTP-C patients, finding in many cases surgeons hesitated to perform elective operations on them [130,133].

Perioperative evaluation conclusions

Despite the conflicting results on the superiority of MELD and CTP scores [119], a 2012 review article ultimately recommends using both models in a complementary fashion to evaluate risk for a better insight into the liver disease status and degree of decompensation [97]. As can be expected, CTP and MELD scores have been found repeatedly to be significantly higher in mortality cases than in non-mortality cases, but do not correlate with intraoperative mortality [130,135]. The addition of integrated-MELD and intraoperative transfusion scores, especially if ≥700 mL (OR 6.3), may be preferred for operative mortality, while CTP may be the best prognostic factor for overall mortality [130]. MELD score of ≥14 may be a better predictor of poor outcome than CTP-C (Sn 77%, Sp 80%, PPV 56%, NPV 91%) [119]. In a review by Bhangui et al., American Society of Anesthesiologists (ASA) class was the best predictor of 7-day postoperative mortality, MELD score was the best predictor of 30-day, 90-day, and long-term postoperative mortality for all types of surgery, with the relative risk (RR) of 30 and 90-day mortality increased by 14% with each 1-point increase in the MELD. Specifically, ASA class ≥IV, CTP score ≥7, MELD score ≥10, and MELDNa score ≥10 were independent risk factors for 90-day mortality [97,123,131,135]. In a study of 120 cirrhotics [121] undergoing nonhepatic abdominal surgeries from 2001 to 2011, albumin levels ≤3.05 mg/dL and a hematocrit ≤35.55% were also independent predictors of 30-day mortality or requiring LT. When added to CTP or MELD scores [121], albumin and hematocrit improved the Sn and Sp by 6.1 and 32.1%, respectively. In addition the authors found it added the highest utility, or J-statistic, by combining it to CTP-A (J=0.62; p<0.01) and MELD≥10 (J=0.53, p<0.01) (Table 2). These findings are corroborated by Paolino et al., by adding an albumin ≤2.5 mg/dL to MELD ≥15 significantly increased mortality predictability to 60% compared to 14% without those criteria in a study of 100 cirrhotic patients undergoing abdominal surgery [135,136]. Albumin and hematocrit may also serve as markers of nutritional well-being and ability to tolerate blood loss [137,138]. There is no relationship between elevated PT/INR, BUN, or Cr and poor surgical outcomes. Harrington et al. suggests coagulopathy and renal impairment from LC may not play as large of a role in surgical outcomes as expected [121]. Finally, due to theoretical improvements with Refit-MELD and Refit-MELDNa, by using updated coefficients for each variable and newer upper and lower levels for Cr resulting in a modest improvement in the c-statistic, both have good predictability for 3-month mortality in patients with LC and ascites [139]. However, predictability was lower in alcoholic LC compared to viral LC, commented by probable continued alcohol use and irregular dietary habits.

Anesthesia Considerations

As LC causes many metabolic changes which may affect anesthetic management. Although the uptake and onset of anesthetic drug action is unaffected, hepatic clearance is dependent upon volume of distribution, functional hepatic blood flow (HBF), hepatic extraction ratio, hepatic microsomal and cytochrome-P450 enzyme activity, decreased plasma-binding proteins (PBP), and decreased biliary excretion (Table 3) [63,140-147]. In general, short to intermediate half-live drugs at lower doses with longer dose intervals should be used [140,141]. All volatile anesthetics decrease the mean arterial pressure and portal blood flow, compared to sevoflurane, in addition to mechanical ventilation, hypotension, hemorrhage, hypoxemia, and hypercarbia often encountered during surgery [140,148]. Induction agents, with the exception of ketamine and propofol, decrease HBF [63,149] without a change in clearance [140]. Care should be taken with benzodiazepines and paralytics, due to a reduction in both CYP-3A4 metabolism and PBP resulting in prolonged duration [1,140-142,144,147,150,151], whereas atracurium, lorazepam, oxazepam, and temazepam undergo non-hepatic conjugation [140,152]. Opioids in LC have significantly reduced metabolism [141,147,153] and prolonged half-lives, potentially exaggerating sedative and respiratory depressant effects, in contrast to fentanyl [1,141,147]. Tricyclic antidepressants, pregabalin, and gabapentin do not require hepatic metabolism and are successful in neuropathic pain management [141]. Analgesia methods are surgery dependent, however, thoracic epidural analgesia provides excellent analgesia for liver resections [154], despite a debate on the effects on reducing gastrointestinal paralysis compared with systemic opioids [155,156].

