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EDITED BY
Giuseppe Gatti,
Azienda Sanitaria Universitaria Giuliano Isontina, Italy

REVIEWED BY
Artur Rebelo,
University Hospital in Halle, Germany
Antonio Gangemi,
University of Illinois at Chicago, United States

*CORRESPONDENCE
Juan C. Lopez-Delgado
juancarloslopezde@hotmail.com
Alessandro Putzu
Alessandro.Putzu@hcuge.ch

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The importance of liver function assessment before cardiac surgery: A narrative review

Juan C. Lopez-Delgado[1,2]*, Alessandro Putzu[3]* and Giovanni Landoni[4,5]

[1]Hospital Clinic de Barcelona, Area de Vigilancia Intensiva (ICMiD), Barcelona, Spain, [2]IDIBELL (Institut d'Investigació Biomèdica Bellvitge; Biomedical Investigation Institute of Bellvitge), L'Hospitalet de Llobregat, Barcelona, Spain, [3]Division of Anesthesiology, Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland, [4]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy, [5]Vita-Salute San Raffaele University, Milan, Italy

The demand for cardiac surgery procedures is increasing globally. Thanks to an improvement in survival driven by medical advances, patients with liver disease undergo cardiac surgery more often. Liver disease is associated with the development of heart failure, especially in patients with advanced cirrhosis. Cardiovascular risk factors can also contribute to the development of both cardiomyopathy and liver disease and heart failure itself can worsen liver function. Despite the risk that liver disease and cirrhosis represent for the perioperative management of patients who undergo cardiac surgery, liver function is often not included in common risk scores for preoperative evaluation. These patients have worse short and long-term survival when compared with other cardiac surgery populations. Preoperative evaluation of liver function, postoperative management and close postoperative follow-up are crucial for avoiding complications and improving results. In the present narrative review, we discuss the pathophysiological components related with postoperative complications and mortality in patients with liver disease who undergo cardiac surgery and provide recommendations for the perioperative management.

KEYWORDS

cardiac surgery, cardiac anesthesia, liver disease, cirrhosis, preoperative evaluation, postoperative complications, postoperative outcome

Introduction

The ageing of the population and the increase in the incidence of cardiovascular risk factors have caused a high demand for cardiac surgery in the past decades (1). At the same time, improvement in the medical care of patients with advanced liver disease led to an increased eligibility of these high-risk patients for CS (2). Furthermore, longevity contributed to the increased incidence of coronary artery disease and hepatocellular carcinoma in cirrhotic patients (3). In addition, in western countries there is an expansion of non-alcoholic fatty liver disease, also known as non-alcoholic steatohepatitis, which has risk factors similar to those of cardiovascular disease and is a frequent cause of chronic liver disease (4, 5). Viral hepatitis reached epidemic rates worldwide, and some studies showed an association between coronary artery disease and chronic hepatitis C due to enhanced endothelial injury caused by chronic

inflammation in patients with liver disease (6). All these factors lead towards a high prevalence of liver disease among the whole cardiac surgery population.

Cardiac surgeons are reluctant to operate patients with advanced liver disease since this is a major perioperative risk factor in cardiac surgery with associated worse outcomes. Indeed, the severity of liver dysfunction is strongly related to an increased likelihood of complications, and the staging of liver disease must be taken into consideration in order to evaluate candidates for cardiac surgery (1). Some liver scores, such as the Child-Turcotte-Pugh (CTP) and the model for end-stage liver disease (MELD) score can be used for this purpose (see variables from CTP and MELD in **Table 1**) (7–11). Despite the fact that liver disease has a great impact on morbidity and mortality after cardiac surgery, it is not weighed enough within the main different systems for evaluating perioperative risk (see **Table 2**) in the last decade, such as the Society of Thoracic Surgeons score (STS) and European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (12). These scores tend to underestimate operative risk in patients with liver disease and patients with the same characteristics have similar operative mortality risk independently of the presence of liver disease. Based on our example (see **Table 3**), the increase in operative risk is minimal, even when liver disease is estimated in STS score, whereas the real operative risk is quite higher (see below / **Table 4**). Thus, the predictability of current scores are poor in certain populations and liver function should have more weight in prognosis assessment in patients with confirmed or suspected liver disease.

