Chapter 5
Anesthesia for Surgical Procedures in Cirrhotic Patients Other than Liver Transplantation: Management, Concerns, and Pitfalls

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Introduction

In 2010, 101,000 patients were admitted with chronic liver disease and cirrhosis as their primary diagnosis. These patients were predominately male (62%) with chronic alcoholic cirrhosis (52.5%) [1]. Chronic liver disease represents the 12th leading cause of mortality nationwide in the USA [2]. Because of improved treatments and extended life expectancies, the percentage of patients with chronic end-stage liver disease (ESLD) undergoing procedures is increasing. Patients with cirrhosis are at relatively increased risk of biliary obstruction requiring cholecystectomy, and ascites predisposes patients to inguinal and ventral hernias requiring repair.

In a review of the Nationwide Inpatient Sample, 22,569 patients with cirrhosis underwent cholecystectomies, colectomies, abdominal aortic repair, and coronary artery bypass grafting between 1998 and 2005. Of these surgeries, cholecystectomy was the most frequently performed operation on cirrhotic patients (63%) followed by colectomies (26%). As expected, mortality, hospital length of stay, and cost are significantly increased in patients with ESLD and increased further in patients with portal hypertension. Even after adjusting for risk factors and comorbid diseases, patients with compensated cirrhosis undergoing elective surgery have a 3.4–8 times increased risk of mortality depending on the type of surgery [3]. In another study of 733 patients with the diagnosis of cirrhosis, who had surgery between 1980 and

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1991, the 30-day postsurgical mortality was 11.6% and the complication rate was 30.1%. Postoperative pneumonia was the most frequent complication [4]. Therefore, a detailed evaluation of preoperative risk and potential risk reduction strategies is prudent in patients with known liver disease.

Perioperative Risk Associated with Liver Disease

Prior to surgery, the etiology, duration, and severity of hepatic dysfunction should be determined including history of complications related to portal hypertension, including encephalopathy, ascites, gastrointestinal bleeding, and renal dysfunction. Routine laboratory assessment includes evaluation of hemoglobin, electrolytes, and coagulation (INR, fibrinogen and platelets). In patients with fever, leukocytosis, or acute deterioration, infection should be considered as well as a diagnostic paracentesis to rule out spontaneous bacterial peritonitis.

Based on a retrospective, small case series from the 1960s and 1970s, acute hepatitis confers a prohibitive risk for elective surgery. In a series of 36 patients with undiagnosed hepatitis who underwent laparotomy for diagnosis nearly one-third died and the majority suffered complications i.e. bacterial peritonitis, wound dehiscence, and hepatic failure. All patients with acute hepatitis, either viral or alcohol related, died [5]. When prudent, elective surgery should be postponed in patients with acute hepatitis [6, 7].

A number of studies have investigated the risk of surgery in patients with cirrhosis [8–11]. Each of the studies identified various components of the Child-Turcotte-Pugh score as important prognostic factors for perioperative mortality. In studies conducted over multiple decades, the modified Child score performed similarly in predicting early postoperative mortality: 10% in Child A, 17–30% in Child B, and 60–80% in Child C [10–12]. In comparison, the 3-month mortality for hospitalized patients not undergoing surgery was 4%, 14%, and 51%, respectively, for Child A, B, and C [11].

The MELD score is a useful predictor of 90-day waitlist mortality in liver transplant candidates [13], as well as shows a predictive value of perioperative mortality in cirrhotic patients. In a single-center study of 140 surgical procedures, the *c*-statistic for the MELD score's ability to predict 30-day mortality was 0.72. A *c*-statistic of 0.7 and higher is considered useful. Each MELD point to 20 equated to an additional 1% mortality and each point over 20 equated to an additional 2% mortality. A MELD score between 25 and 30 was associated with a 30-day mortality of 50% [14]. A larger study of 772 cirrhotics found similar results: a MELD score of 25 had a 30-day mortality of 50% [15]. Besides MELD score, other important predictors of perioperative mortality were age (>70 years = 3 MELD points) and coexisting diseases (ASA physical status > 4 = 5.5 MELD points). Common perioperative complications include liver failure, postoperative bleeding, infection, and renal failure. Teh et al. concluded that patients with a MELD score less than 11 have low postoperative mortality, and elective surgery can be considered relatively

Table 5.1 Cardiopulmonary Syndromes Related to Portal Hypertension

Diagnosis	Screening method	Perioperative consequences
Cirrhotic cardiomyopathy (CCM)	Echocardiography assessment of LV diastolic function	Congestive heart failure[a]
Hepatopulmonary syndrome (HPS)	Room air hypoxemia (PaO_2 <70 mmHg) in the absence of other causes; confirmed by bubble echo	Although hypoxemia is typically responsive to supplemental oxygen, HPS is associated with increased infectious risk and perioperative mortality during liver transplantation[b]
Portopulmonary hypertension (POPH)	Echocardiographic estimate of RVSP; confirmed by right heart catheterization	Moderate to severe POPH associated with right heart failure and perioperative mortality during liver transplantation[c]

