Liver Cirrhosis Surgical Patient Management - Adult

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1. Purpose of guideline

To optimise the perioperative care of patients with liver cirrhosis within the Auckland District Health Board (Auckland DHB).

2. Definitions

The following terms are used within this document:

Term	Definition
CTP	Child-Turcotte-Pugh
MELD	Model of end-stage liver disease
FBC	Full blood count
UEC	Urea electrolytes creatinine
LFTs	Liver function tests

3. Summary of recommendations

3.1 Pre-operative assessment

- Review by a hepatologist (inpatient or outpatient*)
- Assess for signs of decompensation, portal hypertension, and degree of fibrosis (fibroscan)
- Notify liver anaesthetist
- Pre-operative investigations: FBC, UEC, LFTs, albumin, coagulation studies, cross-sectional imaging^
- Optimisation of nutritional status, ascites, encephalopathy, coagulopathy
- Advise patients on abstaining from alcohol ingestion
- Calculate MELD, CTP, Mayo model scores.

*depending on emergent or elective nature of surgery
^may be warranted to assess degree of ascites, venous collateral and/or Hepatocellular carcinoma (HCC)

3.2 Determine post-operative mortality risk estimates

- CTP class: A 10%; B 30%; C 76-82% (in-hospital mortality)

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- MELD score: <8 (6%), 12-15 (25%), 16-20 (44%), 21-25 (54%), >26 (90%) (30 day mortality) https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older
- Mayo Postoperative Mortality: https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/post-operative-mortality-risk-in-patients-with-cirrhosis/itt-20434721
- VOCAL Penn Cirrhosis surgical risk score: http://www.vocalpennscore.com/

3.3 Post-operative care

- High dependency/intensive care bed*
- Minimise dietary and intravenous sodium administration
- Reduce dose and interval of narcotic analgesics and avoid sedatives
- Early introduction of lactulose, enemas +/- rifaximin for prevention of encephalopathy
- Monitor for and manage decompensation/complications e.g. ascites, encephalopathy, infections, haemorrhage/thrombosis.

*may not be needed in the setting of well compensated disease and minor procedures

4. Peri-operative recommendations

1. Patients with chronic liver disease/cirrhosis should be assessed by a hepatologist prior to undergoing surgery. Patients can be reviewed in the outpatient setting before elective surgery or as an inpatient before emergency surgery. The hepatology registrar can be contacted on **021412015** or **021 416720** to facilitate patient assessment.
2. Patients with risk factors for chronic liver disease (e.g. alcohol use disorder, history of intravenous drug use (IVDU), metabolic syndrome) or established chronic liver disease should be assessed for clinical signs of decompensation (e.g. jaundice, ascites, encephalopathy). Recommended pre-operative blood tests include LFTs, EUCs, albumin, platelet count, and coagulation studies. Staging the degree of hepatic fibrosis should be performed with transient elastography pre-operatively (the Hepatology service can facilitate this).
3. Patients drinking alcohol should be advised to abstain pre-operatively. Post-operative complications rates have been observed to occur more frequently in active drinkers, particularly those with higher Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scores (Bradley et al., 2011; Harris et al., 2011)..
4. Endoscopic screening for gastro-oesophageal varices should be performed prior to elective operations (Garcia-Tsao, Abraldes, Berzigotti, & Bosch., 2017). Primary prophylaxis with non-selective beta blockers and/or band ligation should be considered if varices are present.
5. Treatment of ascites with salt restriction, diuretics and/or paracentesis is recommended prior to elective surgery. Ascites is of particular concern in abdominal surgery, as its presence increases the risk of wound dehiscence, and infection (Odom et al., 2013).
6. Malnutrition and sarcopaenia are common in cirrhotic patients, occurring in up to 80% (Kim, Kang, Kim, & Baik, 2017; Tsiaousi, Hatzitolios, Trygonis, & Savopoulos, 2008). These patients should be identified and offered nutritional support pre-operatively, as this has been associated with improved post-operative outcomes (Jie et al., 2012).
7. Pre-operative optimisation of haemostasis should be considered. This may include correction of thrombocytopaenia immediately pre or intraoperatively, with an aim of a total platelet count of >50,000uL. Current guidelines do not recommend correcting INR values given the

efficacy of administrating various clotting factors, including cryoprecipitate, fresh frozen plasma, vitamin K and Factor VIIa, is unclear (DeAngelis et al., 2016; Yates, Gavva, Agrawal, & Sarode, 2016). Case by case discussion with the hepatologist, surgeon, and anaesthetist is required to formulate a plan for optimising haemostasis peri-operatively. Use of thromboelastography may be useful to guide administration of blood products. Additionally, pre-operative optimisation of renal function is warranted, as uraemic induced platelet dysfunction can contribute to the bleeding risk.

