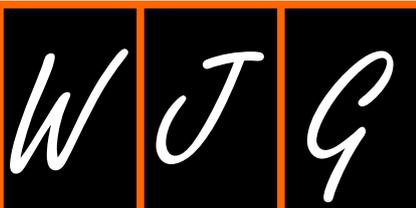


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Considerations for bariatric surgery in patients with cirrhosis

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Abstract

With the ever increasing global obesity pandemic, clinical burden from obesity related complications are anticipated in parallel. Bariatric surgery, a treatment approved for weight loss in morbidly obese patients, has reported to be associated with good outcomes, such as reversal of type two diabetes mellitus and reducing all-cause mortality on a long term basis. However, complications from bariatric surgery have similarly been reported. In particular, with the onslaught of non-alcoholic fatty liver disease (NAFLD) epidemic, in associated with obesity and metabolic syndrome, there is increasing prevalence of NAFLD related liver cirrhosis, which potentially connotes more risk of specific complications for surgery. Bariatric surgeons may encounter, either expectedly or unexpectedly, patients with non-alcoholic steatohepatitis (NASH) and NASH related cirrhosis more frequently. As such, the issues and considerations surrounding their medical care/surgery warrant careful deliberation to ensure the best outcomes. These considerations include severity of cirrhosis, liver synthetic function, portal hypertension and the impact of surgical factors. This review explores these considerations comprehensively and emphasizes the best approach to managing cirrhotic patients in the context of bariatric surgery.

Key words: Cirrhosis; Portal hypertension; Non-alcoholic fatty liver disease; Bariatric surgery; Complications

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Core tip: Bariatric surgery can be performed in patients with well compensated cirrhosis, typically of Child's A status, with minimal complication risks from surgical or hepatic factors. Patients need to be carefully selected and optimised, while surgical technique and modality also play equally important roles. With the onslaught of the non-alcoholic fatty liver disease epidemic and anticipated increase in patients with non-alcoholic steatohepatitis cirrhosis, bariatric surgery may provide an elixir as part of the armamentarium of therapeutic options.

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INTRODUCTION

The global obesity pandemic continues unabated, accompanied with increasing healthcare and economic burden^[1]. In 2005, 23.2% of the world's adult population were overweight and 9.8% were considered obese, translating to 937 million and 396 million overweight and obese adults, respectively. Projections have estimated the prevalence of overweight and obese adults to increase to 1.35 billion and 573 million adults by 2030 respectively^[2]. Obesity is commonly associated with a plethora of chronic diseases, among them being non-alcoholic fatty liver disease (NAFLD), the most common chronic liver diseases seen in gastroenterology clinics^[3]. NAFLD represents a spectrum of disease, of which a subset with more severe liver disease; namely non-alcoholic steatohepatitis (NASH) may progress to cirrhosis^[4]. Cirrhosis represents advanced stage liver disease where cumulative liver injury and necroinflammation result in fibrogenesis of the liver. This fibrogenesis is characterised by diffuse nodular regeneration, surrounded by dense fibrous septa, leading to parenchymal loss and collapse/distortion of normal liver architecture. Clinically, this correlates with the development of portal hypertension and hepatic synthetic dysfunction^[5].

With increasing recognition of efficacy in treating obesity and obesity related diseases, bariatric surgery has been increasingly performed worldwide. Not unexpectedly, bariatric surgeons may encounter patients with NASH and NASH related cirrhosis, especially with the rising prevalence of obesity. A survey of bariatric surgeons found that 39% of them had unexpected discovery of cirrhosis during bariatric surgery, accounting for an incidence rate of 0.14%^[6]. More importantly, the presence of cirrhosis often presents a vexing dilemma whether to proceed with surgery or not. This review explores the various important considerations in this context and suggests the best approaches to managing such patients.

