Anaesthesia in patients with liver disease

Malgorzata H. Starczewska[a], *Wint Mon*[b], *and Peter Shirley*[a]

Purpose of review
The purpose of this review is to summarize the most recent up to date research data and recommendations regarding anaesthetic management of patients with liver disease undergoing surgery. The incidence of chronic liver disease (CLD) continues to rise and perioperative mortality and morbidity remains unacceptably high in this group. Meticulous preoperative assessment and carefully planned anaesthetic management are vital in improving outcomes in patients with liver disease undergoing surgery.

Recent findings
The presence of cirrhosis is associated with a significantly increased risk of postoperative morbidity and mortality in patients undergoing elective surgery. The Child–Pugh–Turcotte scale and model for end-stage liver disease (MELD) score remain the most commonly applied scoring systems in preoperative risk assessment, but new MELD-based indices and novel scoring systems might offer better prognostic value. Propofol and new inhalational agents (sevoflurane, desflurane) are recommended hypnotic agents. The titration of opiates in the perioperative period is recommended because of their altered metabolism in patients with liver disease. Perioperative management should include close haemodynamic monitoring and admission to a critical care area should be considered.

Summary
Patients with liver disease undergoing anaesthesia pose significant challenges and advanced planning and preparation are required in order to improve perioperative outcomes in this group.

Video abstract
http://links.lww.com/COAN/A43.

Keywords
chronic liver disease, cirrhosis, high, perioperative medicine, risk patients scoring systems

INTRODUCTION

Approximately 29 million people in the European Union are diagnosed with chronic liver disease (CLD) [1]. From autopsy studies the prevalence of cirrhosis is estimated to be between 4.5 and 9.5% in the general population [2]. Recent data from a large international prospective cohort study demonstrated that amongst patients undergoing elective surgery the prevalence of cirrhosis is 0.8% [3]. This would equate to approximately 25 million cirrhotic patients undergoing surgery each year worldwide. The presence of cirrhosis is independently associated with 47% increased risk of postoperative complications and over two and a half increased risk of in-hospital mortality in patients undergoing elective surgery [3]. Meticulous preoperative assessment and carefully planned anaesthetic management of these patients is required in this high-risk population.

PREOPERATIVE RISK ASSESSMENT OF THE PATIENT WITH CHRONIC LIVER DISEASE

The primary liver dysfunction and the impact of CLD on other organ systems places these patients at high risk. A study detailing 24 282 patients with liver cirrhosis and 97 128 controls undergoing major surgery in Taiwan showed evidence of preexisting organ dysfunction in the form of increased

[a]Adult Critical Care Unit, Royal London Hospital, Barts Health NHS Trust and [b]University College London Hospitals NHS Foundation Trust, London, United Kingdom

Correspondence to Peter Shirley, Adult Critical Care Unit, Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London E1 1BB, UK. Tel: +44 0203 594 0345; fax: +44 203 594 0347; e-mail: Peter.Shirley@bartshealth.nhs.uk

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KEY POINTS

- Liver disease is associated with particularly high mortality and morbidity in the perioperative period.
- CTP and MELD scoring are recommended prognostic tools used in preoperative risk assessment, but new scores are being developed.
- Careful choice of anaesthetic agents, including hypnotics, muscle relaxants and analgesia should take into account altered pharmacokinetics in patients with CLD.
- Perioperative management should focus in monitoring and prevention of CLD decompensation and associated other organs dysfunctions.

comorbidities in the cirrhosis group (i.e. stroke, hypertension, chronic renal disease, congestive cardiac failure and chronic lung disease) [4]. A Danish mortality study of 39 840 colorectal cancer patients showed a 30-day mortality of 8.7% in those without liver disease and 13.3% with CLD. Amongst those with proven cirrhosis, the 30-day mortality was 24.1% [5].