Anesthetic	**Metabolism**	**Comments** [1,63,140-156]
Volatile Agents		
Halothane	CYP-2A6	↓ HBF and ↑ drug induced hepatitis
Sevoflurane Desflurane Isoflurane	CYP-2E1 CYP-2E1 CYP-2E1	Preserves HBF Clinical unremarkable ↑ AST/ALT/ALP, especially Sevoflurane
Induction Agents		
Etomidate Thiopental	N/A N/A	↑ hepatic arterial resistance +/- ↓ CO → ↓HBF ↑ clinical recovery time due to ↑ Vd
Ketamine	CYP-2B6/3A4/2C9	Preserve HBF; ↑ clinical recovery time due to ↑Vd
Propofol	Glucuronidation CYP-2B6	↑ arterial and portal venous flow while ↓ MAP ~10 mmHg ↑ clinical recovery time despite no change in elimination in LC
Midazolam	CYP-3A4/PBP	Metabolism slightly impaired in LC
Lorazepam	Glucuronidation	Minimally affected by age or LC

Oxazepam Temazepam		
Paralytic Agents		
Vecuronium Rocuronium	CYP-3A4 CYP-2D6	Steroid base → liver metabolism ↓ clearance, ↑ half-life, ↑ neuromuscular blockade in LC
Atracurium	Non-hepatic/renal	Unaffected by cirrhosis
Opioid Agents		
Morphine Codeine Oxycodone Hydromorphone Hydrocodone	Glucuronidation CYP-2D6 CYP-3A4/2D6 Glucuronidation CYP-2D6	Avoid morphine in renal failure due to ↑ toxic metabolite LC → ↓ conjugation; ↑ half-life ↑ sedative and respiratory effects with LC
Fentanyl	CYP-3A4	Not affected by liver dysfunction vs. alfentanil and remifentanil Despite short duration 30 m-1 hr IV, ↑ fat accumulation → prolonged effects with infusion
Tramadol	CYP-3A4/2D6 Glucuronidation	Intractable pain due to peripheral pain pathways, partial SSRI ↓ opioid receptor affinity → ↓ sedation and respiratory depression
CYP: Cytochrome P-450; HBF: Hepatic Blood Flow; Vd: Volume of Distribution; PGP: P-Glycoprotein; SSRI: Selective Serotonin Reuptake Inhibitor; n/a: no Known Knowledge Available/non-specific.		

Table 3: Effects of liver cirrhosis on the use of common anesthetic agents during surgery

Operative Mortality

As can be expected, surgical morbidity and mortality rates [157] in LC vary greatly depending not only on underlying liver disease severity, but also the nature of the disease and advancement of surgical techniques [144] (Table 4). Limitations of the current literature include studies that often do not provide information on liver disease severity, are retrospective, or have limited patient size [97,134]. Hospital mortality rates after various non-LT surgical procedures range from 8.3% to 25% compared to 1.1% in non-cirrhotic patients (Table 4) [97,130,134,135].

Operation	Statistical Parameter Findings	Comments
Laparoscopy (Lap) vs. Open techniques	2011 Cholecystectomy Mortality: Lap (0.74%); Open (2.00%) [167,168]. 2000 Open Appendectomy: 30 d mortality was 9% cirrhotics, 0.7% non-cirrhotics [169]. 2001 Appendectomy: length of stay 8 d vs. 14 wound infection and bleeding (0% vs. 20% for both), with non-significant cost difference (p<0.05) [170]. 2014 HCC resection: less blood loss (P < 0.001), required transfusion RR=0.19 (P < 0.001), wider resection margins (P=0.011), no difference in operative times (P=0.142), shorter length of stay (P < 0.001) for lap [171].	2011 paper included 44 studies spanning 1984-2011 of laparoscopic vs. open cholecystectomy Poulson et al.'s 2000 study used patients from 1977 to 1993, and did not include Lap techniques. 2001 study performed in Japan, 40 patients total. Conclusion: Laparoscopy has reduced overall blood loss, postoperative complications, shorter length-of stay, with overall costs and operative time being similar, but most studies are small with exclusively CTP-A/B patients. Also, these studies demonstrate the advancement of surgical techniques over the last decade [144].
Abdominal – Overall	2010 study: MELD score >17 had a 6.9 OR (P=0.01) for postoperative mortality; broken down by CTP A, B, and C class were 2, 12, and 12%, with an overall 30 day postoperative mortality of 7% [135].	
Hernia	2005 LC effects in emergency repair: Morbidity rates in LC vs. non-cirrhotics of 17.3% vs. 14.5% (P=0.04) and mortality rates of 3.8% vs. 0.5% (P < 0.0001). [172,173] Historically in LC, overall mortality was 5%, 11% after emergency surgery, and 2% after elective surgery, with an 8-14% recurrence rate [134,174]. Current recurrence rate is 2.7% [175] and mortality is < 1%, [176,177] especially with the introduction of polypropylene and dual meshes [177-179].	Incidence ranges from 16-24%, depending on the presence of ascites, while umbilical hernias are 20% [177,180]. Elective repair of umbilical hernias has been well advocated [172,177,181,182] even with CTP B and C patients and decompensated cirrhosis [183,184], while conservative management results in higher complication rates 60-80% [185]. Both open and laparoscopic repairs are safe, despite the LAP studies were performed with all CTP-A patients [186,187]. Postoperative complications are not dependent on either CTP class or LC itself, excluding ascites [175].