CONSIDERATION OF LIVER FACTORS: SEVERITY OF CIRRHOSIS

Traditionally, surgical procedures in cirrhotic patients have been recognised to confer significant morbidity and mortality. Compared to non-cirrhotic patients undergoing surgery, patients with cirrhosis were reported to have longer length of hospital stay and higher hospitalisation charges^[7]. Early studies report an overall 30% postoperative mortality and 11.6% thirty day postoperative mortality after various surgical procedures^[8]. Further characterisation of surgical risk has identified severity of liver disease, nature and type of surgery to be important dependant factors. The Child-Turcotte-Pugh (CTP) score based on a combination of 5 clinical and laboratory parameters, correlates well with surgical risk and has been validated in several studies; in general, patients with Child's A cirrhosis have postoperative mortality rates of 10%, rising to 30% and 80% with Child's B and C, respectively^[9-11]. One criticism of the CTP score is the subjective nature of assessing two components of the CTP score; ascites and encephalopathy, which may lead clinicians to under or over-estimate actual liver function^[12]. The model for end stage liver disease (MELD) score, a more recently developed score, has also been shown to effectively predict postoperative mortality, in particular 30-d mortality, where a linear relationship is observed, with mortality rising 1% for each MELD point below 20 and 2% thereafter^[13]. In general, a MELD score above 8 predicts a poor outcome^[12]. The advantage of the MELD score is that it is less subjective than the CTP score as it utilises only objective laboratory parameters (serum bilirubin, international normalised ratio and creatinine). However, based on current literature, the superiority of one score over the other has not been clearly established^[14]. In the setting of NASH, lifestyle modifications including sustained weight loss form the cornerstone of treatment. In this respect, bariatric surgery may provide the most consistent and effective method of achieving and maintaining adequate weight loss, as compared to exercise/diet and other lifestyle measures. In addition, the benefits of bariatric surgery in NASH may extend from direct effects of weight loss to indirect effects of improved insulin resistance and pro-inflammatory state^[15]. Pooled data from a meta-analysis of 15 studies demonstrated improvement/resolution in steatosis (91.6%), steatohepatitis (81.3%) and fibrosis (65.5%)^[16]. However, the current literature available consists only of data from cohort studies and not randomised controlled trials. Furthermore, most of the data pertained to subjects without advanced fibrosis/cirrhosis. As such, a 2010 Cochrane review was unable to provide any recommendations in this aspect^[17]. Moreover, considering the invasive nature of bariatric surgery, there is an urgent need for well-designed randomised controlled studies to clarify the efficacy of such interventions in the treatment of NASH and specifically NASH cirrhosis.

CONSIDERATION OF LIVER FACTORS: PORTAL HYPERTENSION

Portal hypertension is another important factor to consider while assessing surgical risk. Portal hypertension is a frequent sequelae of cirrhosis, where fibrosis, scarring and the presence of regenerating nodules result in architectural distortion of the liver and in turn increased portal pressures^[18]. Increased portal pressures contribute to the pathogenesis of many complications seen in cirrhosis, such as splenomegaly with thrombocytopenia, hyperkinetic circulatory state with ascites/unstable hemodynamics, gastro-oesophageal varices, hepatorenal syndrome and portopulmonary syndrome^[19]. Intuitively, in the context of surgery, the thrombocytopenia connotes increased bleeding risk, presence of ascites may impact on healing and wound complications particularly in abdominal surgery, while also promoting atelectasis and pulmonary complications through reduced lung expansion. Perioperative hemodynamics and fluid balance may be difficult to manage. Perioperative developments of hepatorenal or portopulmonary syndromes compromise the renal and respiratory systems, making surgery all the more difficult and complicated.