*LV*left ventricle, *RVSP* right ventricle systolic pressure
[a]Ruiz-del-Arbol L, et al. World J Gastroenterol 2015; 21(41): 11502–21; Zardi EM, et al. J Am Coll Cardiol 2010; 56(7): 539–49
[b]Gupta S, et al. Am J Transpl 2010; 10(2): 354
[c]Ramsay M, et al. Curr Opin Anaesthesiol 2010; 23(2): 145–50

safe, preferably at institutions with a liver transplant center. In patients with a MELD score ≥ 20, the high mortality contraindicates elective procedures until after liver transplantation. If surgery is unable to be postponed or the patient has an intermediate MELD score (between 12 and 19), then liver transplant work-up should be underway prior to elective surgery in case the need for urgent postoperative transplantation arises. An online calculator of postoperative mortality risk in patients with cirrhosis can be found online at http://www.mayocinic.org/meld/mayomodel9.html.

Nearly every organ system is affected by liver disease. Specific cardiopulmonary consequences related to portal hypertension include cirrhotic cardiomyopathy (CCM), hepatopulmonary syndrome (HPS), and portopulmonary hypertension (POPH). Patients with even mild cirrhosis should be screened for these conditions if undergoing extensive surgery. The screening methods and the perioperative consequences of these conditions can impact perioperative outcomes (see Table 5.1) [16, 17].

Medical management to optimize cirrhotic patients undergoing surgery should be directed toward treating active infection, optimizing central blood volume and renal status while minimizing ascites and improving encephalopathy. However, there is little evidence to support specific goal-directed targets for preoperative care in any of these areas. In particular, preoperative INR correction has little support. Evidence suggests that transfusion of plasma in the absence of bleeding increases central blood volume and worsens portal hypertension, which can lead to an increased risk of variceal bleeding [18]. Recent reviews argue against prophylactic plasma administration [19]. In an observational study of over 1200 patients with preoperative INR > 1.5 undergoing noncardiac surgery, 11% received preoperative plasma transfusion. Despite this, WHO grade 3 bleeding occurred in 53% of those

receiving plasma compared to 32% in those who did not (OR 2.35, 95% CI 1.65–3.36) [20]. Standard doses of plasma rarely correct the coagulopathy of cirrhosis and, by worsening portal hypertension, can be harmful [21]. The INR has been recognized as an inadequate indicator of preoperative bleeding risk since PT/INR values depend upon the levels of procoagulants (factors I, II, V, VII and X) without accounting for low levels of endogenous anticoagulant factors. Due to elevated levels of endothelial-derived factor VIII and low levels of protein C, chronic liver disease patients often generate normal or high levels of thrombin [22]. Chronic liver disease patients are often in a delicate balance between inadequate hemostasis and excessive coagulation [23]. With bleeding, fibrinogen levels should be maintained >150–200 mg/dL with transfusion of cryoprecipitate or if available, human fibrinogen concentrate [19].

Perioperative risk depends more on the operative site and the degree of liver impairment than the anesthetic technique [24]. In a retrospective study of 733 cirrhotic patients, mortality was associated with the Child score (ascites, elevated creatinine), male gender, cryptogenic cirrhosis (vs. other etiologies), preoperative infection, higher ASA physical status, and surgery on the respiratory system. One-year mortality in patients with six risk factors was over 80%; mortality with two risk factors was 30% [4].

In addition to optimizing medical management, minimizing surgical risk should be considered. Gallstones are twice as common in cirrhotic patients as in patients without cirrhosis [8]. Laparoscopic surgery is safe in patients with Child A and B cirrhosis [25]. However, Child C patients may benefit from percutaneous drainage of the gallbladder over cholecystectomy [26]. In a series of over 4200 laparoscopic cholecystectomies, cirrhotics ($n = 226$) had a mortality of approximately 1/100, compared to 1/2000 without [27]. Preoperative decompression of portal hypertension by TIPS may improve outcomes in patients with severe portal hypertension [28].

Intraoperative Management

Monitoring and Vascular Access

In addition to standard noninvasive monitors, arterial pressure monitoring should be considered for patients with ESLD. The decision is based on preoperative hypotension due to vasodilatation, anticipated blood loss, the need for intraoperative laboratory studies, coexisting disease, and age. The usefulness of CVP monitoring to predict fluid responsiveness is debatable [29]. Many have abandoned CVP monitoring in the setting of liver resection [30–32]. In our practice, we do not place a central venous catheter exclusively for CVP monitoring. Pulmonary artery catheterization is used for patients with known or suspected pulmonary artery hypertension and/or low cardiac ejection fraction. Transesophageal echocardiography (TEE) is a sensitive monitor for the assessment of preload, contractility (including regional wall motion), ejection fraction, static and dynamic valvular abnormalities, emboli, and pericardial fluid. In a small series of patients with esophageal varices, TEE

universally aided in diagnosis and was not associated with bleeding complications, although transgastric views were avoided to minimize esophageal manipulation [33]. Other authors have confirmed the safety of TEE in this population [34, 35].

