

## 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].

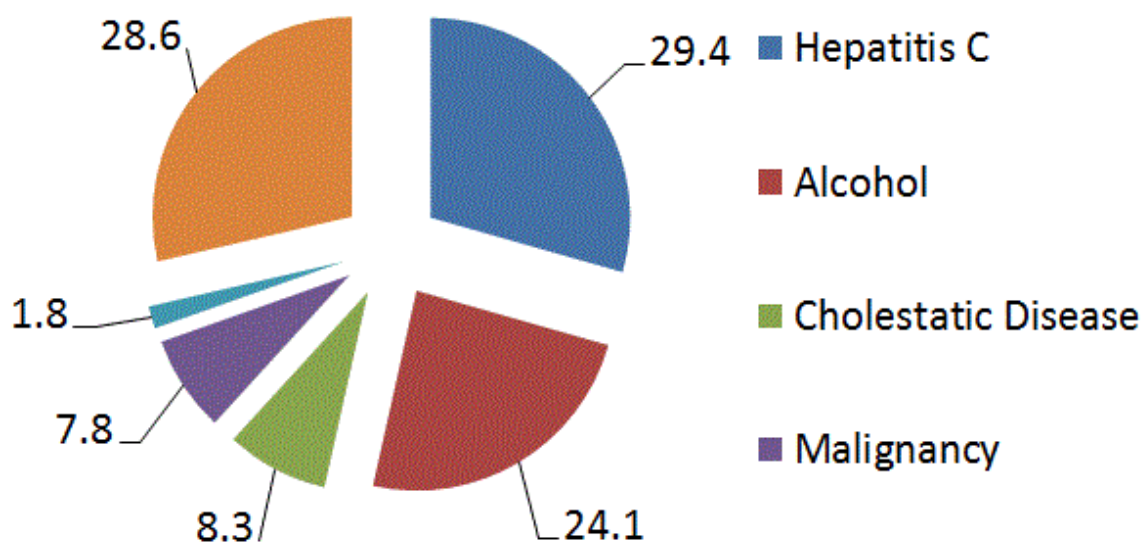
Hepatitis B and C viruses (HBV/HCV) can cause chronic viral hepatitis, possibly culminating in LC and hepatocellular carcinoma (HCC). HBV is a DNA virus with increased incidence in sub-Saharan Africa and Asia [6], while HCV is a RNA virus that chronically infects 80% of patients and further causes LC 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<sup>2</sup>) [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
<b>Immunology/Hematology</b>	
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]

<p>Coagulopathy: Antithrombotic 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</p>	<p>Vit. K 1-5 mg po depending on bleed                  Blood products: [160]                  RBC transfusion                  Cryoprecipitate &gt;&gt; FFP                  Depends on volume status                  Maintain Fibrinogen &gt;120</p>
<p>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</p>	<p>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]</p>
<p><b>Cardiopulmonary</b></p>	
<p>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</p>	<p>Liver transplant [36,47,48]                  Post-op death predictors: [46-48,54]                  PO2 &lt;50 mmHg                  Large intrapulmonary shunts                  Oxygen administration and supplemental care</p>
<p>Portopulmonary Hypertension [35-37]                  ↑ pulmonary vascular resistance, similar to PAH                  PHTN of 15 mmHg, or portocaval gradient &gt; 5 mmHg                  mPAP &gt; 25 mmHg and mPAOP &lt; 15 mmHg                  mPAP - mPAOP (transpulmonary gradient) &gt; 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</p>	<p>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]</p>
<p>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]</p>	<p>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</p>

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

	Terlipressin 3-12.5 mg qtt 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]
<b>Central Nervous System</b>	
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

Thrombocytopenia, 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  $PO_2 < 50$  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  $\geq 50$  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  $\beta$ -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,  $\geq 50\%$  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 adrenocorticotrophic 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- $\alpha$ , IL-1 $\beta$ , 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 vasoconstrictor 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  $\geq 1.5$  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  $\geq 6$  defining PHTN. As HVPG rises  $\geq 10$ , 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  $\leq 10$  mmHg demonstrated a 90% probability of not developing clinical decompensation within 4 years, and every 1 mmHg  $\geq 10$ , 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  $\leq 2.7$  g/dL associated with surgical complications [78,102]. Albumin, a recurring therapy in LC, appears to restore endothelial glycoylax 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= $\sim$ 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 ( $\geq$ 0.80)	
AST/ALT ratio > 1 [167]	Sn (0.24); Sp (0.87)	

<b>APRI &gt; 0.80</b> [167]	Sn (0.61); Sp (0.83); PPV (0.62); NPV (0.82); Accuracy (0.70)		
<b>FibroTest®</b> [104,111]	Sn (0.71); Sp 0.87); +LR (5.49); -LR (0.33); OR (16.77)		
<b>Hyaluronic Acid</b> [112]	Sn (0.68); Sp (0.71)		
<b>Evaluation Method</b>	Mortality Statistical Parameters		
<b>MELD Mortality 30 d (L) vs. 90 d (R)[%]</b> [122]	MELD 6-9	1.9	3.5
	MELD 10-14	3.6	8.9
	MELD 15-19	3.6	14.3
	MELD 20-24	12.5	12.5
	MELD ≥25	36.4	63.6
<b>MELD Conclusion</b>	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%)		
<b>MELDNa Mortality 30 d (L) vs. 90 d (R)[%]</b> [123,131]	MELD 6-9	1.2	1.9
	MELD 10-14	3.9	6.2
	MELD 15-19	1.9	13.2
	MELD 20-24	11.8	20.6
	MELD ≥25	31.3	50
<b>MELDNa Conclusion</b>	Cutoff score for MELDNa ≥10=best Sn (30-d: 83.0%, 90-d: 86.0%) Cutoff score for MELDNa ≥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)		
<b>CTP Class [%]</b> [123]	CTP-A (H. 10%)	1.0	2.1
	CTP-B (H. 30-31%)	9.5	22.1
	CTP-C (H. 73-82%)	22.1	54.5
<b>30-d MELD + Albumin + HCT vs. Traditional MELD (Sn/Sp/PPV/NPV) [%]</b> [121]	Combination Method	Traditional Method	
	MELD ≥10: 63/90/31/97	67/61/13/96	
	MELD ≥15: 38/97/50/95	44/88/24/95	
	MELD ≥20: 38/100/100/95	33/95/38/95	
<b>30-d CTP + Albumin + HCT vs. Traditional CTP (Sn/Sp/PPV/NPV) [%]</b> [121]	CTP-A: 80/82/29/98	67/44/11/93	
	CTP-B: 60/91/38/97	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 Ratio (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, α2-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 meta-analysis (Table 2) [118]. De Robertis et al. noted LS measurements should be postponed  $\geq 3$  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<sup>®</sup>, 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<sup>®</sup> 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  $\geq 26$  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  $\geq 10$  having better Sn while MELD  $\geq 25$  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  $\geq 20$  [125].