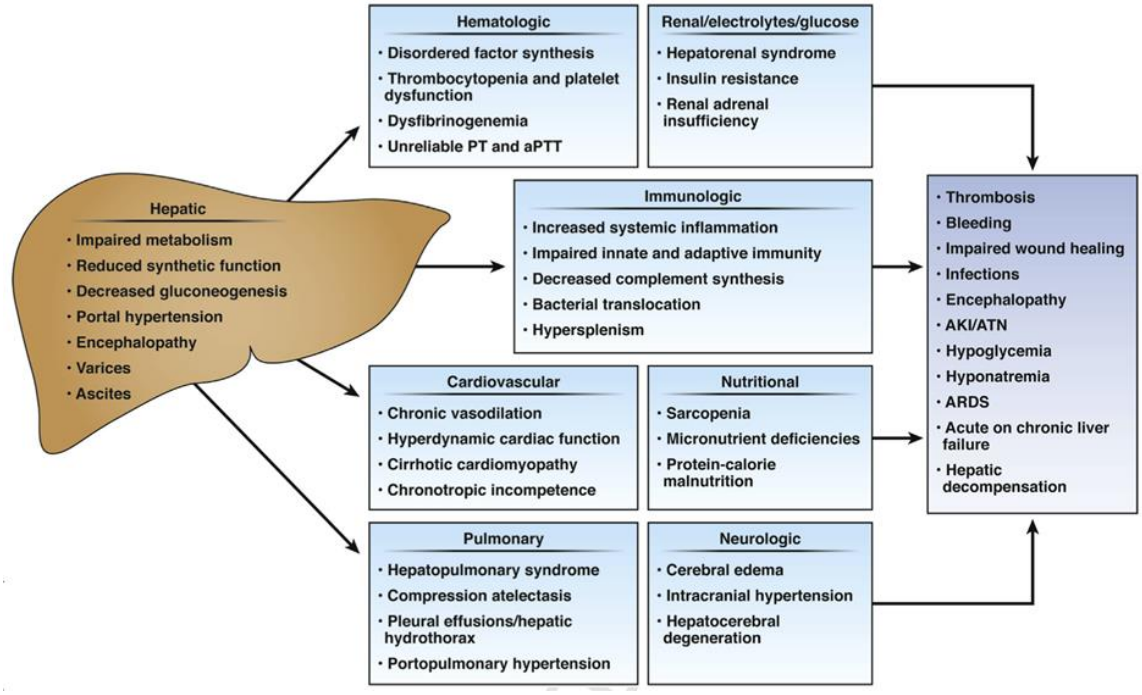
8. Patients with cirrhosis undergoing surgery need to be discussed with the liver anaesthetist pre-operatively. General considerations include use of low sodium intravenous fluids, minimising benzodiazepine and narcotic administration and avoiding spinal/epidural anaesthesia due to the risk of haematoma and neurological sequeale.
9. Patients with decompensated liver disease (e.g. hepatic encephalopathy, ascites, jaundice) should be co-managed with the hepatology team, liver anaesthetist and intensive care team. Joint care may better facilitate optimisation of liver disease pre-operatively, and management of hepatic complications post-operatively.
10. The CTP, MELD, and the Mayo Postoperative Risk Score should be used to estimate surgical risk for each patient. However, these scores have limitations (see Assessing peri-operative risk) and do not replace a holistic patient assessment. The hepatology team can assist in discussion with patients and their next of kin regarding the peri-operative risks.

5. Background

Patients with chronic liver disease are at increased risk of surgical and anaesthesia related morbidity and mortality. The peri-operative mortality rate is 2-10 times greater compared to non-cirrhotic patients, with magnitude of risk increasing with worsening severity of underlying liver disease, and with more invasive procedures (Newman et al., 2019; Northup, Wanamaker, Lee, Adams, & Berg, 2005; Teh et al., 2007).