Liver dysfunction not only affects liver physiology; it also affects the normal function of other organs, and the surgery-related inflammation may further contribute to postoperative organ dysfunctions (30). A high proportion (approximately 50%) of patients with advanced liver disease could have cardiac dysfunction, the so-called cirrhotic cardiomyopathy, a clinical syndrome characterised by reduced contractile response to stress but normal to increased cardiac output and contractility at rest (31). This may contribute to the development of acute kidney injury (AKI) or enhance chronic renal insufficiency after cardiac surgery, conditions which are closely associated with short and long-term high morbidity and mortality rate (32, 33).

Preoperative evaluation may serve to identify and optimise chronic diseases related to liver disease, such as renal disease or cirrhotic cardiomyopathy. Postoperative management and close postoperative follow-up are also crucial for avoiding severity of complications and improving outcome (34).

This narrative review aims to provide an overview of the perioperative issues related to postoperative complications in patients with liver disease who undergo cardiac surgery. However, we do not review nor give specific recommendations for liver-related complications (e.g., gastrointestinal haemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy) which were recently reported elsewhere (35). In order to provide the most rigorous data, we performed a narrative review check list to show our scientific approach in the present research (see **Table S1** of **Supplementary Material**).

TABLE 1 Variables from model for end-stage liver disease (MELD) score and child-turcotte-pugh score for cirrhosis mortality (CTP) score.

Variables	MELD[b]	CTP[c]
Renal	Creatinine	
Liver	Bilirubin	
	International Normalized Ratio	
		Albumin
		Ascites
		Encephalopathy
Electrolyte (Liver-related)	Serum sodium level[a]	

[a]The presence of hyponatremia is a complication associated with liver disease that worsens prognosis.
[b]Adapted from Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33: 464-70, and Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008; 359: 1018-26.
[c]Adapted from Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders 1964:50-64.

The importance of addressing the severity of liver disease before cardiac surgery

Long-term outcomes of patients with liver disease who undergo cardiac surgery are closely related to the preoperative severity of liver disease and to the incidence of complications during the perioperative period (13). We identified the following predictors of mortality after cardiac surgery in these patients: older age, increased preoperative total plasma bilirubin, increased International Normalised Ratio (INR), low preoperative serum cholinesterase levels, high central venous pressure, preoperative congestive heart failure, preoperative weight loss, preoperative and postoperative thrombocytopenia; prolonged cardiopulmonary bypass (CPB) time; and prolonged operative time (2, 8, 10, 14–25, 36, 37). Thus, both liver-related variables (i.e., preoperative) and those related to the development of the inflammatory response after cardiac surgery (i.e., intraoperative) have a higher impact on the outcome of these patients.

As we previously mention, the EuroSCORE and the STS score are both widely accepted in Europe and America, respectively, as valuable scores in cardiac surgery, but they do not consider liver function (38, 39). Liver scores such as MELD or CTP can be useful for staging liver function before

TABLE 2 Comparison between different variables included within main systems for evaluating perioperative risk in adult cardiac surgery.