### MELD scoring variations: $\Delta$ MELD and MELDNa

There have been attempts by adding variables or monitoring changes in in MELD to improve its accuracy [69]. For example, a  $\Delta$ MELD 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  $\geq 10$  had better Sn than  $\geq 25$  [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  $\geq 700$  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  $\geq 14$  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  $\geq IV$ , CTP score  $\geq 7$ , MELD score  $\geq 10$ , and MELDNa score  $\geq 10$  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  $\leq 3.05$  mg/dL and a hematocrit  $\leq 35.55\%$  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  $\geq 10$  (J=0.53,  $p < 0.01$ ) (Table 2). These findings are corroborated by Paolino et al., by adding an albumin  $\leq 2.5$  mg/dL to MELD  $\geq 15$  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-life 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]
<b>Volatile Agents</b>		
Halothane	CYP-2A6	↓ HBF and ↑ drug induced hepatitis
Sevoflurane	CYP-2E1	Preserves HBF
Desflurane	CYP-2E1	Clinical unremarkable ↑ AST/ALT/ALP, especially Sevoflurane
Isoflurane	CYP-2E1	
<b>Induction Agents</b>		
Etomidate	N/A	↑ hepatic arterial resistance +/- ↓ CO → ↓ HBF
Thiopental	N/A	↑ 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		
<b>Paralytic Agents</b>		
Vecuronium Rocuronium	CYP-3A4 CYP-2D6	Steroid base → liver metabolism ↓ clearance, ↑ half-life, ↑ neuromuscular blockade in LC
Atracurium	Non-hepatic/renal	Unaffected by cirrhosis
<b>Opioid Agents</b>		
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 remifentanyl 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
<b>Laparoscopy (Lap) vs. Open techniques</b>	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].
<b>Abdominal – Overall</b>	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].	
<b>Hernia</b>	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].

<p><b>Cholecystectomy</b></p>	<p>LC creates a 3.4-fold higher mortality rate than non-cirrhotics [134].</p> <p>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].</p> <p>Pre-Lap mortality ranged 7.5-26%, due to high representation of CTP-C patients [168] with a mortality of 23-50% [97].</p>	<p>Prevalence of gallstones in cirrhotics is estimated at 29-46%. [168,188]</p> <p>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].</p>
<p><b>Gastric</b></p>	<p>Emergency surgery: Complicated peptic ulcer repair in cirrhotics ranges from 23% to 64% [97].</p> <p>2010 Gastric cancer: Radical gastrectomy, historically, has a 56% overall morbidity, and CTP-A and B mortality were 54% and 67%, respectively [134,192].</p> <p>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].</p>	<p>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].</p> <p>Lap surgery, combined with a PPI and endoscopic hemostatic techniques, has reduced the need for surgical resection and reduced emergency surgery mortality [97,196].</p> <p>In Guo et al.'s study, mortality is more frequent in CTP-B than CTP-A (<math>p &lt; 0.05</math>), 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].</p>
<p><b>Pancreatic</b></p>	<p>2013 study: Cirrhotics are at risk for higher amount of statistically significant intraoperative blood loss of over 500 ml (<math>P=0.015</math>) [197].</p> <p>2011 study: Cirrhotics have a higher complication rate (47% vs. 22%, <math>P=0.035</math>), reoperation requirements (34% vs. 12%, <math>P=0.039</math>), and prolonged hospital stay (28 vs. 24 days) during which required twice the ICU stay and twice as many transfusions [198].</p>	<p>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].</p> <p>2013 study by Nakeet et al., was between 2002 and 2011.</p> <p>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 (<math>n=2</math>), and 30-day mortality was 3% equally between CTP-A and non-cirrhotics.</p>
<p><b>Colorectal</b></p>	<p>Mortality rate, historically ranged from 48 to 77% [135,136,200].</p> <p>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].</p> <p>2013 study: Overall colorectal surgery mortality was 8.7% (non-liver disease) vs. 13.3% (non-cirrhotics), and 24.1% (cirrhotics) [203].</p>	<p>Meunier et al. in 2008 found postoperative infection as the largest risk for mortality, increasing it from 11% to 53% [204].</p> <p>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].</p>
<p><b>Cardiac</b></p>	<p>2012 Overall study: Mortality of 5, 32-35, and 67-70% for CTP-A, B, and C [133,205].</p> <p>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].</p> <p>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].</p> <p>2013 CABG study: LC (<math>n=6,446</math>) was independently associated with increased mortality (OR 6.9), morbidity (OR 1.6), length of stay (+1.2 days; <math>p &lt; 0.001</math>), and hospital charges (+\$22,491; <math>p &lt; 0.001</math>). Off-pump CABG was unaffected by LC unless severe, while on-pump CABG increased mortality regardless of LC severity [208].</p>	<p>Historically associated with a very high mortality [97,134], with Bhangu 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].</p> <p>Bare Metal Stents consensus: BMS are favored due to minimal duration of dual antiplatelet therapy and inherent bleeding risks [207,212-215].</p> <p>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].</p> <p>A 2015 study by Lopez-Delgado provides additional considerations not covered in this review specifically on cardiac surgery [51].</p>
<p><b>Emergency</b></p>	<p>Incidence of cirrhosis is ~1% of all trauma admissions [217].</p> <p>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].</p> <p>2013 LC Trauma Center Study: Emergency surgery mortality is lower at Level I centers vs. others (10.3% vs. 14.0%, <math>p=0.001</math>; OR 0.70, <math>p=0.004</math>) [217].</p>	<p>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 &gt;1/3 of patients with severe injuries are admitted to nontrauma centers [217].</p> <p>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% (<math>p=0.003</math>), with a similar trend in MELD scores of <math>\geq 10</math> vs. <math>&lt; 10</math> (30.0% vs. 9.5%, OR 4.07, <math>p=0.016</math>) [219].</p>

	<p>2013 LC Trauma Surgery Study: Overall complication rate in cirrhotics and controls were higher (31.5% vs. 7.1%, <math>P &lt; 0.001</math>), in-hospital mortality (20.7% vs. 6.5%, <math>p=0.001</math>) [219].</p>	<p>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].</p>
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**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.