The gold standard technique of assessing portal hypertension is using hepatic venous pressure gradient measurement (HVPG), which is a strong prognostic factor in cirrhosis. Clinically significant portal hypertension is observed when HVPG increased above 10 mmHg^[18,20,21]. Other signs to suggest significant portal hypertension would include presence of gastro-oesophageal varices, splenomegaly with thrombocytopenia and presence of ascites. With respect to hepatic resection for hepatocellular carcinoma in cirrhotic patients, both European (European Association for the Study of the Liver) and American (American Association for the Study of Liver Diseases) liver society guidelines consider portal hypertension to be a relative contraindication for surgery^[22,23], based on clinical studies observing increased risk of postoperative liver failure, complications and mortality in patients with portal hypertension compared to those without portal hypertension^[24-26]. Similarly, in a nationwide population based American study on mortality following colorectal surgery, patients with cirrhosis and portal hypertension had significantly higher in-patient mortality compared to patients with cirrhosis but without portal hypertension (29% vs 14% mortality rate)^[27]. This was consistent with a separate study exploring the impact of cirrhosis and portal hypertension on inpatient mortality across four specific types of surgery; cholecystectomy, colectomy, abdominal aortic aneurysm repair and coronary artery bypass grafting). Patients with cirrhosis and portal hypertension were at higher risk of mortality (Hazard ratio 7.8 to 22.7) compared to patients with cirrhosis alone (Hazard ratio 3.4 to 8) and patients without cirrhosis^[7]. One method of addressing the issue of portal hypertension is through portal decompression using Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement, which has been used to treat complications

such as bleeding varices, refractory ascites, hepatic hydrothorax and hepatorenal syndromes^[28]. Several small case series have suggested the potential role and benefits of TIPS placement in reducing perioperative complications and mortality rates across a variety of surgical procedures, showing one year survival ranging between 56% and 100%^[29-32]. Having said that, the potential benefits of preoperative TIPS must be weighed against the risk of TIPS placement. Progressive hepatic failure is a rare but most feared complication post TIPS placement. It is often the reflection of decreased liver blood perfusion due to shunting of blood away from the liver, culminating in hepatic ischemia and progressive dysfunction in an already poorly functioning liver^[33]. In addition, the incidence of new or worsening hepatic encephalopathy following TIPS is 20%-31%, which may limit the enthusiasm for this procedure^[34,35]. Increasing age, liver dysfunction and shunt diameter are important risk factors associated with hepatic encephalopathy post-TIPS placement^[36]. Hence, caution must be exercised when selecting appropriate patients to undergo a TIPS procedure^[28].

In summary, common cirrhosis (including portal hypertension driven) related complications to be vigilant about in the post-operative setting would include worsening or new onset ascites, worsening or new onset hepatic encephalopathy, coagulopathy, fluid overload, renal failure or liver failure.

CONSIDERATION OF SURGICAL FACTORS

The nature and type of surgery impacts on the morbidity and mortality in cirrhotic patients. While postop mortality and morbidity rates have been high historically, better identification/awareness, preoperative assessment/optimisation, newer anaesthetics and surgical techniques have mitigated such risks. Overall, better outcomes are observed with laparoscopic surgery over open surgery. In a small case series of 50 predominantly mild to moderately cirrhotic patients undergoing a variety of laparoscopic surgical procedures, Cobb *et al*^[37] found an overall morbidity rate of 16% with no incidence of hepatic decompensation or mortality. A separate population-based study advocated the preference of laparoscopic cholecystectomy over open cholecystectomy in cirrhotic patients, with improved mortality (1.3% vs 8.3%), less post-operative infection (0.7% vs 3.5%) and lower requirement for blood transfusion (14.4% vs 19.2%)^[38]. In general, laparoscopic techniques have improved outcomes over a range of surgical procedures in patients with mild to moderate cirrhosis^[37].

Separately, emergency surgery is generally regarded to have higher associated morbidity and mortality compared to elective surgery^[39,40]. In addition, the surgical procedure itself has important implications and considerations in cirrhotic patients. Cardiac and major abdominal surgeries are considered high-risk surgeries in cirrhotic patients^[14]. Assessing nationwide mortality rates

post elective surgery in cirrhotic patients, Csikesz *et al*^[7] found disparate mortality rates among different surgical procedures (Hazard ratio 3.4, 3.7, 5.0 and 8.0 for cholecystectomy, colectomy, abdominal aortic aneurysm repair and coronary artery bypass grafting, respectively).

In summary, common surgical related complications among patients with cirrhosis would include sepsis, wound infection/dehiscence/impaired healing and bleeding.