Data from the 1970-80's showed unacceptably high mortality rates in cirrhotic patients undergoing intra-abdominal surgery (67% at 30 days). The worst prognoses were seen in those with severe synthetic dysfunction (INR >2.5), and in those undergoing emergency surgery (Aranha & Greenlee, 1986). Over the last two to three decades, with careful patient selection, both perioperative and in hospital mortality rates have dramatically decreased.

Multiple factors contribute to poorer post-surgical outcomes in patients with cirrhosis.



1. Advanced cirrhosis is associated with cardiovascular changes including a hyperdynamic circulation, decreased peripheral vascular resistance, and hepatic hypoperfusion. During anaesthesia hepatic blood flow may fall by 30-50%, making the liver susceptible to hypoxic-ischaemic injury (Gholson, Provenza, & Bacon, 1990).
2. The risk of intra-operative hypoxia is increased by the presence of ascites, hepatic hydrothorax, as well as hepatopulmonary syndrome or portopulmonary hypertension. Additionally, ascites and encephalopathy increase the risk of pulmonary aspiration post-operatively (Friedman, 2010).
3. Progressive hepatic synthetic dysfunction, protein-calorie malnutrition and sarcopaenia can impair wound healing as well as physical recovery post-operatively (Northup, Friedman, & Kamath, 2019).
4. The risk of haemorrhage is increased in cirrhotic patients via two mechanisms: portal hypertension, and impaired haemostasis. Portal hypertension worsens with progressive cirrhosis, increasing the risk of haemorrhage from collateral vessels arising from the splanchnic circulation. This is of particular concern during intra-abdominal and cardiothoracic surgery (Northup, Friedman, & Kamath, 2019). Haemostasis may be impaired due to thrombocytopaenia and coagulopathy. The thrombocytopaenia in cirrhosis is primarily due to splenic platelet sequestration, and to a lesser extent thrombopoietin deficiency. Coagulation studies may be abnormal due to hepatic synthetic dysfunction. However, the international normalised ratio (INR) does not correlate directly with bleeding risk in cirrhotic patients, as deficiencies in both pro- and anti-coagulant factors co-exist. Hence these patients are at risk of both thrombosis and bleeding. External factors may tip the balance towards either coagulation and haemorrhage (Tripodi & Mannucci, 2011). Thromboelstography can be used to guide administration of clotting factors and platelets but requires an experienced practitioner to interpret the test.
5. Cirrhotic patients suffer from co-existing immunological deficiencies as well as an exaggerated response to inflammation (Albillos, Lario, & Álvarez-Mon, 2014). Synthetic liver failure contributes to a deficiency in innate immune response proteins, while increased gut

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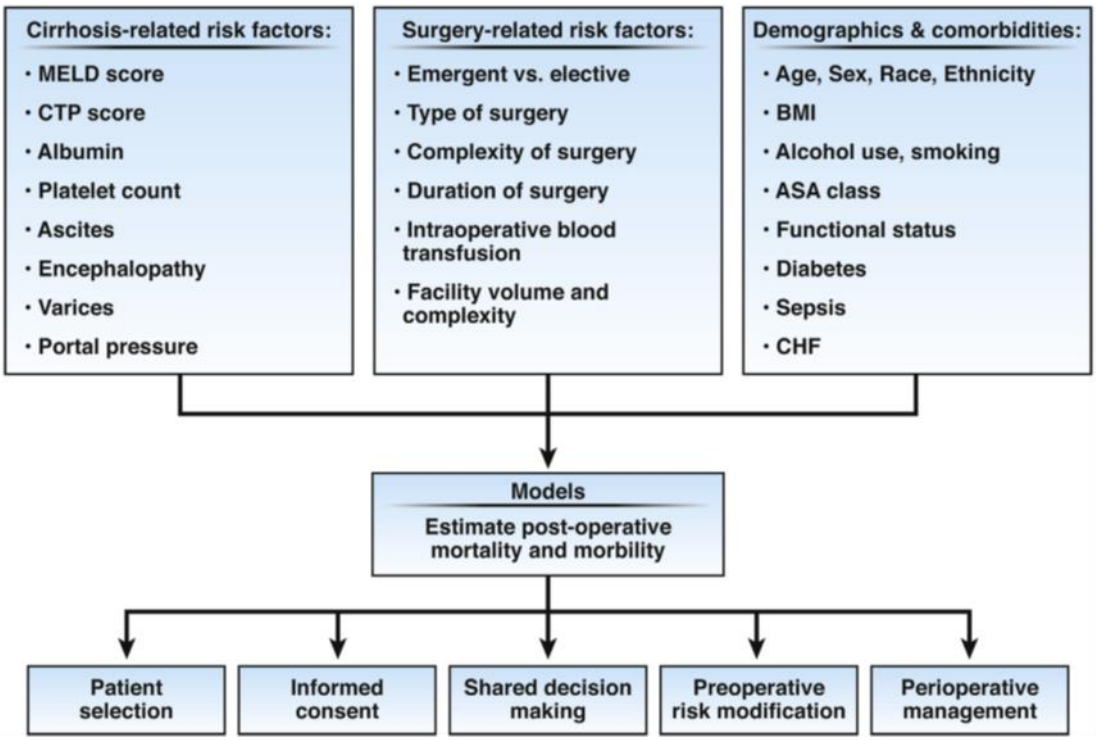
permeability, intestinal dysbiosis and bacterial translocation promote chronic systemic inflammation (Bajaj et al., 2014; Muñoz et al., 2012. These immunological alterations may contribute to increased rates of infection and hepatic decompensation post-operatively.