## References

- Hanje AJ, Patel T (2007) Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol* 4: 266-276.
- Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, et al. (2015) The Epidemiology of Cirrhosis in the United States: A Population-based Study. *J Clin Gastroenterol* 49: 690-696.
- Shawcross DL, Austin MJ, Abeles RD, McPhail MJ, Yeoman AD, et al. (2012) The impact of organ dysfunction in cirrhosis: survival at a cost? *J Hepatol* 56: 1054-1062.
- Ioannou GN, Boyko EJ, Lee SP (2006) The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. *Am J Gastroenterol* 101: 76-82.
- Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, et al. (2012) Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *J Hepatol* 56: 234-240.
- Lefton HB, Rosa A, Cohen M (2009) Diagnosis and epidemiology of cirrhosis. *Med Clin North Am* 93: 787-799, vii.
- Leandro G, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, et al. (2006) Relationship Between Steatosis, Inflammation, and Fibrosis in Chronic Hepatitis C: A Meta-Analysis of Individual Patient Data. *Gastroenterology* 130:1636-1642.
- Rehm J, Mathers C, Popova S, Thavncharoensap M, Teerawattananon Y, et al. (2009) Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 373: 2223-2233.
- Orman ES, Odena G, Bataller R (2013) Alcoholic liver disease: pathogenesis, management, and novel targets for therapy. *J Gastroenterol Hepatol* 1:77-84.
- Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, et al. (1997) Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 41: 845-850.
- Bradley KA, Rubinsky AD, Sun H, Bryson CL, Bishop MJ, et al. (2011) Alcohol screening and risk of postoperative complications in male VA patients undergoing major non-cardiac surgery. *J Gen Intern Med* 26:162-169.
- World Health Organization. Global Status Report On Noncommunicable Diseases 2014.
- Bedogni G, Nobili V, Tiribelli C (2014) Epidemiology of fatty liver: an update. *World J Gastroenterol* 20: 9050-9054.
- Yilmaz Y (2012) Review article: Is non-alcoholic fatty liver disease a spectrum, or are steatosis and non-alcoholic steatohepatitis distinct conditions? *Aliment Pharmacol Ther* 36:815-823.
- Arroyo V, García-Martínez R, Salvatella X (2014) Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 61: 396-407.
- Wiest R, Lawson M, Geuking M (2014) Reply to: "bacterial translocation in liver cirrhosis: site and role in fibrogenesis". *J Hepatol* 61: 710-711.
- Albillos A, Lario M, Álvarez-Mon M (2014) Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 61: 1385-1396.
- Muñoz L, José Borrero M, Ubeda M, Lario M, Díaz D, et al. (2012) Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. *Hepatology* 56:1861-1869.
- Jenne CN, Kubes P (2013) Immune surveillance by the liver. *Nat Immunol* 14: 996-1006.
- Berry K, Taylor J, Liou IW, Ioannou GN (2015) Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. *Clin Gastroenterol Hepatol* 13: 585-593.
- Pradella P, Bonetto S, Turchetto S, Uxa L, Comar C, et al. (2011) Platelet production and destruction in liver cirrhosis. *J Hepatol* 54: 894-900.
- Weksler BB (2007) Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. *Aliment Pharmacol Ther* 26 Suppl 1: 13-19.
- Arshad F, Stoof SC, Leebeek FW, Ruitenbeek K, et al. (2015) Infusion of DDAVP does not improve primary hemostasis in patients with cirrhosis. *Liver Int* 35: 1809-1815.
- Violi F, Ferro D, Basili S (2011) Coagulopathy of chronic liver disease. *N Engl J Med* 365: 1453.
- Tripodi A, Mannucci PM (2011) The coagulopathy of chronic liver disease. *N Engl J Med* 365: 147-156.

26. Cerini F, Gonzalez JM, Torres F, et al. (2015) Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. *Hepatology* 62: 575-583.
27. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W; Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology (2007) Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 46: 922-938.
28. Montalto P, Vlachogiannakos J, Cox DJ, Pastacaldi S, Patch D, et al. (2002) Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *J Hepatol* 37: 463-470.
29. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, et al. (2010) Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. *Hepatology* 52: 249-255.
30. Gatt A, Riddell A, Calvaruso V, Tuddenham EG, Makris M, et al. (2010) Enhanced thrombin generation in patients with cirrhosis-induced coagulopathy. *J Thromb Haemost* 8: 1994-2000.
31. Akamatsu N, Sugawara Y, Nakazawa A, Nishioka Y, Kaneko J, et al. (2015) Hemostatic status in liver transplantation: association between preoperative procoagulants/anticoagulants and postoperative hemorrhaging/thrombosis. *Liver Transpl* 21:258-265
32. Millwala F, Nguyen GC, Thuluvath PJ (2007) Outcomes of patients with cirrhosis undergoing non-hepatic surgery: risk assessment and management. *World J Gastroenterol* 13: 4056-4063.
33. French CJ, Bellomo R, Angus P (2003) Cryoprecipitate for the correction of coagulopathy associated with liver disease. *Anaesth Intensive Care* 31: 357-361.
34. Qi X, Dai J, Yang M, Ren W, Jia J, et al. (2015) Association between Portal Vein Thrombosis and Survival in Non-Liver-Transplant Patients with Liver Cirrhosis: A Systematic Review of the Literature. *Gastroenterol Res Pract* 2015: 480842.