Coagulation Management

Viscoelastic coagulation testing using thromboelastography or thromboelastometry may be a useful guide, more accurately reflecting the overall effects of altered levels of endogenous pro- and anticoagulant factors [36]. Abnormalities in platelet number and function are in part compensated for by increased levels of von Willebrand factor (VWF), a platelet adhesive protein, and by decreased levels of ADAMTS13, the VWF cleaving protease. Thrombin generation is preserved with platelet counts exceeding 50×10^9 / L, making this value a practical target in the setting of active bleeding [37].

Anesthetic Technique: Neuraxial Versus General Anesthesia

The effect of neuraxial or epidural anesthesia on hepatic blood flow appears related to alterations of systemic blood pressure [38, 39]. Standard contraindications to neuraxial blockade should be considered and weighed against the benefits on a case-by-case basis. Many patients with advanced hepatic disease may not be candidates for neuraxial techniques due to coagulopathy and/or thrombocytopenia. Nerve blockade may be appropriate even when neuraxial blockade is contraindicated. The transversus abdominal plane (TAP) block has been used successfully for abdominal surgery, including hepatobiliary procedures [40, 41]. However, the efficacy has been questioned and reported complications include abdominal wall hematoma.

Volatile Anesthetics

Volatile anesthetics decrease hepatic blood flow to varying degrees. Commonly used agents, isoflurane and sevoflurane, have less significant effects on hepatic blood flow than halothane [42]. Desflurane appears to more substantially decrease hepatic blood flow at one MAC, causing a 30% reduction [43]. At higher anesthetic concentrations, isoflurane causes a dose-dependent reduction in hepatic blood flow not seen with sevoflurane. In animal studies, both sevoflurane and isoflurane maintain the hepatic arterial buffer response, which increases hepatic arterial blood flow in the presence of reductions of portal blood flow [44, 45].

Concerns exist regarding the production of reactive intermediates during the metabolism of inhaled anesthetics. There is little evidence, however, to suggest that volatile anesthetics besides halothane are responsible for hepatic complications. Most volatile anesthetics undergo metabolism that yields reactive trifluoroacetylated (TFA) intermediates. These intermediates bind to hepatic proteins, producing an immunologic reaction leading to liver injury. The incidence of liver injury correlates

to the extent to which inhaled anesthetics undergo this oxidative metabolism (halothane 20%, isoflurane 0.2%, desflurane 0.02%). Notably, sevoflurane metabolism does not result in TFA intermediates [46].

Nitrous Oxide

Nitrous oxide administration has not been shown to cause hepatocellular injury in the absence of hepatic hypoxemia [47]. Due to sympathomimetic effects, nitrous oxide can decrease hepatic blood flow, and inhibition of methionine synthase can occur after even brief exposures. However, the clinical significance of these effects is unclear [48].

Intravenous Anesthetics

Intravenous anesthetics and sedatives including propofol, etomidate, and midazolam do not appear to alter hepatic function when given for short durations. The effects of IV anesthetics after prolonged infusions in patients with advanced liver disease are not well studied. Propofol infusion syndrome (lactic acidosis, lipemia, rhabdomyolysis, hyperkalemia, and myocardial failure) has resulted in patient deaths [49]. Liver dysfunction resulting in altered lipid metabolism may predispose to cirrhotics to propofol infusion syndrome [50]. Patients on prolonged propofol infusions should be monitored for progressive lactic acidosis and escalating vasopressor requirements.

There is no evidence that opioids have an effect on hepatic function independent of hepatic blood flow. All opioids increase sphincter of Oddi pressure. Some authors have suggested that morphine causes spasm in the sphincter of Oddi, but a review failed to show a differential effect, concluding that morphine may be preferred over meperidine for the treatment of patients with acute pancreatitis due to less risk of seizures [51].

Pharmacokinetic and Pharmacodynamic Alterations

Decreased hepatocellular mass and portocaval shunts lead to reduced metabolism of drugs that rely on hepatic metabolism. Factors that affect hepatic clearance include blood flow to the liver, the fraction of the drug unbound to plasma proteins, and intrinsic clearance. Drugs with low extraction ratios < 0.3, have restrictive hepatic clearance. Clearance of drugs in this class is affected by protein binding, the induction or inhibition of hepatic enzymes, age, and hepatic pathology, but clearance is not significantly affected by hepatic blood flow. Drugs with high extraction ratios (> 0.7) undergo extensive first-pass metabolism, which alters their bioavailability after oral administration. Drugs with high extraction ratios are significantly affected by alteration in hepatic blood flow, which can occur with hemodynamic changes or hepatic inflow clamping during liver resection.