6. Peri-operative fluid balance can be challenging, given the propensity towards intra-vascular volume depletion co-existing with signs of fluid overload in advanced cirrhosis (Friedman, 2010). The use of sodium rich fluids, such as normal saline, can lead to rapid accumulation of ascites, hepatic hydrothorax, pulmonary oedema and peripheral oedema.
7. Patients with advanced cirrhosis and portal hypertension are at risk for post-operative encephalopathy, particularly after administration of sedatives (especially benzodiazapines) and narcotic analgesics. This is due to both portosystemic shunting and reduced hepatic metabolism.

6. Assessing peri-operative risk

Postoperative mortality in patients with cirrhosis can be predicted from severity of liver failure and portal hypertension, pre-existing comorbidities and type of surgery (Figure 2).



6.1 CTP class

In studies from the pre-MELD era, the CTP score showed a consistent correlation with post-surgical mortality, with excellent survival rates seen in class A disease, and progressively lower survival rates in those with class B and C disease (Farnsworth, Fagan, Berger, & Awad, 2004). However, the CTP has been criticised for including subjective parameters (ascites and encephalopathy), as well as only having three classes (A, B and C) with heterogeneous scores within each. The CTP can stratify patient risk into low, intermediate, and high risk but cannot

precisely predict post-operative risk. Broad estimates of mortality rates following general surgery are as follows: Childs A 10%; Childs B 30%; Childs C 76-82% (Nicoll, 2012).

Recent studies however have shown a weaker correlation between CTP class and post-surgical outcomes, in part due to low numbers of decompensated cirrhotics undergoing surgery (Telem et al., 2010). CTP class has largely been superseded by the MELD score and combination Mayo model calculator (see below) in estimating surgical risk in patients with cirrhosis (Befeler et al., 2005). However the CTP class may be more effective in estimating surgical risk in patients with portal hypertension and relatively intact synthetic function (Northup et al., 2019). It is important to note that in Childs A patients with portal hypertension, the surgical risk is equivalent to that seen in Childs B patients (Friedman, 2010). Pre-operative TIPS placement for decompression of varices, has been reported in uncontrolled case reports/series, but cannot be routinely recommended based on current data (Northup et al., 2019).

6.2 MELD score

The MELD score is widely used to prioritize organ allocation in liver transplant candidates, after initially being developed to estimate mortality following placement of a transjugular intrahepatic portosystemic shunt (TIPS) (Malinchoc et al., 2000 . It can also be used predict post-operative surgical mortality risk (Northup et al., 2005).

Compared to the CTP class, the MELD score incorporates only objective variables: creatinine, international normalised ratio (INR), and serum bilirubin. Additionally, a wider score range (between 6-40) is possible than with CTP scores, and each 1-point increase correlates with increased mortality risk. This allows for more precise post-operative outcome estimates (O'Leary & Friedman, 2007). A large single centre retrospective study including patients undergoing abdominal, cardiothoracic and orthopaedic surgeries, showed a stepwise increase in post-operative mortality with increasing MELD scores (Teh et al., 2007). Multiple other studies have also shown that the MELD score independently predicts post-operative mortality (Farnsworth et al., 2004; Northup et al., 2019; Northup et al., 2005) .