35. Herve P, Le Pavec J, Sztrymf B, Decante B, Savale L, et al. (2007) Pulmonary vascular abnormalities in cirrhosis. *Best Pract Res Clin Gastroenterol* 21: 141-159.
36. Aldenkortt F, Aldenkortt M, Caviezel L, Waeber JL, Weber A, et al. (2014) Portopulmonary hypertension and hepatopulmonary syndrome. *World J Gastroenterol* 20: 8072-8081.
37. Grace JA, Angus PW (2013) Hepatopulmonary syndrome: update on recent advances in pathophysiology, investigation, and treatment. *J Gastroenterol Hepatol* 28: 213-219.
38. Enache I, Oswald-Mammosses M, Woehl-Jaegle ML, Habersetzer F, Di Marco P, et al. (2013) Cirrhotic cardiomyopathy and hepatopulmonary syndrome: prevalence and prognosis in a series of patients. *Respir Med* 107: 1030-1036.
39. Nunes H, Lebrec D, Mazmanian M, Capron F, Heller J, et al. (2001) Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. *Am J Respir Crit Care Med* 164: 879-885.
40. Sztrymf B, Libert JM, Mougeot C, Lebrec D, Mazmanian M, et al. (2005) Cirrhotic rats with bacterial translocation have higher incidence and severity of hepatopulmonary syndrome. *J Gastroenterol Hepatol* 20: 1538-1544.
41. Lee RF, Glenn TK, Lee SS (2007) Cardiac dysfunction in cirrhosis. *Best Pract Res Clin Gastroenterol* 21: 125-140.
42. Jalan R, Bernardi M (2013) Effective albumin concentration and cirrhosis mortality: from concept to reality. *J Hepatol* 59: 918-920.
43. Hervé P, Lebrec D, Brenot F, Simonneau G, Humbert M, et al. (1998) Pulmonary vascular disorders in portal hypertension. *Eur Respir J* 11: 1153-1166.
44. Bernardi M (2013) Cirrhotic Cardiomyopathy Main Features of Cirrhotic Cardiomyopathy Pathophysiology of Cirrhotic Clinical Relevance of Cirrhotic Cardiomyopathy 2:99-101.
45. Horvatis T, Drolz A, Roedl K, Herkner H, Ferlitsch A, et al. (2014) Von Willebrand factor antigen for detection of hepatopulmonary syndrome in patients with cirrhosis. *J Hepatol* 61: 544-549.
46. Bozbas SS, Eyuboglu F (2011) Evaluation of liver transplant candidates: A pulmonary perspective. *Ann Thorac Med* 6: 109-114.
47. Swanson KL, Wiesner RH, Krowka MJ (2005) Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology* 41: 1122-1129.
48. Nusrat S, Khan MS, Fazili J, Madhoun MF (2014) Cirrhosis and its complications: evidence based treatment. *World J Gastroenterol* 20: 5442-5460.
49. Pan H, Jenq C, Tsai M, Fan P, Chang C, et al. (2014) Alimentary Pharmacology and Therapeutics Scoring systems for 6-month mortality in critically ill cirrhotic patients?: a prospective analysis of chronic liver failure - sequential organ failure assessment score ( CLIF-SOFA ).
50. Rahman S, Mallett SV (2015) Cirrhotic cardiomyopathy: Implications for the perioperative management of liver transplant patients. *World J Hepatol* 7: 507-520.
51. Lopez-Delgado JC, Esteve F, Javierre C, Ventura JL, Mañez R, et al. (2015) Influence of cirrhosis in cardiac surgery outcomes. *World J Hepatol* 7: 753-760.
52. Karagiannakis DS, Papatheodoridis G, Vlachogiannakos J (2014) Recent Advances in Cirrhotic Cardiomyopathy. *Dig Dis Sci*.
53. Coeytaux RR, Schmit KM, Kraft BD, Kosinski AS, Mingo AM, et al. (2014) Comparative effectiveness and safety of drug therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. *Chest* 145: 1055-1063.
54. Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, et al. (2014) Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest* 146: 449-475.
55. Arab JP, Candia R, Zapata R, Muñoz C, Arancibia JP, et al. (2014) Management of nonalcoholic fatty liver disease: an evidence-based clinical practice review. *World J Gastroenterol* 20: 12182-12201.
56. Sasaki A, Nitta H, Otsuka K, Umemura A, Baba S, et al. (2014) Bariatric Surgery and Non-Alcoholic Fatty Liver Disease: Current and Potential Future Treatments. *Front Endocrinol (Lausanne)* 5:1-6.
57. Stojakovic T, Claudel T, Putz-Bankuti C, Fauler G, Scharnagl H, et al. (2010) Low-dose atorvastatin improves dyslipidemia and vascular function in patients with primary biliary cirrhosis after one year of treatment. *Atherosclerosis* 209:178-183.
58. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER (2010) Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. *Mayo Clin Proc* 85: 349-356.
59. Marik PE, Gayowski T, Starzl TE; Hepatic Cortisol Research and Adrenal Pathophysiology Study Group (2005) The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med* 33: 1254-1259.
60. Yaguchi H, Tsutsumi K, Shimono K, Omura M, Sasano H, et al. (1998) Involvement of high density lipoprotein as substrate cholesterol for steroidogenesis by bovine adrenal fasciculo-reticularis cells. *Life Sci* 62:1387-1395.
61. Jäättelä M, Ilvesmäki V, Voutilainen R, Stenman UH, Saksela E (1998) Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. *Endocrinology* 128:623-692.
62. Molijn GJ, Spek JJ, van Uffelen JC, de Jong FH, Brinkmann AO, et al. (1995) Differential adaptation of glucocorticoid sensitivity of peripheral blood mononuclear leukocytes in patients with sepsis or septic shock. *J Clin Endocrinol Metab* 80:1799-803.
63. Forman SA (2011) Clinical and molecular pharmacology of etomidate. *Anesthesiology* 114: 695-707.