Benzodiazepines have a low extraction ratio and the elimination half-life can be prolonged (diazepam $t_{1/2}$ = 43 h). Studies have shown conflicting effects of cirrhosis on the metabolism of midazolam, possibly due to changes in protein binding [52, 53]. As hepatic protein synthesis declines, the drug fraction bound to protein decreases. While the pharmacokinetic implications of ESLD are complex, patients with encephalopathy display an increased sensitivity to sedatives and analgesics.

Opioid metabolism is reduced in patients with liver disease, so dosing intervals should be increased to avoid drug accumulation. The clearance of the meperidine metabolite normeperidine is reduced in liver disease, which can lead to neurotoxicity [54]. The elimination of a single IV opioid bolus is less affected than a continuous infusion through redistribution to storage sites. Opioid dosages in patients with advanced disease should be reduced to avoid precipitating or worsening encephalopathy.

The intermediate duration neuromuscular blocking agents vecuronium and rocuronium are metabolized by the liver and exhibit a prolonged duration of action [55, 56]. Despite this, a resistance to the initial dose of neuromuscular blocker typically occurs due to elevated γ-globulin concentrations and an increase in the volume of distribution (due to edema and/or ascites). Atracurium and cisatracurium undergo organ-independent elimination and their durations of action are not affected by liver disease. Succinylcholine metabolism is altered due to reduced plasma cholinesterase activity in cirrhotic patients, but the clinical impact is rarely significant.

Vasopressors and Volume Resuscitation

In contrast to sedatives, patients with liver disease exhibit a reduced responsiveness to endogenous vasoconstrictors including angiotensin II, vasopressin, and norepinephrine [57]. Hyporesponsiveness to catecholamines may be modulated by the release of nitric oxide, prostacyclin, and other endothelial-derived factors in response to humoral and mechanical stimuli [58]. Many patients present with hyperdynamic circulation characterized by low systemic vascular resistance, borderline hypotension and elevated cardiac output. These patients frequently cannot tolerate induction or maintenance of anesthesia without vasopressor support. In patients undergoing abdominal surgery, fluids should be restricted (with or without CVP monitoring) in order to lower portal pressures.

When need for volume resuscitation arises, the fluid and blood products administered are similar in patients with and without liver disease, but with several notable exceptions. In ESLD, serum albumin function is quantitatively and qualitatively decreased [59]. Albumin has three major indications in the treatment of cirrhotic patients [60]:

1. After large volume (4–5 L) paracentesis [61]
2. The presence of spontaneous bacterial peritonitis to prevent renal impairment in patients with preexisting elevations of bilirubin or creatinine [62]
3. In conjunction with splanchnic vasoconstrictors for type I hepatorenal syndrome

In a randomized trial of terlipressin with and without albumin, a higher proportion (77%) of the group that received albumin showed a complete response compared to terlipressin alone (25%) [63]. In patients with hyponatremia, hypotonic sodium should be administered to avoid a rapid rise in serum sodium, which can be associated with central pontine demyelination and permanent neurologic injury.

Transjugular Intrahepatic Portosystemic Shunt (TIPS) Procedure

Sedation is commonly used to facilitate placement, although general anesthesia is preferred by some to limit patient movement, control diaphragmatic excursion, and reduce the risk of aspiration. Complications include pneumothorax or vascular injury during access to the jugular vein. Dysrhythmias can occur during catheter insertion and extrahepatic artery or portal vein puncture can result in significant hemorrhage [64].

Hepatic Resection

Hemorrhage remains a major complication in hepatic resections, although transfusion is necessary in less than 20% of cases [65, 66]. Newer transection techniques using ultrasonic dissectors, high-pressure water jets, and harmonic scalpels may be helpful, but they have not been proven to be superior to conventional clamp crush techniques [67–69]. Techniques to maintain CVP at normal or low (<5 cm H_2O) levels have been suggested to limit blood loss [70]. In a single-center, uncontrolled series of nearly 500 hepatic resections managed with low CVP, no cases of renal failure were attributed to the technique [71]. There is conflicting data regarding the correlation between low CVP technique and blood loss. Two series of living liver donor surgeries concluded that CVP is not a predictor of blood loss during hepatic resection [72, 73]. A recent meta-analysis found that low CVP does not decrease morbidity, but does reduce blood loss [74]. Another recent study found that fluid restriction, confirmed by high stroke volume variation, resulted in less blood loss [75]. Aside from CVP, vasopressors can reduce splanchnic pressure and decrease blood loss through their direct effects on splanchnic vessels [76].