A cohort study in Denmark detailing primary hip and knee arthroplasty and risk of complications in cirrhotic/noncirrhotic patients also revealed that cirrhotic patients had a higher burden of comorbidities. The chance of an uncomplicated procedure was 81% in cirrhotic patients and 90% in the noncirrhotic [6▪]. U.S. researchers showed a doubling of risk of hepatic decompensation in cirrhotic patients within 90 days of orthopaedic surgery, as compared to cirrhotic controls. They compared 853 orthopaedic cases with 4263 cirrhotics and demonstrated that a progressive decrease in serum albumin postsurgery and an incremental increase in the Charleson comorbidity index (CCI) were significantly associated with decompensation after surgery. The CCI is a predictor of 1-year mortality for patients who may have a range of comorbid conditions (22 conditions in total) [7,8▪▪].

SCORING SYSTEMS FOR CHRONIC LIVER DISEASE AND SURGICAL RISK

The Child–Turcotte–Pugh (CTP) scoring has traditionally been used to assess the risk of mortality in patients with liver disease presenting for surgery [9]. It was initially introduced as a predictor for patients having porto-systemic shunts but has subsequently been used as a risk marker for nonhepatic surgery (Table 1 [9]). Model for end-stage liver disease (MELD)scoring was developed to help prioritize liver transplantation waiting list patients [10]. There have been conflicting studies regarding the predictive value of these scores despite recommendations to use both scores [11]. A 79 patient study comparing CTP-based, MELD-based and MELD-based indices has suggested that CTP is the best prognostic indicator for overall mortality but that integrated-MELD (iMELD; incorporating sodium and age) and intra-operative transfusion scores are the best prognostic indicators for operative mortality [12]. This study needs to be set against another study of 64 cirrhotic patients undergoing nonhepatic surgery, which concluded that CTP was better at estimating 30-day mortality, MELD for 3-month mortality and MELD-Sodium (MELD-Na) for 1-year mortality [13]. The refinements to MELD scoring, including the use of sodium and age, along with some other concerns of the use of MELD scoring in the allocation of transplant candidates has led some authors to suggest that MELD-Na will become the new standard for mortality prediction in patients with end-stage liver disease (Table 2 [14,15]) [16▪].

Table 1. Child—Turcotte–Pugh (CTP) classification

Parameter	1 point	2 points	3 points
Hepatic encephalopathy grade	None	1–2	3–4
Ascites	Absent	Mild	Moderate
Prothrombin time (INR)	<1.7	1.7–2.3	>6
Serum albumin (g/l)	>35	28–35	<28
Total bilirubin (mg/dl)	<2	2–3	>3
Points	5–6	7–9	10–15
CTP class	A	B	C

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There is continued work to develop other scoring systems as mortality predictors. Japanese researchers have established a new scoring system based on 2197 cirrhotic patients undergoing major surgery. They have developed the adequate operative treatment for liver cirrhosis (ADOPT-LC) score using the patients age, CTP class, duration of anaesthesia and the CCI to predict in-hospital mortality [17▪▪]. Whilst the CTP class is predictive of a higher in-hospital mortality, the duration of anaesthesia is also a major predictive factor (Table 3 [17▪▪]).

Not insignificant numbers of cirrhotic patients are admitted to ICU. There have been attempts to refine the well established sequential organ failure assessment (SOFA) score for CLD patents. The chronic liver failure – SOFA score has been devised and compared with acute physiology and chronic health evaluation (APACHE) III scoring for day one admission to ICU [18]. Prospective data on 250 patients with cirrhosis showed that CLIF-SOFA was a better discriminator of 6-month mortality

Table 2. Model of end-stage liver disease (MELD) scoring and MELD-Na

MELD = 3.78 × ln[serum bilirubin (mg/dl)] + 11.2 × ln[INR] + 9.57 × ln[serum creatinine (mg/dl)] + 6.43(aetiology: 0 if cholestatic or alcoholic; 1 otherwise)
Reproduced with permission [13]
MELD-Na = MELDNa = MELD-Na − [0.025 × MELD(140 − Na)] + 140
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than APACHE III. A variation on this using a CLIF-consortium organ failure score (CLIF-COFs) validated in 1349 patients has also shown a higher predictive mortality value than MELD, MELD-Na or CTP in patients with decompensated cirrhosis [19]. Interestingly, data published from France, surveying admissions over 13 years in 32 ICUs of 2383 patients with septic shock and cirrhosis has shown that ICU survival has improved from 26 to 35% over the study period [20]. Both these studies may have implications for cirrhotic patients presenting for emergency surgery who may require ICU admission or those who have developed hepatic decompensation after major elective surgery.