6.3 Mayo Post-Operative Surgical Risk Score

In addition to the MELD, Teh, et al (2017) observed higher mortality rates with increasing ASA classifications, and ages ≥ 70, in a large series of cirrhotic patients under-going abdominal, orthopaedic, or cardiovascular surgery. The type of surgical procedure in this series was not an independent predictor of mortality, nor was emergent surgery. Combining the ASA, age, and MELD score improved the ability to predict post-operative mortality, compared to the MELD score alone. This data was used to derive the Mayo Post-Operative Surgical Risk Score. However limitations of the model includes exclusion of common minor surgical procedures and the inability to stratify risk according to the nature of the procedure e.g. elective vs emergent.
The calculator allows prediction of post-operative mortality in cirrhotic patients at seven days, 30 days, 90 days, one year and five years, and is available at https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/post-operative-mortality-risk-in-patients-with-cirrhosis/itt-20434721. Furthermore, this data has been externally validated in a Korean cohort (Song et al., 2011).

Note: Bilirubin and Creatinine values need to be converted to SI units prior to entry into the model

6.4 VOCAL-Penn Cirrhosis Surgical Risk Score

This is the most recently published and validated risk calculator derived in almost 5000 patients with cirrhosis who underwent diverse surgical procedures. VOCAL-Penn predicts post-operative mortality for patients with cirrhosis. It incorporates the type and circumstance of surgery under consideration, and utilises other important and readily available clinical data. Predictions may be used to risk-stratify patients for surgery and help inform decisions to pursue surgical or non-surgical management.

The calculator allows prediction of post-operative mortality in cirrhotic patients at 30 days, 90 days, 180 days, and is available at http://www.vocalpennscore.com (Mahmud et al., (2021).
Note: Bilirubin and Albumin values need to be converted to SI units prior to entry into the model

Table 2: Validated scoring systems to assess mortality risk in patient with cirrhosis undergoing surgery. Adapted from Newman et al., 2019.

Model	**Components of score**	**Outcomes predicted**	**Limitations of the score/model**
CTP	Encephalopathy, ascites, albumin, bilirubin, INR	In hospital mortality, 30 day mortality rates	Includes subjective variables. Heterogeneous scores stratified into only one of three classes; A, B or C. Does not account for non-hepatic factors such as nature of surgery and other comorbidities
MELD	Bilirubin, creatinine, INR, dialysis	In hospital mortality, 30 and 90 day mortality rates, liver transplantation	Does not account for non-hepatic factors such as nature of surgery and other comorbidities
Mayo Model	MELD, American Society of Anesthesiologists (ASA) physical status classification , Age	7 days, 30 days, 90 days, one year, and five year mortality	Not distinguish between emergency vs elective surgery. Crude measure of non-hepatic comorbidities (ASA).
VOCAL -Penn Cirrhosis Surgical Risk Score	Age, Body Mass Indes, ASA, Emergency vs elective surgery Abdominal vs other surgery	30 day, 90 day and 180 day mortality	Does not account for type of liver disease Crude measure of non-hepatic comorbidities (ASA).

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7. Specific surgical risks

7.1 Abdominal surgery

7.1.1 Hepatic resection:

The MELD can predict mortality and morbidity following hepatic resection for HCC in patients with cirrhosis. A study of 82 subjects identified a cut-off MELD of ≤ 8 was associated with 0% post-operative mortality, compared with 29% if the MELD was ≥ 9 (Teh et al., 2005)). Additionally, the MELD can predict the development of post-operative liver failure. One retrospective series identified zero cases of liver failure post hepatic resection with MELD scores ≤ 8 (Cucchetti et al., 2006). Current guidelines suggest liver resection for HCC be restricted to patients with a solitary tumour, excellent hepatic function (Childs A), and the absence of portal hypertension European Association For The Study Of The Liver, 2018. Several surrogate markers for lack of portal hypertension have been studied, including a peripheral platelet count of >100,000 /μL, the absence of varices on endoscopy and venous collaterals on imaging studies, a hepatic venous pressure gradient of <10mmHg, and hepatic stiffness measurement via transient elastography although the optimal cut-off remains unclear (Northup et al., 2019.