Cholecystectomy	LC creates a 3.4-fold higher mortality rate than non-cirrhotics [134]. Lap has almost zero mortality described for CTP A and B patients [187,188], however mortality after open cholecystectomy currently varies between 0% and 7.7% [134]. Pre-Lap mortality ranged 7.5-26%, due to high representation of CTP-C patients [168] with a mortality of 23-50% [97].	Prevalence of gallstones in cirrhotics is estimated at 29-46%. [168,188] If not an appropriate elective surgical candidate or medical approach fails, or if condition worsens, percutaneous cholecystostomy should be utilized [189] until endoscopic balloon sphincterotomy followed by elective laparoscopic cholecystectomy, especially if suspicion of CBD stones [190,191]. Despite these interventions, a 7% mortality risk remains [70].
Gastric	Emergency surgery: Complicated peptic ulcer repair in cirrhotics ranges from 23% to 64% [97]. 2010 Gastric cancer: Radical gastrectomy, historically, has a 56% overall morbidity, and CTP-A and B mortality were 54% and 67%, respectively [134,192]. 2015 Gastric Cancer: CTP-A and B combined, complications and mortality rate (71.9%, 25%) in D2 node dissection, vs. (37.5%, 4.2%) in D1 node dissection, respectively; longer survival in CTP-A vs. CTP-B [193].	Peptic ulcers affect 8-20% cirrhotics [194], especially alcoholics [195], with mortality of peptic ulcer bleeding in both compensated and decompensated LC at 3.9% vs. 6.6% [196]. Lap surgery, combined with a PPI and endoscopic hemostatic techniques, has reduced the need for surgical resection and reduced emergency surgery mortality [97,196]. In Guo et al.'s study, mortality is more frequent in CTP-B than CTP-A ($p < 0.05$), and concluded D1 lymph node dissection is recommended in CTP-B, and radical gastrectomy was fatal for all CTP-C patients in their study [193].
Pancreatic	2013 study: Cirrhotics are at risk for higher amount of statistically significant intraoperative blood loss of over 500 ml (P=0.015) [197]. 2011 study: Cirrhotics have a higher complication rate (47% vs. 22%, P=0.035), reoperation requirements (34% vs. 12%, P=0.039), and prolonged hospital stay (28 vs. 24 days) during which required twice the ICU stay and twice as many transfusions [198].	Pancreaticoduodenectomy (PD) alone is a high-risk surgery for malignant pancreatic and periampullary disease, including some benign lesions, with an operative mortality of 5%, and postoperative complication ranging from 30-60%, even without LC [197,199]. 2013 study by Nakeet et al., was between 2002 and 2011. 2011 study by Warnick et al., was between 1997 and 2008, and did not recommend surgery in CTP-B due to 100% 30-day mortality (n=2), and 30-day mortality was 3% equally between CTP-A and non-cirrhotics.
Colorectal	Mortality rate, historically ranged from 48 to 77% [135,136,200]. In-hospital mortality after elective surgery was 14% (cirrhotics, OR 3.91), and 29% (cirrhotics with PHTN, OR 11.3), compared to 5% (non-cirrhotic), with emergency surgery mortality rate of 20.9% (cirrhotics, OR 2.40) and 35.8% (cirrhotics with PHTN, OR 5.88) [134,201,202]. 2013 study: Overall colorectal surgery mortality was 8.7% (non-liver disease) vs. 13.3% (non-cirrhotics), and 24.1% (cirrhotics) [203].	Meunier et al. in 2008 found postoperative infection as the largest risk for mortality, increasing it from 11% to 53% [204]. The 2013 Danish 30-day study included 29,840 surgeries, sub-group analysis resulted with a higher mortality in surgery of the colon versus rectal, with 9, 14, and 27% vs. 6, 10, and 19% mortality of non-liver disease, non-cirrhotics, and LC, respectively [203].
Cardiac	2012 Overall study: Mortality of 5, 32-35, and 67-70% for CTP-A, B, and C [133,205]. 2007 Bypass study: Between 1998 and 2004, no operative mortality with the use of revascularization without the use of bypass, however mortality after bypass with CTP-B and C were 50-100% [134,206]. 2011 Percutaneous Coronary Intervention study: No difference in hospital mortality between cirrhotics undergoing PCI, conventional CABG, or off-pump CABG compared to non-cirrhotics [207]. 2013 CABG study: LC (n=6,446) was independently associated with increased mortality (OR 6.9), morbidity (OR 1.6), length of stay (+1.2 days; $p < 0.001$), and hospital charges (+$22,491; $p < 0.001$). Off-pump CABG was unaffected by LC unless severe, while on-pump CABG increased mortality regardless of LC severity [208].	Historically associated with a very high mortality [97,134], with Bhangui et al. in 2012 referring to several studies (1954-2004) [209-211], and was corroborated by a meta-analysis by Modi et al. of nine cardiac surgery trials [205]. Bare Metal Stents consensus: BMS are favored due to minimal duration of dual antiplatelet therapy and inherent bleeding risks [207,212-215]. Previous CABG studies: de Goede et al. [134] concluded CABG in LC had an increased risk of mortality (17 vs. 3%, OR 6.67), complications (43 vs. 28%, OR 1.99), longer hospitalization, and costs compared to non-cirrhotics [216]. Mortality rate skyrocketed from 7.7% for less than two complications to 59% for those with two or more (OR 17.48) [207]. A 2015 study by Lopez-Delgado provides additional considerations not covered in this review specifically on cardiac surgery [51].
Emergency	Incidence of cirrhosis is ~1% of all trauma admissions [217]. Emergency surgery in LC has been repeatedly shown to be associated with a higher morbidity and mortality (50% vs. 18%) as compared to elective surgery [97,201,218]. 2013 LC Trauma Center Study: Emergency surgery mortality is lower at Level I centers vs. others (10.3% vs. 14.0%, p=0.001; OR 0.70, p=0.004) [217].	Buker et al., concluded although 85% of the North American population lives within a 1-hour catchment area of a trauma center, under-triage still occurs for various reasons and >1/3 of patients with severe injuries are admitted to nontrauma centers [217]. 2013 LC Trauma Surgery Study: Further breakdown of that prospective 2008-2011 study revealed CTP-A, B, and C mortality ranged from 8, 32, and 45% (p=0.003), with a similar trend in MELD scores of ≥10 vs. <10 (30.0% vs. 9.5%, OR 4.07, p=0.016) [219].