	STS score	EuroSCORE II
Patient related factors		
Demographics	Age	
	Gender	
	Ethnicity	
Anthropometrics	Body Surface Area	
Toxic habits	Alcohol, tobacco and illicit drugs use	
Cardiovascular	Hypertension	
	Diabetes	Diabetes on insulin
	Peripheral artery disease	
	Family history of premature CAD	
	Syncope	
Central Nervous System	Previous cerebrovascular disease	Poor mobility
	Degree of right and left carotid stenosis	>50% of right and left carotid stenosis
Liver	Presence of Liver disease	
Lung	Sleep apnea	
	Chronic Lung Disease (i.e., lung function)	Presence of Chronic Lung Disease
	Use of home oxygen	
Renal	Preoperative creatinine levels	Renal Impairment[a]
	Need of dialysis	
Immune	Presence of Immunocompromise	
Hematology	Preoperative WBC levels	
	Preoperative Platelet levels	
Other previous severe illnesses or related treatments	Endocarditis (treated or active)	Active endocarditis
	Pneumonia	
	Cancer (within previous 5 years)	
	Mediastinal radiation	
Critical preoperative state	Inotropes	Inotropes
	Previous need of resuscitation	Preoperative cardiac massage
	IABP support	IABP support
	ECMO support	
	Catheter Based Assist Device Used	
Previous treatment	ADP inhibitors	
	ACE or ARB	
	Beta blockers	
	Steroids	
	Glycoprotein IIb/IIIa	
	Operational & surgical related factors	
	Previous procedure	
	Type of previous procedure (e.g., second re-op)	
	Type of current procedure	Weight of the intervention
		Surgery on thoracic aorta
	Number of diseased Wessels or valvular diagnosis	
	Urgency of the procedure	Urgency of the procedure
	Cardiac related factors on admission previous to surgery	
	Timing of previous MI	Recent MI (i.e., MI within 90 days)
	Symptoms of angina on admission	CCS class 4 (i.e., angina at rest)
	Heart failure timing	
	NYHA classification	NYHA classification
	Presence of cardiogenic shock	
	Presence & Timing of arrhythmia (e.g., AF, flutter, ventricular, sick sinus)	
	Presence & Timing of heart block	
	Left Ventricular Ejection Fraction	Left Ventricular function
		Pulmonary Hypertension

STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; CAD, Coronary Artery Disease; MI, Myocardial Infarction; WBC, White Blood Cells; CCS, Canadian Cardiovascular Society grading of angina pectoris; NYHA, New York Heart Association; AF, Atrial Fibrillation; ADP, Adenosine diphosphate receptor; ACE, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; IABP, Intra-aortic Balloon Pump; ECMO, Extra-Corporeal Membrane Oxygenation.
[a]Based on creatinine clearance calculated using Cockcroft-Gault formula.

TABLE 3 Example of predicted mortality with main cardiac surgery scores compared with liver scores in patients without and with liver disease.

Characteristics of the patient		Predicted mortality			
		Cardiac surgery scores		Liver disease score	
• Male, 64 years old (75 Kg, 172 cm) • Myocardial infarction one year ago • Chronic Hepatitis C • Laboratory analysis: 42% hematocrit, 8,900 leukocytes, 220,000 platelets, creatinine 82 μmol·L^{-1} • 60% Ejection Fraction * Presence of stable Liver disease (Bilirubin: 3 mg·L^{-1}, Serum Sodium Level: 136 mmol·L^{-1}, INR:1.2, Albumin: 36 g·L^{-1} without any other liver associated complication)		STS	Euro SCORE II	MELD[1]	CTP[2]
Type of surgery	• Three diseased vessels • Programmed Bypass surgery	0.58% (*0.95%)	0.56% (*0.56%)	6 points *6% of estimated 3-month mortality	6 points (Child A) *10% of estimated perioperative mortality
	• Severe aortic stenosis • Programmed aortic valve replacement	0.67% (*1.007%)			
	• Two diseased vessels plus moderate mitral insufficiency • Programmed combined surgery (mitral valve replacement plus Bypass surgery)	2.01% (*2.9%)	0.97% (*0.97%)		

STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; MELD, Model for End-stage Liver Disease score; CTP, Child-Turcotte-Pugh Score for Cirrhosis Mortality score; INR, International Normalized Ratio; CTP, Child-Turcotte-Pugh score; Pts., number of patients.
*Mortality with liver disease.

TABLE 4 Associated in-hospital mortality of patients with liver disease who undergo cardiac surgery based on child-turcotte-pugh score (2, 8, 10, 13, 14–25).