It is clear that the severity of liver disease, comorbidities, age and emergency surgery are all poor prognostic indicators for patients with CLD. Whatever the merits of the different scoring systems, they are all designed to inform the decision making process and in themselves do not militate against the risks involved. Aside from the duration of anaesthesia there is no current evidence suggesting the type of anaesthesia has a bearing on mortality [21]. The decision of when (or when not) to offer surgery is complex and should involve clear discussions between the treating teams (surgical / anaesthesia / critical care) and the patient. It is beyond the scope of this review to give advice about when surgery or anaesthesia shouldn't be offered.

Table 3. ADOPT-LC scoring system

Variable	Score
Age (years)	
≤65	0
>65	1
CTP class	
A	0
B	1
C	3
Charleson comorbidity index	
≤2	0
3–5	1
≥6	2
Duration of anaesthesia (min)	
≤180	0
181–420	1
>420	2
Score range	0–8

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INTRA-OPERATIVE MANAGEMENT OF PATIENTS WITH LIVER DISEASE

Invasive pressure and cardiac output monitoring should be considered as standard for patients with end-stage liver disease undergoing major surgery. Bispectral index and neuromuscular blockade monitoring should also be applied as the duration of action of some anesthetic agents is affected by liver failure and associated renal insufficiency.

Choice of anaesthetic agent is based on variables such as protein binding, distribution and drug metabolism [22]. For procedures requiring sedation, propofol is preferable to benzodiazepines as it has a shorter time to sedation and a shorter recovery time in cirrhotic patients [23]. Propofol is the induction agent of choice for general anesthesia because of its rapid redistribution but can cause vasodilation, potentially reducing liver perfusion [24]. Propofol can also be administered by target-controlled infusion (TCI). A study showed that the patients with the most severe liver dysfunction required the least amount of propofol when administered by TCI [25]. Thiopentone can have a prolonged duration of action because of a reduction in plasma proteins, resulting in an increased unbound fraction of the drug.

Halogenated inhalation agents are mainly excreted via the respiratory system; because of their lipophilic property, some are absorbed and require hepatic metabolism [26]. The resultant metabolite, trifluoroacetylate stimulates an immune mediated reaction leading to liver cell damage [27]. Newer agents, such as sevoflurane and desflurane, undergo hepatic metabolism to a lesser extent compared to halothane and are safer in cirrhotic patients. Although xenon is suitable for cirrhotic patients, improvement in anesthetic delivery is necessary to make it more cost-effective [28].

Atracurium and *cis*-atracurium are suitable neuromuscular blocking agents, as they do not undergo hepatic metabolism. Other agents, such as vecuronium and rocuronium, are metabolized by the liver, and their duration of action is prolonged [24]. Fujita *et al.* [29] reported that the mean time from the administration of sugammadex (for reversal of rocuronium) to recovery of the train-of-four ratio to 0.9 and was not significantly different between those with liver dysfunction group and controls. Succinylcholine is metabolized by plasma cholinesterase, which can be significantly reduced in cirrhotic patients causing the prolongation of succinylcholine action.

Most available analgesics are metabolized in liver, and eliminated by kidneys, which presents difficulties in patients with CLD. Although acetaminophenis well tolerated in most patients, its dose should be reduced in those with decompensated hepatic disease, particularly if they are malnourished [30▪]. Nonsteroidal anti-inflammatory drugs are not recommended because of their side-effects, including gastrointestinal bleeding and renal impairment. Long-acting opioids, such as morphine, are generally avoided but titrated doses of fentanyl or sufentanil are well tolerated in patients with cirrhosis. Co-prescription of laxatives is essential to avoid constipation and encephalopathy [31]. Regional anesthesia is recommended as part of multimodel analgesia in patients with acceptable coagulation profile. Dose should be carefully calculated and the patient monitored for possible side-effects [32].