	2013 LC Trauma Surgery Study: Overall complication rate in cirrhotics and controls were higher (31.5% vs. 7.1%, P < 0.001), in-hospital mortality (20.7% vs. 6.5%, p=0.001) [219].	Part of a de Goede et al.'s analysis [134] of three earlier studies from 2004-2011 [219-221] mortality of cirrhotic vs. non-cirrhotic trauma patients was 12% vs. 6% (OR 5.65), with an overall severe complication rate of 10% vs. 4% (OR 2.05), while trauma laparotomy mortality increased to 40-45% vs. 15-24% (OR 4.35-7.60). In general, the cirrhotics had longer surgical ICU stays, higher hospital costs compared to non-cirrhotics [134].

Table 4: Comparison of operative mortality statistics in different settings, organ systems, and techniques used.

Conclusion

LC clearly has a potentially profound adverse effect for poor outcomes with surgery. Complicated pathophysiology interactions, combined with a general lack of LC controlled trials or even ejection of LC stages from clinical trials, makes finding guidance in LC management difficult. This review attempted to deconstruct and explore the juxtaposition of these complex aspects. In general, the earlier LC is diagnosed and the lower the stage, the better the outcomes are for the entire perioperative management. However, the timing of surgery often does not allow proper preparation, which is why insight and understanding of the complexities for these patients is critical to best direct patient selection for surgery, but also to optimize the complete perioperative management.

5 Best Practice Recommendations

Maintain appropriate levels of albumin, hematocrit, and sodium during the perioperative period.

Use a lower threshold for AKI than historically proposed. Current evidence is >50% increase in serum creatinine level from the stable baseline value in <6 months or an increase of >0.3 mg/dL in <48 hours. This definition of AKI accurately predicts 30-day mortality, length of hospital stay, and organ failure.

If preoperative patient optimization is not possible, a cost-benefit decision should be made between laparoscopic and open surgery with respect to type of surgery and conversion time required if necessary, in order to minimize blood loss and anesthetic exposure. Liver cirrhosis in the surgical setting is best optimized with early diagnosis, routine evaluation by a combination of imaging, CTP, and MELD scores, with medication adjustments for complications, and abstinence from causative factors if applicable.

Refrain from NSAID and morphine derivative usage, rather opt for Fentanyl for analgesia.

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