7.1.2 Non-hepatic abdominal surgery:

In a series of 138 cirrhotic patients undergoing nonhepatic abdominal surgery (99 intra-abdominal surgery, 39 abdominal wall surgery), hepatic function, emergent surgery, as well as the nature of the surgery (intra-abominal vs abdominal wall surgery) were all associated with mortality. Mortality rates were higher in patients undergoing emergency surgery compared with elective surgery (47% vs 9%, p<0.001), as well as with intra-abdominal surgery compared with abdominal wall surgery (35 vs 8%, p=0.001). Mortality rates were also higher with increasing CTP scores (A10%, B 29%, C 63%, p<0.001) and increasing MELD scores (<10, 9%; 10-15, 19%; >15, 54%; p<0.001) (Neeff, Mariaskin, Spangenberg, Hopt, & Makowiec, 2011).

Specific mention of abdominal hernaie is warranted. Cirrhotic patients are at increased risk of developing herniae, particularly umbilical herniae. The mechanism is likely due to the presence of increased intra-abdominal pressure from ascites, and abdominal wall muscle wasting (Shlomovitz, Quan, Etemad-Rezai, & McAlister, 2005). Recurrent ascites is associated with wound dehiscence and recurrence of herniae (Northup et al., 2019. Emergency surgery for complicated herniae, including incarceration, is an independent predictor for mortality, compared with elective repair. Hence elective repair should be considered with appropriate pre-operative optimisation, particularly complete control of ascites (Andraus et al., 2015; Pinheiro et al., 2020). If medical control of ascites is not possible, TIPS can be considered prior to abdominal surgery, in selected patients (Lahat et al., 2018).

7.2 Cardiovascular surgery

Cardiovascular comorbidities are common in cirrhotic patients, particularly those with non-alcoholic steatohepatitis (NASH). Therefore, the need for cardiac surgery in this patient group is expected to increase with the increasing prevalence of the metabolic syndrome. Reported mortality rates following cardiac bypass graft surgery are variable (4-70%) (Northup et al., 2019). Data assessing perioperative risk are limited to series of relatively small numbers of patients and

include mostly those with well compensated liver disease. Macaron et al observed variable 90 day port-operative mortality rates; 4.6% in patients with CTP score of <8, and a 70% mortality rate in those with a CTP score of ≥8 (Macaron et al., 2012).

In general, a MELD of ≥13.5 or CTP score or >7 is considered a contraindication to cardiac surgery ((Suman et al., 2004; Thielmann et al., 2010). Thromboelastography has been assessed in cirrhotic patients intra-operatively to assess haemorrhage risk and used to guide administration of blood products Fleming et al., 2017.

7.3 Orthopaedic surgery

Patients with cirrhosis are at increased risk of hepatic decompensation as well as surgical complications following orthopaedic surgery. A Danish healthcare registry retrospective analysis of 363 cirrhotic patients and 109,159 reference patients, undergoing total hip or knee replacements, found cirrhosis was associated with increased risk of death during hospitalisation or within 30 days of discharge (1.4% vs 0.4%), readmission (15% vs 8%), deep prosthesis infection (3.1% vs 1.4%) and the need for surgical revision (3.7% vs 1%), compared to non-cirrhotic controls (Deleuran, Vilstrup, Overgaard, & Jepsen, 2015). The risk of hepatic decompensation within 90 days post-operatively has been observed to occur at increased rates compared to cirrhotic matched controls who did not undergo surgery (12.8% vs 4.9%) (32). Additionally complication rates following instrumental lumbar surgery, including wound infections and hepatic decompensation, occur more frequently in cirrhotic patients with a CTP score ≥ 6, compared with non-cirrhotic controls (Lin et al., 2014).

7.4 Head and Neck surgery

Patients with head and neck cancers often share risk factors for chronic liver disease, particularly alcohol use disorder. In a retrospective study of 19,138 patients undergoing head and neck surgery, the prevalence of liver disease was 6.8%. Furthermore the 30-day mortality rates following major head and neck surgery (e.g. total laryngectomy, total glossectomy) in patients with advanced liver disease (MELD ≥ 10), mild liver disease (MELD <10) and no liver disease was 14.6%, 3.0%, and 0.9%, respectively. Even after non-major head and neck surgery (e.g. thyroidectomy, neck dissection), advanced liver disease was associated with a 10-fold increase in mortality compared to controls. On multivariate analysis, advanced liver disease conveyed a six-fold higher 30-day mortality rate (Cramer, Patel, Samant, Yang, & Smith, 2017).