Patients with decompensated CLD have an increased risk of aspiration because of delayed gastric emptying, co-existing gastro-esophageal reflux disease and ascites. Cricoid pressure and endotracheal intubation are recommended to prevent pulmonary aspiration. Perioperative antibiotics that cover gram-negative bacteria, such as a third generation cephalosporin, should be given to patients with ascites to reduce the risk of bacterial peritonitis [33].

Paediatric patients with liver disease should be transferred to a tertiary centre for their surgery. Choice of anesthetic and analgesic agents is dependent on the liver and renal function. Careful perioperative fluid management is necessary, even for minor procedures in order to prevent hypovolaemia and hypoglycaemia. Postoperative intensive care may be required, particularly if opioid analgesia is used [34] (Table 4).

PERIOPERATIVE MANAGEMENT

In decompensated CLD, acute viral hepatitis, alcoholic hepatitis, acute liver failure and with deterioration of any other liver disease-associated organ failures, surgery should be postponed unless urgent, because of the significant risks [35].

CLD was assumed to be associated with bleeding diathesis because of impaired production of clotting

Table 4. Checklist for chronic liver disease patients undergoing anaesthesia

1. Assessment	Physician lead preoperative assessment to include, baseline blood tests, ECG, CxR, ECHO and cardio-pulmonary exercise testing
2. Risk stratification	Use of a liver-specific scoring system (CTP or MELD) to inform potential morbidity and mortality. Consider use of newer scoring systems (ADOPT-LC) which may prove to have better prognostic value
3. Conduct of anaesthesia	a. Propofol preferable to benzodiazepines
	b. Atracurium preferable to vecuronium / rocuronium (and consider using suggamadex if these are used)
	c. Avoid suxamethonium as action can be prolonged
	d. Newer volatiles (Desflurane, sevoflurane) preferable to older halogenated agents
	e. Consider use of invasive monitoring and maintain euvolamia
	f. Utilize in-theatre visco-elastic tests of coagulation (TEG or ROTEM)
	h. Avoid NSAIDS
	i. Consider regional anaesthesia as an adjunct where possible to minimize use of opiates
4. Immediate postoperative care	a. Be prepared for extended recovery and be aware of prolonged recovery times
	b. Monitor for signs of on-going bleeding
	c. Monitor for signs of hepatic decompensation
	d. Monitor for signs of acute kidney injury
5. Critical care	a. Admission to high dependency area (level 2) for major surgical cases
	b. Consider admission to intensive care (level 3) for patients with additional significant comorbidities or these undergoing emergency surgery

factors further aggravated by thrombocytopaenia. Current data suggest that a new balance between diminished production of prohaemorrhagic, procoagulant and antifibrinolytic factors is established and compensatory mechanisms, such as increased production of factor VIII, von Willebr and factor or diminished secretion of its cleaving protease (ADAMTS-13) are seen [36]. Therefore, conventional coagulation tests such as prothrombin time (PT), platelet count and fibrinogen concentration poorly reflect the status of the haemostatic system and do not predict bleeding in CLD [37]. Viscoelastic testing (TEG/ROTEM) has demonstrated that a significant proportion of patients with CLD are hypercoagulable and the prevalence of this may vary from 5% in patients with noncholestatic cirrhosis to 28 and 43% of patients with primary biliary cirrhosis and primary sclerotizing cholangitis respectively [38]. Viscoelastic testing reflects complex interactions between plasma, blood cells and platelets in clot formation, as well as providing information about fibrinolysis and hypercoagulability. These point-of-care tests are superior in their assessment of haemostasis in patients with liver disease [38]. However, recent prospective observational study suggested that ROTEM-predicted hypocoagulability was associated with preserved or increased coagulation profile reflected by a thrombin generation test. This might limit the value of viscoelastic tests in this population of patients and further tests may need to be developed in the future [39▪].