IMPACT OF BARIATRIC SURGERY ON THE LIVER

There have been several case series on the impact of bariatric surgery on the liver. In the 1960s to early 1980s, the jejunoileal bypass (JIB) was among the first bariatric surgical procedures used to treat morbid obesity. However, this procedure has since been abandoned due to multiple side effects of this procedure, including the development of hepatic failure^[41]. In a longitudinal follow up study of patients who had undergone JIB, the risk of development of hepatic fibrosis and cirrhosis at 15 years post JIB was 45% and 8%, respectively^[42]. Several other studies have confirmed the risk of progressive liver dysfunction following JIB, where rapid weight loss, protein-caloric malnutrition, global malabsorption and endotoxin effects have all been implicated^[43-45]. Hepatic decompensation (albeit inconsistent evidence) has also been reported following biliary pancreatic diversion and long limb Roux en Y gastric bypass^[46-48]. There has been less evidence of detrimental effects on the liver following the other bariatric surgical procedures. As such, in a survey of 126 bariatric surgeon responders, 59% would perform banded gastroplasty, 39% standard Roux en Y gastric bypass and only 5% biliary pancreatic diversion in patients with cirrhosis^[6]. Bariatric surgery may also be associated with nutritional deficiencies, depending on the type of procedure performed. In particular, protein deficiency remains a significant concern which can manifest as oedema, loss of lean muscle mass, as well as biochemical features of anaemia and hypoalbuminemia. Changes in taste/food preference, potential macronutrient mal-digestion or absorption contribute to reduced protein intake, coupled with the generally higher protein demand following surgery, leads to a compromised nitrogen balance and connotes an important problem^[49,50]. This takes on even more consequence in the setting of cirrhosis, where pre-existing malnutrition, sarcopenia and impaired protein metabolism are prevalent^[51]. Hence, the predicament being that cirrhotic patients may not be able to achieve adequate protein intake with the pre-existing cirrhosis and additional demands placed by the bariatric surgery.

REPORTED COMPLICATIONS OF BARIATRIC SURGERY IN PATIENTS WITH CIRRHOSIS

There have been relatively few studies describing com-

plications of bariatric surgery in patients with cirrhosis (Table 1). In an early survey of 126 bariatric surgeons worldwide who had collectively performed almost 87000 bariatric surgeries, 125 cases of cirrhosis with overall incidence of 0.14% were unexpectedly encountered. While there was no intraoperative mortality observed, 4 deaths perioperatively (within 30 d) were related to overwhelming sepsis or fulminant hepatic failure. In addition, a further 7 late deaths were accounted for predominantly from liver failure. Separately, within the same paper, Brolin reported on 8 of his own patients with cirrhosis out of an overall series of 580 patients; hepatic failure accounted for 1 perioperative and 1 late mortality^[6]. With the advent of laparoscopic approaches to bariatric surgery, surgical outcomes have improved further. Dallal *et al*^[52] performed a retrospective review of 2119 patients who had undergone laparoscopic bariatric surgery and identified 30 patients with cirrhosis (1.4%), the majority of which were discovered intraoperatively. While there were no perioperative deaths, need for conversion to open laparotomy or liver related complications, early postoperative complications occurred in 9 of the cirrhotic patients, including anastomotic leak, acute tubular necrosis, prolonged intubation, ileus and blood transfusion. In addition, there were no major late complications other than 1 unrelated death from esophageal cancer one year post gastric bypass^[52]. A subsequent case series of 23 cirrhotic patients who had undergone a combination of laparoscopic bariatric procedures (RYGB, sleeve gastrectomy, adjustable gastric banding) reported complications in 8 patients including anastomotic leak, structuring, infected hematoma, pneumonia and bleeding requiring blood transfusion. However, there was no liver decompensation after surgery and no perioperative mortality was reported. Of note, 2 of the cirrhotic patients successfully underwent laparoscopic sleeve gastrectomy after TIPS procedure to control their portal hypertension^[53]. Takata *et al*^[54] also advocated the safety and benefits of laparoscopic bariatric surgery in patients with cirrhosis; 2 out of 6 patients with cirrhosis who underwent laparoscopic sleeve gastrectomy had only minor complications (1 patient developed ascites that responded to medical therapy while the other patient developed hepatic encephalopathy secondary to urinary tract infection that also responded to standard therapy)^[54]. Additional support for laparoscopic sleeve gastrectomy in cirrhotic patients was provided by Rebibo and colleagues, who reviewed 13 patients with Child's A cirrhosis and observed no postoperative mortality or cirrhosis specific complications^[55]. A unique complication of portal vein thrombosis with associated mesenteric ischaemia was described by Hughes and colleagues in a cirrhotic patient two weeks post laparoscopic sleeve gastrectomy. However, the patient recovered well post resection of her ischaemic bowel^[56]. Further experiences of bariatric surgery in the context of cirrhosis patients were reported by Woodford *et al*^[57], who reported two surgical complications, but no operative mortality in their series of 14 patients with compensated cirrhosis that underwent