Even in patients with normal preoperative coagulation profiles, the INR and platelet count can be abnormal after liver resection. The severity of the derangement correlates with the extent of the resection, peaks postoperative day one to two, and takes up to five or more days to resolve [77, 78]. This postoperative coagulopathy may be a contraindication to continuous epidural analgesia, increasing the risk of epidural hematoma during catheter removal. Some authors advise against preoperative epidural catheter placement, while others recommend correcting coagulation abnormalities prior to catheter discontinuation [79]. Using viscoelastic testing, brief hypercoagulability after liver resection despite prolonged prothrombin times have been reported [80]. Alternatives that avoid epidural catheter placement include intrathecal opioid and local anesthesia infusion systems [81].

Conclusion

In general, contraindications to elective surgery in patients with ESLD include acute viral or alcoholic hepatitis, fulminant liver failure, Child's class C cirrhosis, severe coagulopathy due to splenic sequestration of platelets or prolongation of the INR despite vitamin K repletion, and severe extrahepatic complications secondary to hepatopulmonary syndrome, portopulmonary hypertension, hepatorenal syndrome, or cardiomyopathy [7]. Elective surgery is considered relatively safe with MELD scores below 11 and contraindicated until after liver transplantation when MELD exceeds 20 [15].

Preoperative optimization includes effective control of ascites through diuretics or paracentesis to improve oxygenation and increase functional residual capacity. Elevated INR is not an independent risk factor for increased perioperative bleeding. When available, viscoelastic testing may be a more accurate reflection of coagulopathy to guide repletion of clotting factors, fibrinogen, and platelets.

In the absence of particular contraindications (primarily significant coagulapthy), neuraxial, regional, as well as general anesthesia have all been successful in ESLD patients. Because of decreased hepatic metabolism and increased volume of distribution, initial dosing and dosing intervals will have to be adjusted, particularly for opioids and intermediate-acting neuromuscular blockers.

Advances in surgery, anesthesia, and intensive care have led to improved outcomes in patients with significant liver disease. These advances are related to comprehensive preoperative screening and preparation that avoids further hepatic injury. However, when deterioration occurs, liver transplantation should be considered early as it is the only definitive treatment for irreversible hepatic failure.