Rapid intraoperative drainage of large volume ascites (>5 l) might lead to paracentesis-induced circulatory dysfunction (PICD), which occurs in up to 80% of patients when there is no additional therapeutic management and 15–35% when volume expanders are applied [40]. The presence of PICD may lead to faster re-accumulation of ascites, increased incidence of hepato-renal syndrome (HRS) and increased mortality. Patients with large volume ascites should be optimized by treatment with a low sodium diet (<2 g/day), diuretics and therapeutic paracentesis. It is recommended, that a replacement with 6 to 8 g of albumin per litre of ascites removed is given [40]. Alternatively, a trans-jugular intra-hepatic porto-systemic shunt (TIPS) might be considered preoperatively in order to decrease portal hypertension prior to abdominal surgery [41].

Acute kidney injury (AKI) is present in up to 20% of in-patients with decompensated liver cirrhosis [42]. A recent study has demonstrated that patients with liver cirrhosis undergoing nonhepatic surgery have 52% higher risk of developing AKI in the postoperative period, in comparison to matched controls without cirrhosis [4]. Also any acute deterioration of liver function in the postoperative period can lead to the development or worsening of preexisting HRS by aggravating renal hypoperfusion, portal hypertension and intra-abdominal pressures. The most important type of HRS in patients with CLD undergoing general anaesthesia is type 1 HRS, which presents as AKI characterized by doubling baseline serum creatinine to a level above 2.5 mg/dl in less than 2 weeks; this may require renal replacement therapy in the postoperative period. To prevent AKI in patients with CLD undergoing general anaesthesia, it is vital to ensure euvolaemia and avoid nephrotoxic agents, including contrast agents and NSAIDs. Should type 1 HRS occur, an albumin infusion with combination of vasoconstrictor is recommended. Amongst the vasoconstrictor agents, terlipressin, noradrenaline and a combination of the α-agonist midodrine with octreotide are proven in the management of type 1 HRS [43]. A recent meta-analysis suggested that there might also be a dose–response relationship between infused albumin and HRS reversal and survival of patients with type 1 HRS [43]. A small prospective randomized study has shown that a perioperative infusion of N-acetylocysteine in cirrhotic patients undergoing major abdominal surgery may reduce the incidence of AKI diagnosed with cystatin C. This treatment was also associated with preservation of renal and liver function in the postoperative period and reduced ICU and hospital length of stay [44].

A multicentre observational study has demonstrated that preoperative CLD doubles the risk of the postoperative respiratory failure in patients undergoing surgery under any type of anaesthesia [45]. The mechanism is likely to be multiple pathophysiological changes such as decreased functional residual capacity because of atelectasis and diaphragmatic splinting in patients with ascites, hepatic hydrothorax, hepatopulmonary syndrome and muscle wasting leading to increased work of breathing [22]. Liver cirrhosis is also independently associated with increased risk of pneumonia after nonhepatic surgery [4]. Preoperative screening in patients with CLD with resting dysponoea should include arterial blood gases and imaging of the chest. There also needs to be screening for hepatopulmonary syndrome [46]. There is no evidence of beneficial effects of routine postoperative use of continuous positive pressure ventilation or high-flow oxygen nasal cannula therapy in patients with liver disease undergoing anaesthesia.

A hyperdynamic circulation with reduced systemic vascular resistance and increased resting heart rate are associated with CLD. Blunted chronotropic and inotropic responses to stress, impaired diastolic relaxation and prolonged QT interval are also seen and in the absence of other cardiac disease

is referred to as cirrhotic cardiomyopathy [47▪]. Recent studies suggest that it may be present in 40–50% of patients with cirrhosis. It is usually remains asymptomatic at rest; rapid changes in preload and afterload can manifest this acutely [47▪]. There is no specific treatment for cirrhotic cardiomyopathy; conventional heart failure management should be employed, using of invasive haemodynamic monitoring in the perioperative period. The use of ACE-inhibitors in-advisable because of their vasodilatatory potential; patients are better treated with β-blockers to reduce portal hypertension, which may further aggravate symptoms of cirrhotic cardiomyopathy when it occurs [47▪].

CONCLUSION

Patients with liver disease undergoing major surgery continue to pose a significant challenge in the perioperative period. Detailed preoperative assessment and optimization along with careful management in the perioperative period is vital for improving mortality and morbidity in this patient group. The use of scoring systems may aid in prognostication and the early utilization of intensive care should be considered.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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