8. Contraindications to elective surgery

The following conditions are considered contraindications to elective surgery, given unacceptable post-operative mortality rates: acute hepatitis, acute alcoholic hepatitis, and acute liver failure (Friedman, 2010). The recommendation to avoid surgery in patients with acute hepatitis is based on data from the 1950's and 60's which reported mortality rates of 10-13% following diagnostic laparotomy (Harville & Summerskill, 1963; Strauss et al., 1959). While modern surgical care would likely be associated with improved outcomes, the recommendation to avoid surgery, if possible, remains.

Surgery, other than liver transplantation, is contraindicated in patients with acute liver failure (defined as onset of jaundice, encephalopathy and coagulopathy within 26 weeks of acute liver injury, and the absence of pre-existing liver disease) (Friedman, 2010).
Elective surgery in acute alcoholic hepatitis is associated with extremely high mortality rates (>50%), and hence should be avoided (Greenwood, Leffler, & Minkowitz, 1972; Powell-Jackson, Greenway, & Williams, 1982).

9. Post-operative monitoring

Patients require monitoring in the post-operative period for signs of hepatic decompensation/failure e.g. ascites, encephalopathy, jaundice, coagulopathy. Hepatic synthetic dysfunction is best detected by elevations in the prothrombin time. Elevations in bilirubin can signify hepatic failure. However, hyperbilirubinaemia can also be due to reabsorption of extravasated blood, infection, and haemolysis.

Hypoglycaemia can occur due to exhaustion of hepatic glycogen content. Close monitoring of blood glucose levels (BGL) is recommended in suspected post-operative liver failure.
As mentioned above, careful attention to fluid balance is required as intra-vascular volume depletion can occur concurrently with signs of fluid overload. Adequate hydration minimises the risk of pre-renal dysfunction. However, overzealous administration of sodium containing fluids and dietary sodium can result in the development of ascites and pulmonary oedema, and complications thereof including wound dehiscence and hypoxia, respectively. Finally, bowel care, with early introduction of lactulose and enemas reduce the chance of post-operative encephalopathy (Friedman, 2010; Nicoll, 2012).

Post-operative analgesia can be challenging, due to altered drug metabolism/elimination in cirrhotic patients. These patients are at particular risk of drug-toxicity in the setting of cumulative narcotic medication administration. Hepatic drug metabolism is impaired relative to the degree of hepatic impairment (Chandok & Watt, 2010).

Paracetamol is safe to use, however with long term administration, a dose reduction to 2-3g daily is advised by some clinicians. Non-steroidal anti-inflammatory drugs (NSAIDS) should be avoided given the risk of renal impairment, and gastrointestinal haemorrhage (Imani, Motavaf, Safari, & Alavian, 2014).

Opioids should be given in smaller doses and increased time intervals, than in non-cirrhotic patients, given the observed increased bioavailability, reduced plasma clearance, and prolonged half-life (Tegeder, Lötsch, & Geisslinger, 1999). Tramadol at doses of 50mg twice daily has been shown to be safe (Kotb, Fouad, Fares, Mostafa, & Abd El-Rahman, 2008).

10. Rescue liver transplantation

Candidacy for liver transplantation should be established prior to proceeding with elective surgical procedures. If a patient is a transplant candidate, discussion regarding postponing elective surgery until after liver transplantation is suggested. If the surgery cannot be postponed, completion of

liver transplant assessment prior to proceeding with surgery is suggested. If the patient is not a transplant candidate it should be clearly documented in the clinical notes prior to surgery, to avoid revisiting the issue and causing distress to the next of kin, in the event of hepatic failure post-operatively (Northup et al., 2019).

11. Supporting evidence

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12. Disclaimer

No guideline can cover all variations required for specific circumstances. It is the responsibility of the health care practitioners using this Auckland DHB guideline to adapt it for safe use within their own institution, recognise the need for specialist help, and call for it without delay, when an individual patient falls outside of the boundaries of this guideline.

13. Corrections and amendments

The next scheduled review of this document is as per the document classification table (page 1). However, if the reader notices any errors or believes that the document should be reviewed ***before*** the scheduled date, they should contact the owner or Document Control without delay.