References

1. Prevention CD and C. Hepatitis statistics: surveillance for viral hepatitis – United States. 2013. http://www.cdc.gov/hepatitis/statistics/2013surveillance/commentary.htm.
2. Prevention CD and C. Death rates by age and age-adjusted death rates for the 15 leading causes of death in 2013: United States. 1999–2013. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf.
3. Csikesz NG, Nguyen LN, Tseng JF, Shah SA. Nationwide volume and mortality after elective surgery in cirrhotic patients. J Am Coll Surg. 2009;208(1):96–103. doi:10.1016/j.jamcollsurg.2008.09.006.
4. Ziser A, Plevak DJ, Wiesner RH, Rakela J, Offord KP, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology. 1999;90(1):42–53. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9915311
5. Powell-Jackson P, Greenway B, Williams R. Adverse effects of exploratory laparotomy in patients with unsuspected liver disease. Br J Surg. 1982;69(8):449–51. http://www.ncbi.nlm.nih.gov/pubmed/7104630
6. Rizvon MK, Chou CL. Surgery in the patient with liver disease. Med Clin North Am. 2003;87(1):211 - +. doi:10.1016/s0025-7125(02)00153-0.
7. Friedman LS, Xu J, Murphy SL, Kochanek KD, Bastian BA, Statistics V. Surgery in the patient with liver disease. Trans Am Clin Climatol Assoc. 2010;121(2):192–204. discussion 205.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20697561
8. Aranha GV, Sontag SJ, Greenlee HB. Cholecystectomy in cirrhotic patients: a formidable operation. Am J Surg. 1982;143(1):55–60. http://www.ncbi.nlm.nih.gov/pubmed/7053656
9. Doberneck RC, Sterling Jr WA, Allison DC. Morbidity and mortality after operation in non-bleeding cirrhotic patients. Am J Surg. 1983;146(3):306–9. http://www.ncbi.nlm.nih.gov/pubmed/6604465
10. Garrison RN, Cryer HM, Howard DA, Polk Jr HC. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. Ann Surg. 1984;199(6):648–55. http://www.ncbi.nlm.nih.gov/pubmed/6732310
11. Mansour A, Watson W, Shayani V, Pickleman J. Abdominal operations in patients with cirrhosis: still a major surgical challenge. Surgery. 1997;122(4):730–6. http://www.ncbi.nlm.nih.gov/pubmed/9347849
12. Neeff H, Mariaskin D, Spangenberg H-C, Hopt UT, Makowiec F. Perioperative mortality after non-hepatic general surgery in patients with liver cirrhosis: an analysis of 138 operations in the 2000s using child and MELD scores. J Gastrointest Surg. 2011;15(1):1–11. doi:10.1007/s11605-010-1366-9.
13. Freeman RB, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8(9):851–8. doi:10.1053/jlts.2002.35927.
14. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. Ann Surg. 2005;242(2):244–51. 00000658-200508000-00013 [pii]
15. Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology. 2007;132(4):1261–9. doi:10.1053/j.gastro.2007.01.040.
16. Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol. 2011;58(3):223–31. doi:10.1016/j.jacc.2011.03.026.
17. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. Ann Gastroenterol. 2015;28(1):31–40. http://www.ncbi.nlm.nih.gov/pubmed/25608575
18. Zimmon DS, Kessler RE. The portal pressure-blood volume relationship in cirrhosis. Gut. 1974;15(2):99–101. http://www.ncbi.nlm.nih.gov/pubmed/4820643
19. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol. 2016;64(3):717–35. doi:10.1016/j.jhep.2015.10.019.
20. Jia Q, Brown MJ, Clifford L, et al. Prophylactic plasma transfusion for surgical patients with abnormal preoperative coagulation tests: a single-institution propensity-adjusted cohort study. Lancet Haematol. 2016;3(3):e139–48. doi:10.1016/s2352-3026(15)00283-5.
21. Northup PG, McMahon MM, Ruhl AP, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol. 2006;101(7):1524–28; quiz 1680. doi:AJG588 [pii]10.1111/j.1572-0241.2006.00588.x.
22. Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009;137(6):2105–11. doi:10.1053/j.gastro.2009.08.045.
23. Lisman T, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. J Hepatol. 2010;52(3):355–61. doi:10.1016/j.jhep.2009.12.001.
24. Viegas O, Stoelting RK. LDH5 changes after cholecystectomy or hysterectomy in patients receiving halothane, enflurane, or fentanyl. Anesthesiology. 1979;51(6):556–8. doi:10.1097/00000542-197912000-00017.
25. Shaikh AR, Muneer A. Laparoscopic cholecystectomy in cirrhotic patients. JSLS. 2009;13(4):592–6. doi:10.4293/108680809X12589999537959.
26. Curro G, Iapichino G, Melita G, Lorenzini C, Cucinotta E. Laparoscopic cholecystectomy in Child-Pugh class C cirrhotic patients. JSLS. 2005;9(3):311–5. http://www.ncbi.nlm.nih.gov/pubmed/16121878

27. Yeh CN, Chen MF, Jan YY. Laparoscopic cholecystectomy in 226 cirrhotic patients. Experience of a single center in Taiwan. Surg Endosc. 2002;16(11):1583–7. doi:10.1007/s00464-002-9026-0.
28. Azoulay D, Buabse F, Damiano I, et al. Neoadjuvant transjugular intrahepatic portosystemic shunt: a solution for extrahepatic abdominal operation in cirrhotic patients with severe portal hypertension. J Am Coll Surg. 2001;193(1):46–51. http://www.ncbi.nlm.nih.gov/pubmed/11442253
29. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134(1):172–8. doi:10.1378/chest.07-2331.
30. Mansour N, Lentschener C, Ozier Y. Do we really need a low central venous pressure in elective liver resection. Acta Anaesthesiol Scand. 2008;52(9):1306–07. doi:AAS1750 [pii]10.1111/j.1399-6576.2008.01750.x.
31. Schroeder RA, Kuo PC. Pro: low central venous pressure during liver transplantation – not too low. J Cardiothorac Vasc Anesth. 2008;22(2):311–4. doi:10.1053/j.jvca.2007.12.009.
32. Niemann CU, Feiner J, Behrends M, Eilers H, Ascher NL, Roberts JP. Central venous pressure monitoring during living right donor hepatectomy. Liver Transpl. 2007;13(2):266–71. doi:10.1002/lt.21051.
33. Spier BJ, Larue SJ, Teelin TC, et al. Review of complications in a series of patients with known gastro-esophageal varices undergoing transesophageal echocardiography. J Am Soc Echocardiogr. 2009;22(4):396–400. doi:10.1016/j.echo.2009.01.002.
34. Myo Bui CC, Worapot A, Xia W, et al. Gastroesophageal and hemorrhagic complications associated with intraoperative transesophageal echocardiography in patients with model for end-stage liver disease score 25 or higher. J Cardiothorac Vasc Anesth. 2015;29(3):594–7. doi:10.1053/j.jvca.2014.10.030.
35. Markin NW, Sharma A, Grant W, Shillcutt SK. The safety of transesophageal echocardiography in patients undergoing orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 2015;29(3):588–93. doi:10.1053/j.jvca.2014.10.012.
36. Tripodi A. Tests of coagulation in liver disease. Clin Liver Dis. 2009;13(1):55 - +. doi:10.1016/j.cld.2008.09.002.
37. Tripodi A, Primignani M, Chantarangkul V, et al. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology. 2006;44(2):440–5. doi:10.1002/hep.21266.
38. Kennedy WF, Everett GB, Cobb LA, Allen GD. Simultaneous systemic and hepatic hemodynamic measurements during high spinal anesthesia in normal man. Anesth Analg Curr Res. 1970;49(6):1016 - &. <Go to ISI>://WOS:A1970H956200026
39. Kennedy WF, Everett GB, Cobb LA, Allen GD. Simultaneous systemic and hepatic hemodynamic measurements during high peridural anesthesia in normal man. Anesth Analg Curr Res. 1971;50(6):1069 - &. doi:10.1213/00000539-197150060-00029.
40. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg. 2007;104(1):193–7. doi:10.1213/01.ane.0000250223.49963.0f.
41. Niraj G, Kelkar A, Jeyapalan I, et al. Comparison of analgesic efficacy of subcostal transversus abdominis plane blocks with epidural analgesia following upper abdominal surgery. Anaesthesia. 2011;66(6):465–71. doi:10.1111/j.1365-2044.2011.06700.x.
42. Frink Jr EJ. The hepatic effects of sevoflurane. Anesth Analg. 1995;81(6 Suppl):S46–50. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7486148
43. Schindler E, Muller M, Zickmann B, Kraus H, Reuner KH, Hempelmann G. Blood supply to the liver in the human after 1 MAC desflurane in comparison with isoflurane and halothane. Anasthesiol Intensivmed Notfallmed Schmerzther. 1996;31(6):344–8. doi:10.1055/s-2007-995933.
44. Matsumoto N, Koizumi M, Sugai M. Hepatolobectomy-induced depression of hepatic circulation and metabolism in the dog is counteracted by isoflurane, but not by halothane. Acta Anaesthesiol Scand. 1999;43(8):850–4. http://www.ncbi.nlm.nih.gov/pubmed/10492415