Table 1 Study characteristics of bariatric surgery in patients with cirrhosis

Author, year	Number. cirrhotics	Childs status	Procedure	Average op time	Average blood loss	LOS	Complication	Mortality	Comments
Brolin 1998	8	NR	7 RYGB, 1 JIB reversal	NR	543 mL	NR	Ascitic fluid leak, marginal ulcer, amputation	1 periop death, 2 late deaths	
Dallal 2004	30	A	27 lap RYGB, 3 lap SG	4 h	290 mL	4	ATN, anastomotic leak, blood transfusion, prolonged ileus, prolonged intubation	1 late unrelated death	%EWL at 12 mo 63%
Takata 2008	6	4 A, 2B	6 Lap SG	141 min	58 mL	4.2	2 pts, development of ascites, HE post UTI	Nil	%EWL at 9 mo 33%
Shimizu 2013	23	22 A, 1B	14 lap RYGB, 8 lap SG, 1 LAGB	NR	NR	4.3	8 pts, anastomotic leak, stricture, infected hematoma, pneumonia	1 death 9 months postop of unknown cause	
Lin 2013	20	NR	Lap SG	151 min	NR	4.2	2 wound infections, 1 transient HE, 1 transient renal insufficiency, 1 bleeding, 1 staple line leak	1 death 4 years postop, 2 deaths on liver tx waiting list	
Rebibo 2014	13	13 A	13 lap SG	75 min	NR	3	1 postop intra-abdo hematoma	Nil	%EWL at 6 mo 61.9%
Hughes 2014	1	A	Lap SG	NR	NR	NR	Portal vein thrombosis with mesenteric ischaemia	Nil	
Woodford 2015	14	NR	14 LAGB	NR	NR	NR	1 postop surgical site infection, 1 revision of malpositioned band	1 unrelated death 11 yr post surg	%EWL at 12 mo 61.3%
Pestana 2015	14	A	11 SG, 3 RYGB	NR	NR	NR	1 unrelated HE 2 yr post-surgery	Nil	%Total weight loss at 24 mo 25.6%
Wolter 2016	12	NR	12 lap procedures	NR	NR	NR	1 staple line leak, 1 intra-abdominal abscess, 1 intraluminal bleed, 1 dysrhythmia	Nil	No significant association betw cirrhosis and periop events

NR: Not recorded; JIB: Jejunioleal bypass; SG: Sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; LAGB: Laparoscopic adjustable gastric banding; BPD: Biliopancreatic diversion; lap: Laparoscopic; %EWL: Percentage excess weight loss.

laparoscopic adjustable gastric banding. Comparable accounts were corroborated by a separate series of 14 cirrhotic patients that underwent sleeve gastrectomy or gastric bypass^[58]. Along similar lines, Wolter *et al*^[59] described 302 patients who had laparoscopic gastric bypass or sleeve gastrectomy performed, of which 12 patients had cirrhosis; there were no significant association between perioperative complications and liver cirrhosis. Nevertheless, in a large scale population based study of bariatric surgery patients, presence of compensated cirrhosis was associated with increased length of hospital stay (4.4 d vs 3.2 d, $P = 0.03$) and increased mortality rates (OR: 2.17, 95%CI: 1.03-4.55). Not unexpectedly, patients with decompensated cirrhosis had even worse outcomes. The combined in hospital mortality rate for both compensated and decompensated cirrhotics was 1.2%, with mortality rates lower at high volume centres (> 100 procedures per year) compared to lower volume centres^[60]. More recently, in a retrospective study of 297 patients with NAFLD who had undergone bariatric surgery, while the median length of hospital stay was higher in patients with advanced liver fibrosis (4 d vs 3 d, $P = 0.002$) compared to those without advanced fibrosis,

there was no significant difference in the proportion of patients with complications over 1 year post operation (36.4% vs 32.8%, $P = 0.54$)^[61].