	Year	CTP A		CTP B		CTP C		Total		
		N Death	N Pts.	N Death	N Pts.	N Death	N Pts.	N Death	N Pts.	%
Klemperer et al. (14)	1998	0	8	4	5	-	-	4	13	31%
Bizouarn et al. (13)	1999	0	10	1	2	-	-	1	12	8.3%
Suman et al. (15)	2004	1	31	5	12	1	1	7	44	15.9%
Hayashida et al. (16)	2004	0	10	2	7	1	1	3	18	16.6%
Kaplan et al. (23)	2005	0	4	3	6	-	-	3	10	30%
Ann et al. (26)	2007	1	17	4	6	1	1	6	24	25%
Filsoufi et al. (27)	2007	1	10	2	11	4	6	7	27	26%
Yamane el al. (24)	2008	0	13	1	7	0	1	1	21	4.7%
Murashita et al. (18)	2009	3	6	1	6	-	-	4	12	33%
Morisaki et al. (28)	2010	0	30	4	12	-	-	4	42	9.5%
Thielmann et al. (8)	2010	6	39	7	14	4	4	17	57	29.8%
Gundling et al. (29)	2010	2	33	7	14	-	-	9	47	19.1%
Vanhuyse et al. (19)	2012	4	22	3	10	2	2	9	34	26.4%
Arif et al. (20)	2012	15	74	14	29	3	6	32	109	29.3%
Sugimura et al. (21)	2012	0	7	1	5	0	1	1	13	7.7%
Lopez et al. (10)	2013	0	34	5	21	2	3	7	58	12%
Morimoto et al. (22)	2013	2	14	3	21	-	-	5	35	14.3%
Komoda et al. (25)	2013	1	45	7	19	-	-	8	64	12.5%
Lin et al. (17)	2014	5	30	3	20	1	5	9	55	16.3%
Total mortality		9.6% (41 / 427)		33.9% (77 / 227)		61.3% (19 / 31)		20% (137 / 685)		

CTP, Child-Turcotte-Pugh score; Pts, number of patients.

cardiac surgery in patients with liver disease (7, 11). Mortality is higher in patients with liver cirrhosis in comparison with the non-cirrhotic population in all CTP score groups, especially in those classified as class B and C (8, 10). We collected and reported in **Table 4** all mortality in-hospital mortality rates of patients who underwent cardiac surgery with liver disease based on CTP score (2, 8, 10, 13–25). The postoperative long-term mortality rates after hospital discharge are even also higher for cirrhotic patients undergoing cardiac surgery, ranging from 40% to 70% at about six years follow-up (34). A high MELD score (see **Table 1**) with a cut-off ranging from 13 to 18 is associated with a worse prognosis after cardiac surgery in patients with liver disease (8–10). MELD has the advantage of being more objective than the CTP score because it has measurable variables, and it reflects dynamic changes in liver function that could be corrected by the improvement of cardiac insufficiency (7, 40). Despite the fact that MELD was a better predictor of mortality in some studies which compare it to CTP, CTP score remains a reliable tool for staging liver disease before cardiac surgery (11, 15, 25). Indeed, the MELD score may overestimate liver disease because it can be influenced by worsening of cardiac insufficiency related renal function or because INR may be affected by the anticoagulation therapies that are used to treat cardiac-related problems such as atrial fibrillation (40, 41).

In the immediate postoperative period, ICU mortality risk scores, such as the simplified acute physiology score (SAPS) III, may be used in this specific population since they include liver-related variables (e.g., albumin, platelets, renal function) (10).

The presence of chronic hepatitis, especially hepatitis C, must be considered for preoperative evaluation because it is associated with high postoperative haemorrhage and surgical revision for bleeding (even in the presence of minor changes in INR), infection and postoperative cardiac complications (42–44). Therefore, viral load should be assessed before cardiac surgery.