45. Crawford MW, Lerman J, Saldivia V, Carmichael FJ. Hemodynamic and organ blood flow responses to halothane and sevoflurane anesthesia during spontaneous ventilation. Anesth Analg. 1992;75(6):1000–6. http://www.ncbi.nlm.nih.gov/pubmed/1443679
46. Njoku D, Laster MJ, Gong DH, Eger 2nd EI, Reed GF, Martin JL. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. Anesth Analg. 1997;84(1):173–8. http://www.ncbi.nlm.nih.gov/pubmed/8989020
47. Sear JW, Prysroberts C, Dye A. Hepatic-function after anesthesia for major vascular reconstructive surgery – a comparison of 4 anesthetic techniques. Br J Anaesth. 1983;55(7):603–9. doi:10.1093/bja/55.7.603.
48. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesth. 1987;59(1):3–13. http://www.ncbi.nlm.nih.gov/pubmed/3548788
49. Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ. 1992;305(6854):613–6. http://www.ncbi.nlm.nih.gov/pubmed/1393073
50. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. Curr Opin Anaesthesiol. 2008;21(5):544–51. doi:10.1097/ACO.0b013e32830f44fb.
51. Thompson DR. Narcotic analgesic effects on the sphincter of oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol. 2001;96(4):1266–72. doi:10.1111/j.1572-0241.2001.03536.x.
52. Trouvin JH, Farinotti R, Haberer JP, Servin F, Chauvin M, Duvaldestin P. Pharmacokinetics of midazolam in anesthetized cirrhotic-patients. Br J Anaesth. 1988;60(7):762–7. doi:10.1093/bja/60.7.762.
53. Macgilchrist AJ, Birnie GG, Cook A, et al. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. Gut. 1986;27(2):190–5. doi:10.1136/gut.27.2.190.
54. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet. 1999;37(1):17–40. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10451781
55. Hunter JM, Parker CJ, Bell CF, Jones RS, Utting JE. The use of different doses of vecuronium in patients with liver dysfunction. Br J Anaesth. 1985;57(8):758–64. http://www.ncbi.nlm.nih.gov/pubmed/2861836
56. Magorian T, Wood P, Caldwell J, et al. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg. 1995;80(4):754–9. http://www.ncbi.nlm.nih.gov/pubmed/7893030
57. Cahill PA. Vasoconstrictor responsiveness of portal hypertensive vessels. Clin Sci. 1999;96(1):3–4. doi:10.1042/cs19980297.
58. Cahill PA, Redmond EM, Sitzmann JV. Endothelial dysfunction in cirrhosis and portal hypertension. Pharmacol Ther. 2001;89(3):273–93. doi:10.1016/s0163-7258(01)00128-0.
59. Alves de Mattos A. Current indications for the use of albumin in the treatment of cirrhosis. Ann Hepatol. 2011;10(Suppl 1):S15–20. http://www.ncbi.nlm.nih.gov/pubmed/21566250
60. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol. 2014;4(4):302–11. doi:10.1016/j.jceh.2014.08.007.
61. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49(6):2087–107. doi:10.1002/hep.22853.
62. Terg R, Gadano A, Cartier M, et al. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. Liver Int. 2009;29(3):415–9. doi:10.1111/j.1478-3231.2008.01877.x.
63. Ortega R, Gines P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology. 2002;36(4 Pt 1):941–8. doi:10.1053/jhep.2002.35819.
64. Quiroga J, Sangro B, Nunez M, et al. Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites – effect on clinical, renal, humoral, and hemodynamic parameters. Hepatology. 1995;21(4):986–94. doi:10.1016/0270-9139(95)90245-7.