APPROACH TO BARIATRIC SURGERY IN PATIENTS WITH CIRRHOSIS

While the few case series on bariatric surgery in patients with cirrhosis do suggest that bariatric surgery can be performed safely in carefully selected patients without prohibitive complication rates, the majority of the studies were based on patients with well compensated cirrhosis. Therefore, it remains to be seen if such surgeries can be similarly performed successfully in patients with poorer hepatic reserves. Preferably, cirrhotic patients should undergo bariatric surgery in high volume centres

The first step is to recognise and diagnose patients with cirrhosis. This is usually based on biochemical and imaging features. Surgical risk can be further stratified using CTP or MELD score to estimate liver reserve. In addition, HVPG to assess degree of portal hypertension would be useful in further management. In the event of

significant portal hypertension, TIPS can be considered to reduce risk of perioperative complications^[32]. Input from a hepatologist to optimise cirrhotic patients perioperatively would be valuable.

There remains no consensus on which bariatric modality is best suited for the patient with cirrhosis^[62]. Current available data suggest that the less invasive laparoscopic approach would be safer to perform in cirrhotics. The bariatric procedures that can be performed laparoscopically would include the RYGB, sleeve gastrectomy and gastric banding, each representing their own distinct advantages and disadvantages.

In general, RYGP provides the most potential for weight loss, but may have a greater risk of vitamin deficiencies compared to sleeve gastrectomy that may further lead to progressive hepatic dysfunction. In addition, due to altered anatomy surgically, the stomach remnant and biliary tree would be inaccessible endoscopically in the event of a gastrointestinal bleed or biliary obstruction. Furthermore, the altered anatomy may render future orthotopic liver transplantation more challenging.

Gastric banding would be the least invasive procedure, but the potential risk of infection with placement of a foreign device in cirrhotic patients already at increased risk of infections would limit the enthusiasm of such a procedure.

Sleeve gastrectomy reduces the risk of malabsorption or placement of a foreign body, but may predispose to bleeding risk in the setting of gastric varices. Increasingly, laparoscopic sleeve gastrectomy has been advocated as the bariatric modality of choice in patients with cirrhosis^[53-55]. Sleeve gastrectomy is well tolerated, technically less challenging with a relatively short learning curve and operating time^[63]. Relative to gastric bypass, sleeve gastrectomy has been shown to be associated with fewer complications overall^[64]. Furthermore, access to the stomach remnants and biliary system would remain possible with sleeve gastrectomy. With respect to liver transplantation, laparoscopic sleeve gastrectomy was observed to be well tolerated while improving candidacy for liver transplantation^[54]. In addition, sleeve gastrectomy has been shown to be safe and feasible in combination with liver transplantation at a single setting or as a staged procedure post liver transplantation^[65, 66].

Nevertheless, there remains important information gaps with regards to bariatric surgery in patients with cirrhosis. More studies are needed to assess the long term outcomes of patients with cirrhosis post bariatric surgery. In addition, more data is required in patients with more advanced cirrhosis. Better characterisation in terms of surgical candidacy, differentiating those who would derive benefit and those who would not, are imperative to develop strategies and recommendations for the improvement of bariatric surgical outcomes in patients with cirrhosis.

CONCLUSION

Bariatric surgery can be performed in patients with

well compensated cirrhosis, typically of Child's A status, with minimal complication risks from surgical or hepatic factors. Patients need to be carefully selected and optimised, while surgical technique and modality also play equally important roles. With the onslaught of the NAFLD epidemic and anticipated increase in patients with NASH cirrhosis, bariatric surgery may provide an elixir as part of the armamentarium of therapeutic options.

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