64. Fede G, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, et al. (2012) Renal failure and cirrhosis: a systematic review of mortality and prognosis. *J Hepatol* 56: 810-818.
65. Moreau R, Lebrech D (2007) Diagnosis and treatment of acute renal failure in patients with cirrhosis. *Best Pract Res Clin Gastroenterol* 21: 111-123.
66. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, et al. (2007) Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. *Hepatology* 45: 223-229.
67. Morabito V, Novelli G, Jalan R (2013) When to use renal replacement therapy and bioartificial support for renal failure in patients with cirrhosis. *Clin Liver Dis* 2:116-119.
68. Arroyo V, Fernández J (2013) Relationship between systemic hemodynamics, renal dysfunction, and fluid retention in cirrhosis. *Clin Liver Dis* 2:120-122.
69. Lau T, Ahmad J (2013) Clinical applications of the Model for End-Stage Liver Disease (MELD) in hepatic medicine. *Hepat Med* 5: 1-10.
70. Peck-Radosavljevic M, Angeli P, Cordoba J, Farges O, Valla D (2015) Managing complications in cirrhotic patients. *United European Gastroenterol J* 3: 80-94.
71. Lenz K, Buder R, Kapun L, Voglmayr M (2015) Treatment and management of ascites and hepatorenal syndrome: an update. *Therap Adv Gastroenterol* 8: 83-100.
72. Afinogenova Y, Tapper EB (2015) The efficacy and safety profile of albumin administration for patients with cirrhosis at high risk of hepatorenal syndrome is dose dependent. *Gastroenterol Rep (Oxf)* 3: 216-221.
73. Runyon BA; AASLD (2013) Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 57: 1651-1653.
74. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, et al. (2015) Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. *Hepatology* 62: 567-574.
75. Dundar H (2015) Management of hepatorenal syndrome. *World J Gastroenterol* 4:277-286.
76. Orlando R, Floreani M, Padriani R, Palatini P (1999) Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis. *Clin Nephrol* 51: 341-347.
77. Tsien CD, Rabie R, Wong F (2013) Acute kidney injury in decompensated cirrhosis. *Gut* 62: 131-137.
78. Fu CM, Chang CH, Fan PC, Tsai MH, Lin SM, et al. (2014) Prognosis of critically ill cirrhotic versus non-cirrhotic patients: a comprehensive score-matched study. *BMC Anesthesiol* 14: 123.
79. Tandon P, Garcia-Tsao G (2011) Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 9:260-265.
80. Wong F, O'Leary JG, Reddy KR, Patton H, Kamath PS, et al. (2013) New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 145: 1280-1288.
81. Garcia-Tsao G, Parikh CR, Viola A (2008) Acute kidney injury in cirrhosis. *Hepatology* 48: 2064-2077.
82. Iwasa M, Takei Y (2015) Pathophysiology and management of hepatic encephalopathy 2014 update: Ammonia toxicity and hyponatremia. *Hepatol Res* .
83. Coltart I, Tranah TH, Shawcross DL (2013) Inflammation and hepatic encephalopathy. *Arch Biochem Biophys* 536: 189-196.
84. Savlan I, Liakina V, Valantinas J (2014) Concise review of current concepts on nomenclature and pathophysiology of hepatic encephalopathy. *Medicina (Kaunas)* 50: 75-81.
85. Cooper AJ, Plum F (1987) Biochemistry and physiology of brain ammonia. *Physiol Rev* 67: 440-519.
86. Ahluwalia V, Heuman DM, Feldman G, Wade JB, Thacker LR, et al. (2015) Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. *J Hepatol* 62: 75-82.
87. Tapper EB, Jiang ZG, Patwardhan VR (2015) Refining the ammonia hypothesis: a physiology-driven approach to the treatment of hepatic encephalopathy. *Mayo Clin Proc* 90: 646-658.
88. Iwasa M, Kobayashi Y, Mifuji-Moroka R, Hara N, Miyachi H, et al. (2013) Branched-chain amino acid supplementation reduces oxidative stress and prolongs survival in rats with advanced liver cirrhosis. *PLoS One* 8: e70309.
89. Als-Nielsen BE, Gluud LL, Gluud CN (2005) [Nonabsorbable disaccharides for the treatment of hepatic encephalopathy--a systematic review of randomized clinical trials--a secondary publication]. *Ugeskr Laeger* 167: 179-182.
90. Bedossa P, Garcia-Tsao G, Jain D (2013) Cirrhosis Regression and Subclassification. *Surg Pathol Clin* 6:295-309.
91. Serpaggi J, Carnot F, Nalpas B, Canioni D, Guéchet J, et al. (2006) Direct and indirect evidence for the reversibility of cirrhosis. *Hum Pathol* 37: 1519-1526.
92. D'Ambrosio R, Aghemo A, Rumi MG, Ronchi G, Donato MF, et al. (2012) A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. *Hepatology* 56: 532-543.
93. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, et al. (2009) Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol* 50:923-928.
94. Tian C, Singal AG (2014) Diagnostic paracentesis is associated with improved survival among hospitalized patients with cirrhosis. *Gastroenterology* 146: 858-859.
95. Terg R, Casciato P, Garbe C, Cartier M, Stieben T, et al. (2015) Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: a multicenter prospective study. *J Hepatol* 62: 1056-1060.
96. Chen RP, Zhu Ge XJ, Huang ZM, Ye XH, Hu CY, et al. (2014) Prophylactic use of transjugular intrahepatic portosystemic shunt aids in the treatment of refractory ascites: meta-regression and trial sequential meta-analysis. *J Clin Gastroenterol* 48:290-299.
97. Bhangui P, Laurent A, Amathieu R, Azoulay D (2012) Assessment of risk for non-hepatic surgery in cirrhotic patients. *J Hepatol* 57: 874-884.
98. Habib A, Desai K, Hickey R, Thornburg B, Vouche M, et al. (2015) Portal Vein Recanalization-Transjugular Intrahepatic Portosystemic Shunt Using the Transsplenic Approach to Achieve Transplant Candidacy in Patients with Chronic Portal Vein Thrombosis. *J Vasc Interv Radiol* 26:499-506.
99. Hongwei C, Zhang L, Maoping L, Yong Z, Chengyou D, et al. (2015) Era of liver transplantation: combined anatomic splenectomy and anticoagulant therapy in prevention of portal vein thrombosis after splenectomy. *Hepatogastroenterology* 62: 405-409.
100. Saab S, Nieto JM, Lewis SK, Runyon BA (2006) TIPS versus paracentesis for cirrhotic patients with refractory ascites. *Cochrane Database Syst Rev*.
101. Sabbagh C, Fuks D, Regimbeau JM (2014) Non-hepatic gastrointestinal surgery in patients with cirrhosis. *J Visc Surg* 151: 203-211.
102. Kao H-K, Chen WF, Chen C-H, Shyu VB-H, Cheng M-H, et al. (2012) The roles of albumin levels in head and neck cancer patients with liver cirrhosis undergoing tumor ablation and microsurgical free tissue transfer. *PLoS One* 7:e52678.
103. Alphonsus CS, Rodseth RN (2014) The endothelial glycocalyx: a review of the vascular barrier. *Anaesthesia* 69: 777-784.
104. Salkic NN, Jovanovic P, Hauser G, Brcic M (2014) FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. *Am J Gastroenterol* 109: 796-809.
105. Bedossa P, Dargère D, Paradis V (2003) Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 38: 1449-1457.
106. Wong GL (2014) Prediction of fibrosis progression in chronic viral hepatitis. *Clin Mol Hepatol* 20: 228-236.

107. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, et al. (2002) Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 97: 2614-2618.
108. Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, et al. (2012) Beyond "cirrhosis": a proposal from the International Liver Pathology Study Group. *Am J Clin Pathol* 137: 5-9.
109. Rastogi A, Maiwall R, Bihari C, Ahuja A, Kumar A, et al. (2013) Cirrhosis histology and Laennec staging system correlate with high portal pressure. *Histopathology* 62: 731-741.
110. Martin J, Khatri G, Gopal P, Singal AG (2015) Accuracy of ultrasound and noninvasive markers of fibrosis to identify patients with cirrhosis. *Dig Dis Sci* 60: 1841-1847.
111. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, et al. (2005) Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 128: 343-350.
112. Kao H-K, Chen WF, Chen C-H, Shyu VB-H, Cheng M-H, et al. (2012) The roles of albumin levels in head and neck cancer patients with liver cirrhosis undergoing tumor ablation and microsurgical free tissue transfer. *PLoS One* 7:e52678.
113. Xie S, Sun Y, Wang L, Yang Z, Luo J, et al. (2015) Assessment of liver function and liver fibrosis with dynamic Gd-EOB-DTPA-enhanced MRI. *Acad Radiol* 22: 460-466.
114. Choi YR, Lee JM, Yoon JH, Han JK, Choi BI (2013) Comparison of magnetic resonance elastography and gadoxetate disodium-enhanced magnetic resonance imaging for the evaluation of hepatic fibrosis. *Invest Radiol* 48:607-613.
115. Venkatesh SK, Wang G, Lim SG, Wee A (2014) Magnetic resonance elastography for the detection and staging of liver fibrosis in chronic hepatitis B. *Eur Radiol* 24: 70-78.
116. Jung KS, Kim SU, Ahn SH, Park YN, Kim DY, et al. (2011) Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology* 53:885-894.
117. De Robertis R, D'Onofrio M, Demozzi E, Crosara S, Canestrini S, et al. (2014) Noninvasive diagnosis of cirrhosis: a review of different imaging modalities. *World J Gastroenterol* 20: 7231-7241.
118. Pavlov CS, Casazza G, Nikolova D, Tsochatzis E, Burroughs AK, et al. (2015) Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. *Cochrane Database Syst Rev* 1: CD010542.
119. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, et al. (2007) Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology* 132: 1261-1269.
120. Hoteit MA, Ghazale AH, Bain AJ, Rosenberg ES, Easley KA, et al. (2008) Model for end-stage liver disease score versus Child score in predicting the outcome of surgical procedures in patients with cirrhosis. *World J Gastroenterol* 14: 1774-1780.
121. Harrington AN, Chu EW, Garg M, Divino CM (2013) Serum markers for predicting abdominal surgery outcomes in patients with cirrhosis. *J Gastrointest Surg* 17: 696-701.
122. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, et al. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334: 693-699.
123. Cho HC, Jung HY, Sinn DH, Choi MS, Koh KC, et al. (2011) Mortality after surgery in patients with liver cirrhosis: comparison of Child-Turcotte-Pugh, MELD and MELDNa score. *Eur J Gastroenterol Hepatol* 23: 51-59.
124. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. (2007) Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 246:502-509.
125. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL (2005) Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg* 242: 244-251.
126. Huo T-I, Wu J-C, Lin H-C, Lee F-Y, Hou M-C, et al. (2005) Evaluation of the increase in model for end-stage liver disease (DeltaMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. *J Hepatol* 42:826-832
127. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, et al. (2003) Longitudinal assessment of mortality risk among candidates for liver transplantation. *Liver Transpl* 9: 12-18.
128. B.E. F, G. G-T (2013) Hypervolemic hyponatremia: Clinical significance and management. *Clin Liver Dis* 2:109-112.
129. Hsu CY, Lin HC, Huang YH, Su CW, Lee FY, et al. (2010) Comparison of the model for end-stage liver disease (MELD), MELD-Na and MELDNa for outcome prediction in patients with acute decompensated hepatitis. *Dig Liver Dis* 42: 137-142.
130. Kim DH, Kim SH, Kim KS, Lee WJ, Kim NK, Noh SH, et al. (2013) Predictors of mortality in cirrhotic patients undergoing extrahepatic surgery: Comparison of Child-Turcotte-Pugh and model for end-stage liver disease-based indices. *ANZ J Surg* 84:832-836.
131. Neeff HP, Streule GC, Drognitz O, Tittelbach-Helmrich D, Spangenberg HC, et al. (2014) Early mortality and long-term survival after abdominal surgery in patients with liver cirrhosis. *Surgery* 155: 623-632.
132. Cooper GS, Bellamy P, Dawson NV, Desbiens N, Fulkerson WJ Jr, et al. (1997) A prognostic model for patients with end-stage liver disease. *Gastroenterology* 113: 1278-1288.
133. Nicoll A (2012) Surgical risk in patients with cirrhosis. *J Gastroenterol Hepatol* 27: 1569-1575.
134. de Goede B, Klitsie PJ, Lange JF, Metselaar HJ, Kazemier G (2012) Morbidity and mortality related to non-hepatic surgery in patients with liver cirrhosis: a systematic review. *Best Pract Res Clin Gastroenterol* 26: 47-59.
135. Telem DA, Schiano T, Goldstone R, Han DK, Buch KE, et al. (2010) Factors that predict outcome of abdominal operations in patients with advanced cirrhosis. *Clin Gastroenterol Hepatol* 8: 451-457, quiz e58.
136. Paolino J, Steinhagen RM (2014) Colorectal surgery in cirrhotic patients. *ScientificWorldJournal* 2014: 239293.
137. Lin TY, Liao JC, Chen WJ, Chen LH, Niu CC, et al. (2014) Surgical risks and perioperative complications of instrumented lumbar surgery in patients with liver cirrhosis. *Biomed J* 37: 18-23.
138. Gibbs J, Cull W, Henderson W, Daley J, Hur K, et al. (1999) Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 134: 36-42.
139. Kim JJ, Kim JH, Koo JK, Choi YJ, Ko SY, et al. (2014) The Refit model for end-stage liver disease-Na is not a better predictor of mortality than the Refit model for end-stage liver disease in patients with cirrhosis and ascites. *Clin Mol Hepatol* 20: 47-55.
140. Dalal A, Lang JDJ (2013) Anesthetic considerations for patients with ischemic heart disease. *Bol Asoc Med P R* 81.
141. Chandok N, Watt KD (2010) Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 85: 451-458.
142. Dwyer JP, Jayasekera C, Nicoll A (2014) Analgesia for the cirrhotic patient: a literature review and recommendations. *J Gastroenterol Hepatol* 29: 1356-1360.
143. Delcò F, Tchambaz L, Schlienger R, Drewe J, Krähenbühl S (2005) Dose adjustment in patients with liver disease. *Drug Saf* 28: 529-545.
144. Krystallis C, Masterton GS, Hayes PC, Plevris JN (2012) Update of endoscopy in liver disease: more than just treating varices. *World J Gastroenterol* 18: 401-411.
145. Kharasch ED, Hankins DC, Fenstamaker K, Cox K (2000) Human halothane metabolism, lipid peroxidation, and cytochromes P(450)2A6 and P(450)3A4. *Eur J Clin Pharmacol* 55: 853-859.
146. Gatecel C, Losser MR, Payen D (2003) The postoperative effects of halothane versus isoflurane on hepatic artery and portal vein blood flow in humans. *Anesth Analg* 96: 740-74, table of contents.