65. Lentschener C, Benhamou D, Mercier FJ, et al. Aprotinin reduces blood loss in patients undergoing elective liver resection. Anesth Analg. 1997;84(4):875–81. http://www.ncbi.nlm.nih.gov/pubmed/9085974
66. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. Br J Surg. 1998;85(8):1058–60. <Go to ISI>://WOS:000075280800006
67. Franco D. Liver surgery has become simpler. Eur J Anaesthesiol. 2002;19(11):777–9. doi:10.1017/s0265021502001254.
68. Lentschener C, Ozier Y. Anaesthesia for elective liver resection: some points should be revisited. Eur J Anaesthesiol. 2002;19(11):780–8. doi:10.1017/s0265021502001266.
69. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med. 2007;356(15):1545–59. doi:356/15/1545 [pii]10.1056/NEJMra065156.
70. Wang W-D, Liang L-J, Huang X-Q, Yin X-Y. Low central venous pressure reduces blood loss in hepatectomy. World J Gastroenterol. 2006;12(6):935–9. <Go to ISI>://WOS:000239994700015
71. Melendez JA, Arslan V, Fischer ME, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg. 1998;187(6):620–5. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9849736
72. Kim YK, Chin JH, Kang SJ, et al. Association between central venous pressure and blood loss during hepatic resection in 984 living donors. Acta Anaesthesiol Scand. 2009;53(5):601–6. doi:10.1111/j.1399-6576.2009.01920.x.
73. Chhibber A, Dziak J, Kolano J, Norton JR, Lustik S. Anesthesia care for adult live donor hepatectomy: our experiences with 100 cases. Liver Transpl. 2007;13(4):537–42. doi:10.1002/lt.21074.
74. Hughes MJ, Ventham NT, Harrison EM, Wigmore SJ. Central venous pressure and liver resection: a systematic review and meta-analysis. HPB. 2015;17(10):863–71. doi:10.1111/hpb.12462.
75. Seo H, Jun IG, Ha TY, Hwang S, Lee SG, Kim YK. High stroke volume variation method by mannitol administration can decrease blood loss during donor hepatectomy. Medicine (Baltimore). 2016;95(2):e2328. doi:10.1097/MD.0000000000002328.
76. Massicotte L, Perrault MA, Denault AY, et al. Effects of phlebotomy and phenylephrine infusion on portal venous pressure and systemic hemodynamics during liver transplantation. Transplantation. 2010;89(8):920–7. doi:10.1097/TP.0b013e3181d7c40c.
77. Matot I, Scheinin O, Eid A, Jurim O. Epidural anesthesia and analgesia in liver resection. Anesth Analg. 2002;95(5):1179–81. table of contents. http://www.ncbi.nlm.nih.gov/pubmed/12401587
78. Borromeo CJ, Stix MS, Lally A, Pomfret EA. Epidural catheter and increased prothrombin time after right lobe hepatectomy for living donor transplantation. Anesth Analg. 2000;91(5):1139–41. http://www.ncbi.nlm.nih.gov/pubmed/11049898
79. Elterman KG, Xiong Z. Coagulation profile changes and safety of epidural analgesia after hepatectomy: a retrospective study. J Anesth. 2015;29(3):367–72. doi:10.1007/s00540-014-1933-4.
80. Barton JS, Riha GM, Differding JA, et al. Coagulopathy after a liver resection: is it over diagnosed and over treated? HPB. 2013;15(11):865–71. doi:10.1111/hpb.12051.
81. Lee SH, Gwak MS, Choi SJ, et al. Prospective, randomized study of ropivacaine wound infusion versus intrathecal morphine with intravenous fentanyl for analgesia in living donors for liver transplantation. Liver Transpl. 2013;19(9):1036–45. doi:10.1002/lt.23691.