As a general rule, cardiac surgery may be performed with higher operative risk in patients without advanced liver disease (i.e., Child A), but mortality is worsened with both higher CTP class and MELD score. Patients staged in CTP class B and MELD between 9 and 14 should be carefully evaluated before cardiac surgery, whereas in patients with CTP class C and MELD $\geq$15, cardiac surgery should be contraindicated. The weight of both liver scores in establishing indication for cardiac surgery may be considered equivalent and complementary. Similar to other major surgeries in high-risk patients, the ultimate decision of performing cardiac surgery should also consider medical past history (e.g., previous liver-related complications), the individual evaluation of the patient in terms of surgical risk and the potential benefit, especially in those patients in whom clinicians have doubts about performing or not cardiac surgery (e.g., CTP class B and MELD 15). For example, the combined presence of severe portal hypertension with liver-related complications, such as several episodes of variceal bleeding, and CTP class B, may imply a high-risk for mortality and a contraindication for surgery. However, indication of cardiac surgery should also balance the urgency in correcting the surgical problem together with the risk that cardiac surgery entails *per se*. If liver function cannot be optimized before surgery, this may represent poor liver functional reserve and cardiac surgery may be contraindicated. We suggest the use of both liver scores in conjunction with cardiac scores for the preoperative evaluation of patients with liver disease before cardiac surgery.

Liver function may be optimised in some patients, even though liver transplantation, in order to shift the stage of liver disease towards a less severe staging and ultimately give the opportunity to perform cardiac surgery. In **Table 5**, we show a summary of recommendations for the improvement of perioperative management in patients who undergo cardiac surgery with liver disease. Despite those recommendations are based in small studies, they are supported by the following pathophysiological considerations.

Pathophysiological considerations of liver disease in cardiac surgery

The progression of liver disease involves the development of portal hypertension, which can lead to ascites, spontaneous bacterial peritonitis, variceal bleeding, and hepatic encephalopathy (35). Liver-related complications may be frequent postoperatively, ranging from 8% to 33% depending on the severity of liver disease (2, 8, 10, 13, 14–25). Variceal bleeding and ascites are the most common complications, especially in the presence of previous portal hypertension or medical past history of variceal bleeding (8, 10). Hepatic encephalopathy is poorly described in these patients, but it may happen when patient suffer from cirrhosis (14). Patients with liver disease are at higher risk of liver-related complications but advanced liver disease (i.e., cirrhosis) further predisposes to higher incidence non-liver-related complications after cardiac surgery (27, 30).

Coagulation

Bleeding is one of the main concerns during cardiac surgery and the liver is the main source of coagulation proteins. Advanced liver disease is associated with a decrease in both pro- and anti-coagulants factors together with thrombocytopenia, and severe bleeding occurs in up to 30% of patients with liver disease after cardiac surgery (30). Hypothermia, haemodilution and hypoperfusion produced by CPB and fluid administration aggravate coagulopathy

TABLE 5 Specific recommendations for the perioperative management of patients with liver disease who undergo cardiac surgery.

	Preoperative	Intraoperative	Postoperative
Liver function	Calculate MELD and CTP scores (7, 11) Avoid cardiac surgery in CTP C and MELD ≥15, and evaluate carefully in CTP A, CTP B and MELD <15 (2, 8, 10, 13–25) Evaluate hepatic reserve (i.e., Evaluate if there is any improvement of INR afer the administration of Vitamin K) (53) Evaluate previous liver-related complications (e.g., ascites, liver encephalopathy, gastric bleeding) and optimise treatment for liver disease (30, 35)	Consider (45–52): - Perfusion flow rates ≥ 2.3 L/min and pulsatile flow - Revascularisation surgery performed by off-pump techniques - Aortic valve replacement performed by means of transcatheter techniques - Albumin as priming solution - Minimise CPB and operation time as much as possible - Avoid urgent procedures	Close monitoring of liver function & optimise treatment for liver disease (e.g., lactulose and avoid diuretics when possible to avoid liver encephalopathy) (30, 34, 35)
Coagulation	Evaluate and correct coagulopathy throughout thromboelastography and platelet function at least 24 h before surgery (23, 54–56)	Guide transfusion therapy by means of thromboelastography (54–56) Avoid hypothermia, haemodilution and massive transfusion (59)	Close monitoring and small increase in dosage when anticoagulant therapy is given (57, 58)
Cardiovascular function	Stress echocardiography with dobutamine to evaluate cardiac reserve and function (31, 32) Consider β-blocker administration (if not contraindicated) (61, 62) Evaluate the degree of cardiac insufficiency and prognosis by means of BNP (63) Optimise preoperative volume status (10)	Avoid positive fluid balance as much as possible (10, 34, 60)	Avoid positive fluid balance & optimise haemodynamic status (10, 34, 60)
Renal Function	Avoid drugs associated with nephrotoxicity before CS (33, 64) Optimise preoperative haemodynamic status / cardiac function (33, 64)		
Immune response (65)	Screening for multi-resistant pathogens	Avoid transfusions	Early diagnosis of infection and administration of antibiotics Prevention of nosocomial infections
Nutritional status (66–69)	Avoid cardiac surgery in patients with albumin <30–35 $g{\cdot}L^{-1}$ and optimize nutritional status Preoperative nutritional support (involve nutritionists & nurses)	Avoid long fasting times	Early nutritional support with oral, enteral or parenteral nutrition
Pulmonary function (70–72)	Preoperative medical history of respiratory failure Screen for pulmonary hypertension when preoperative right heart failure is present and make a diagnosis Avoid surgery in patients with hepatopulmonary syndrome	Avoid positive fluid balance as much as possible	Early physiotherapy Consider the use of non-invasive mechanical ventilation to prevent atelectasis Apply specific treatments for pulmonary hypertension when necessary