147. Soleimanpour H, Safari S, Rahmani F, Jafari Rouhi A, Alavian SM (2015) Intravenous hypnotic regimens in patients with liver disease; a review article. *Anesth Pain Med* 5: e23923.
148. Kharasch ED, Hankins DC, Cox K (1999) Clinical isoflurane metabolism by cytochrome P450 2E1. *Anesthesiology* 90: 766-771.
149. Thomson IA, Fitch W, Hughes RL, Campbell D, Watson R (1986) Effects of certain i.v. anaesthetics on liver blood flow and hepatic oxygen consumption in the greyhound. *Br J Anaesth* 58: 69-80.
150. Restrepo JG, Garcia-Martín E, Martínez C, Agúndez JA (2009) Polymorphic drug metabolism in anaesthesia. *Curr Drug Metab* 10: 236-246.
151. Trouvin JH, Farinotti R, Haberer JB, Servin F, Chauvin M, et al. (1988) Pharmacokinetics of midazolam in anaesthetized cirrhotic patients. *Br J Anaesth* 60: 762-767.
152. Peppers MP (1996) Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. *Pharmacotherapy* 16: 49-57.
153. Imani F, Motavaf M, Safari S, Alavian SM (2014) The therapeutic use of analgesics in patients with liver cirrhosis: a literature review and evidence-based recommendations. *Hepat Mon* 14: e23539.
154. Werawatganon T, Charuluxanun S (2005) Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev*.
155. Kampe S, Weinreich G, Darr C, Eicker K, Stamatis G, Hachenberg T (2014) The impact of epidural analgesia compared to systemic opioid-based analgesia with regard to length of hospital stay and recovery of bowel function: retrospective evaluation of 1555 patients undergoing thoracotomy. *J Cardiothorac Surg* 9:175
156. Jørgensen H, Wetterslev J, Moïniche S, Dahl JB (2000) Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*.
157. Jacobs JP, Mavroudis C, Jacobs ML, Maruszewski B, Tchervenkov CI, et al. (2006) What is operative mortality? Defining death in a surgical registry database: a report of the STS Congenital Database Taskforce and the Joint EACTS-STC Congenital Database Committee. *Ann Thorac Surg* 81:1937-1941
158. Richardson AJ, Laurence JM, Lam VW (2014) Use of pre-operative steroids in liver resection: a systematic review and meta-analysis. *HPB (Oxford)* 16: 12-19.
159. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H (2014) Management of thrombocytopenia due to liver cirrhosis: a review. *World J Gastroenterol* 20: 2595-2605.
160. Amarapurkar PD, Amarapurkar DN (2011) Management of coagulopathy in patients with decompensated liver cirrhosis. *Int J Hepatol* 2011: 695470.
161. Kinjo N, Kawanaka H, Akahoshi T, Matsumoto Y, Kamori M, et al. (2014) Portal vein thrombosis in liver cirrhosis. *World J Hepatol* 6: 64-71.
162. Raja K, Jacob M, Asthana S (2014) Portal vein thrombosis in cirrhosis. *J Clin Exp Hepatol* 4: 320-331.
163. Cui SB, Shu RH, Yan SP, Wu H, Chen Y, et al. (2015) Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. *Eur J Gastroenterol Hepatol* 27: 914-919.
164. Oudiz RJ, Galie N, Olschewski H, Torres F, Frost A, et al. (2009) Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol* 54: 1971-1981.
165. Anastasiadis SN, Giouleme OI, Germanidis GS, Vasiliadis TG (2015) Clinical Medicine Insights? Gastroenterology Relative Adrenal Insufficiency in Cirrhotic Patients 13-17.
166. Tyagi P, Sharma P, Sharma BC, Puri AS, Kumar A, Sarin SK (2011) Prevention of hepatorenal syndrome in patients with cirrhosis and ascites: a pilot randomized control trial between pentoxifylline and placebo. *Eur J Gastroenterol Hepatol* 23:210-217.
167. Ishizuka M, Kubota K, Kita J, Shimoda M, Kato M, Mori S (2014) Aspartate aminotransferase-to-platelet ratio index is associated with liver cirrhosis in patients undergoing surgery for hepatocellular carcinoma. *J Surg Res* 2-7.
168. Laurence JM, Tran PD, Richardson AJ, Pleass HC, Lam VW (2012) Laparoscopic or open cholecystectomy in cirrhosis: a systematic review of outcomes and meta-analysis of randomized trials. *HPB (Oxford)* 14: 153-161.
169. Poulsen TL, Thulstrup AM, Sørensen HT, Vilstrup H (2000) Appendicectomy and perioperative mortality in patients with liver cirrhosis. *Br J Surg* 87: 1664-1665.
170. Tsugawa K, Koyanagi N, Hashizume M, Tomikawa M, Ayukawa K, et al. (2001) A comparison of an open and laparoscopic appendectomy for patients with liver cirrhosis. *Surg Laparosc Endosc Percutan Tech* 11: 189-194.
171. Twaij A, Pucher PH, Sodergren MH, Gall T, Darzi A, et al. (2014) Laparoscopic vs. open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis. *World J Gastroenterol* 20: 8274-8281.
172. Choi SB, Hong KD, Lee JS, Han HJ, Kim WB, et al. (2011) Management of umbilical hernia complicated with liver cirrhosis: an advocate of early and elective herniorrhaphy. *Dig Liver Dis* 43: 991-995.
173. Carbonell AM, Wolfe LG, DeMaria EJ (2005) Poor outcomes in cirrhosis-associated hernia repair: a nationwide cohort study of 32,033 patients. *Hernia* 9: 353-357.
174. Hurst RD, Butler BN, Soybel DI, Wright HK (1992) Management of groin hernias in patients with ascites. *Ann Surg* 216: 696-700.
175. Oh HK, Kim H, Ryou S, Choe EK, Park KJ (2011) Inguinal hernia repair in patients with cirrhosis is not associated with increased risk of complications and recurrence. *World J Surg* 35: 1229-1233.
176. McKay A, Dixon E, Bathe O, Sutherland F (2009) Umbilical hernia repair in the presence of cirrhosis and ascites: results of a survey and review of the literature. *Hernia* 13: 461-468.
177. Chatzizacharias NA, Bradley JA, Harper S, Butler A, Jah A, et al. (2015) Successful surgical management of ruptured umbilical hernias in cirrhotic patients. *World J Gastroenterol* 21: 3109-3113.
178. Ammar SA (2010) Management of complicated umbilical hernias in cirrhotic patients using permanent mesh: randomized clinical trial. *Hernia* 14: 35-38.
179. Guriță RE, Popa F, Bălălu C, Scăunașu RV (2013) Umbilical hernia alloplastic dual-mesh treatment in cirrhotic patients. *J Med Life* 6: 99-102.
180. Belghiti J, Durand F (1997) Abdominal wall hernias in the setting of cirrhosis. *Semin Liver Dis* 17: 219-226.
181. Banu P, Popa F, Constantin VD, Bălălu C, Nistor M (2013) Prognosis elements in surgical treatment of complicated umbilical hernia in patients with liver cirrhosis. *J Med Life* 6: 278-282.
182. Gray SH, Vick CC, Graham LA, Finan KR, Neumayer LA, et al. (2008) Umbilical herniorrhaphy in cirrhosis: improved outcomes with elective repair. *J Gastrointest Surg* 12: 675-681.
183. Patti R, Almasio PL, Buscemi S, Famà F, Craxi A, et al. (2008) Inguinal hernioplasty improves the quality of life in patients with cirrhosis. *Am J Surg* 196: 373-378.
184. Hur YH, Kim JC, Kim DY, Kim SK, Park CY (2011) Inguinal hernia repair in patients with liver cirrhosis accompanied by ascites. *J Korean Surg Soc* 80: 420-425.
185. Eker HH, van Ramshorst GH, de Goede B, Tilanus HW, Metselaar HJ, et al. (2011) A prospective study on elective umbilical hernia repair in patients with liver cirrhosis and ascites. *Surgery* 150: 542-546.
186. Belli G, D'Agostino A, Fantini C, Cioffi L, Belli A, et al. (2006) Laparoscopic incisional and umbilical hernia repair in cirrhotic patients. *Surg Laparosc Endosc Percutan Tech* 16: 330-333.
187. Yeh CN, Chen MF, Jan YY (2002) Laparoscopic cholecystectomy in 226 cirrhotic patients. Experience of a single center in Taiwan. *Surg Endosc* 16: 1583-1587.
188. Machado NO (2012) Laparoscopic cholecystectomy in cirrhotics. *JSL* 16: 392-400.

189. Byrne MF, Suhocki P, Mitchell RM, Pappas TN, Stiffler HL, et al. (2003) Percutaneous cholecystostomy in patients with acute cholecystitis: experience of 45 patients at a US referral center. *J Am Coll Surg* 197: 206-211.
190. Park DH, Kim M-H, Lee SK, Lee SS, Choi JS, Song MH, et al. (2014) Endoscopic sphincterotomy vs. endoscopic papillary balloon dilation for choledocholithiasis in patients with liver cirrhosis and coagulopathy. *Gastrointest Endosc* 60:180-185.
191. Nguyen KT, Kitisin K, Steel J, Jeyabalan G, Aggarwal S, et al. (2011) Cirrhosis is not a contraindication to laparoscopic cholecystectomy: results and practical recommendations. *HPB (Oxford)* 13: 192-197.
192. Jeong S-H, Ahn HS, Yoo M-W, Cho J-J, Lee H-J, et al. (2010) Increased morbidity rates in patients with heart disease or chronic liver disease following radical gastric surgery. *J Surg Oncol* 101:200-204.
193. Guo F, Ma S, Yang S, Dong Y, Luo F, et al. (2014) Surgical strategy for gastric cancer patients with liver cirrhosis: a retrospective cohort study. *Int J Surg* 12: 810-814.
194. Lehnert T, Herfarth C (1993) Peptic ulcer surgery in patients with liver cirrhosis. *Ann Surg* 217: 338-346.
195. Rudler M, Rousseau G, Benosman H, Massard J, Deforges L, et al. (2012) Peptic ulcer bleeding in patients with or without cirrhosis: different diseases but the same prognosis? *Aliment Pharmacol Ther* 36: 166-172.
196. Venkatesh PG, Parasa S, Njei B, Sanaka MR, Navaneethan U (2014) Increased mortality with peptic ulcer bleeding in patients with both compensated and decompensated cirrhosis. *Gastrointest Endosc* 79: 605-614.
197. El Nakeeb A, Sultan AM, Salah T, El Hemaly M, Hamdy E, et al. (2013) Impact of cirrhosis on surgical outcome after pancreaticoduodenectomy. *World J Gastroenterol* 19: 7129-7137.
198. Warnick P, Mai I, Klein F, Andreou A, Bahra M, et al. (2011) Safety of pancreatic surgery in patients with simultaneous liver cirrhosis: a single center experience. *Pancreatol* 11: 24-29.
199. Kollmar O, Moussavian MR, Bolli M, Richter S, Schilling MK (2007) Pancreatojejunal leakage after pancreas head resection: anatomic and surgeon-related factors. *J Gastrointest Surg* 11: 1699-1703.
200. Ghaferi AA, Mathur AK, Sonnenday CJ, Dimick JB (2010) Adverse outcomes in patients with chronic liver disease undergoing colorectal surgery. *Ann Surg* 252: 345-350.
201. Csikesz NG, Nguyen LN, Tseng JF, Shah SA (2009) Nationwide volume and mortality after elective surgery in cirrhotic patients. *J Am Coll Surg* 208: 96-103.
202. Nguyen GC, Correia AJ, Thuluvath PJ (2009) The impact of cirrhosis and portal hypertension on mortality following colorectal surgery: a nationwide, population-based study. *Dis Colon Rectum* 52:1367-1374.
203. Montomoli J, Erichsen R, Christiansen CF, Ulrichsen SP, Pedersen L, et al. (2013) Liver disease and 30-day mortality after colorectal cancer surgery: a Danish population-based cohort study. *BMC Gastroenterol* 13:66
204. Meunier K, Mucci S, Quentin V, Azoulay R, Arnaud JP, et al. (2008) Colorectal surgery in cirrhotic patients: assessment of operative morbidity and mortality. *Dis Colon Rectum* 51: 1225-1231.
205. Modi A, Vohra HA, Barlow CW (2010) Do patients with liver cirrhosis undergoing cardiac surgery have acceptable outcomes? *Interact Cardiovasc Thorac Surg* 11: 630-634.
206. Filsoufi F, Salzberg SP, Rahmanian PB, Schiano TD, Elsiey H, et al. (2007) Early and late outcome of cardiac surgery in patients with liver cirrhosis. *Liver Transpl* 13: 990-995.
207. Marui A, Kimura T, Tanaka S, Miwa S, Yamazaki K, et al. (2011) Coronary revascularization in patients with liver cirrhosis. *Ann Thorac Surg* 91: 1393-1399.
208. Gopaldas RR, Chu D, Cornwell LD, Dao TK, Lemaire SA, et al. (2013) Cirrhosis as a moderator of outcomes in coronary artery bypass grafting and off-pump coronary artery bypass operations: a 12-year population-based study. *Ann Thorac Surg* 96: 1310-1315.
209. Friedman LS (2010) Surgery in the patient with liver disease. *Trans Am Clin Climatol Assoc* 121: 192-204.
210. Hayashida N, Shoujima T, Teshima H, Yokokura Y, Takagi K, et al. (2004) Clinical outcome after cardiac operations in patients with cirrhosis. *Ann Thorac Surg* 77: 500-505.
211. Suman A, Barnes DS, Zein NN, Levinthal GN, Connor JT, et al. (2004) Predicting outcome after cardiac surgery in patients with cirrhosis: a comparison of Child-Pugh and MELD scores. *Clin Gastroenterol Hepatol* 2: 719-723.
212. Raval Z, Harinstein ME, Flaherty JD (2014) Role of cardiovascular intervention as a bridge to liver transplantation. *World J Gastroenterol* 20: 10651-10657.
213. Russo MW, Pierson J, Narang T, Montegudo A, Eskind L, et al. (2012) Coronary artery stents and antiplatelet therapy in patients with cirrhosis. *J Clin Gastroenterol* 46: 339-344.
214. 213. Wray C, Scovotti JC, Tobis J, Niemann CU, Planinsic R, et al. (2013) Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. *Am J Transplant* 13:184-191.
215. Pillarisetti J, Patel P, Duthuluru S, Roberts J, Chen W, et al. (2011) Cardiac catheterization in patients with end-stage liver disease: safety and outcomes. *Catheter Cardiovasc Interv* 77: 45-48.
216. Shaheen AA, Kaplan GG, Hubbard JN, Myers RP (2009) Morbidity and mortality following coronary artery bypass graft surgery in patients with cirrhosis: a population-based study. *Liver Int* 29: 1141-1151.
217. Bukur M, Felder SI, Singer MB, Ley EJ, Malinoski DJ, et al. (2013) Trauma center level impacts survival for cirrhotic trauma patients. *J Trauma Acute Care Surg* 74: 1133-1137.
218. Mansour A, Watson W, Shayani V, Pickleman J (1997) Abdominal operations in patients with cirrhosis: still a major surgical challenge. *Surgery* 122: 730-735.
219. Talving P, Lustenberger T, Okoye OT, Lam L, Smith JA, et al. (2013) The impact of liver cirrhosis on outcomes in trauma patients: a prospective study. *J Trauma Acute Care Surg* 75: 699-703.
220. Georgiou C, Inaba K, Teixeira PG, Hadjizacharia P, Chan LS, et al. (2009) Cirrhosis and trauma are a lethal combination. *World J Surg* 33: 1087-1092.
221. Lin B-C, Fang J-F, Wong Y-C, Hwang T-L, Hsu Y-P (2012) Management of cirrhotic patients with blunt abdominal trauma: analysis of risk factor of postoperative death with the Model for End-Stage Liver Disease score. *Injury* 43:1457-1461.