CS, Cardiac surgery; LD, Liver disease; CTP, Child-Turcotte-Pugh; MELD, Model for end-stage liver disease score; INR, International Normalised Ratio; BNP, Brain natriuretic peptide.

produced by liver disease during cardiac surgery (59). Factors associated with liver disease, such as poor nutrition, hypoalbuminaemia and renal failure may contribute to platelet dysfunction (73). Thus, excessive mediastinal bleeding is a frequent complication that leads to increased transfusion requirements and reoperation for bleeding (23).

The INR is used to assess prognosis in the MELD score, bleeding risk, and to guide treatment of some type of coagulation disturbances in clinical practice. The lack of improvement of INR with the preoperative administration of vitamin K may reflect a poor liver reserve, so it may be used for preoperative evaluation (30). Even though INR provides a good measure of liver function, it only measures the activity of some of the coagulant factors (53). Thromboelastography (TEG) is a tool that might provide better assessment of the degree of coagulopathy, which would enable immediate (i.e., from 30 min to 1 h) and goal-oriented transfusion therapy (54). TEG provides in which component(s) of the coagulation process (i.e., fibrinogen, platelets, intrinsic or extrinsic coagulation pathway) is the coagulative problem (if any) (54). This is especially useful in cardiac surgery because TEG enables a more individualized transfusion therapy, it could optimize preoperative and even perioperative coagulation status, and it may also improve outcomes (i.e., Length of stay, bleeding rate, and mortality) (54–56).

Preventive strategies aiming to optimise coagulopathy after cardiac surgery are also necessary (53–56). Oral anticoagulant use following cardiac surgery may entail higher risk in patients with liver disease and may potentially cause fatal bleeding complications (e.g., intracranial haemorrhage) and anticoagulant-induced liver failure (57, 58). Thus, the use of biological cardiac valves and grafts when possible, and a close bleeding and coagulation monitoring when oral anticoagulants are needed may be suggested. Despite there is an inherent risk of bleeding, deep vein thrombosis prophylaxis should be performed during perioperative period, especially in those patients with liver disease prone to suffer perioperative thrombotic complications (e.g., splanchnic or portal vein thrombosis, liver tumors, venous thromboembolism and Budd Chiari syndrome) (30, 55, 74).

Immune response

The presence of an innate and adaptive immune system dysfunction which is defined as cirrhosis-associated immune dysfunction syndrome, predisposes patients with liver disease to systemic infections. Depression and stimulation of the immune system coexist, resulting in a high susceptibility to acute inflammatory and infective processes (75). There is also a shift towards persistent inflammation leading to liver fibrosis progression and development of different complications, such as portal hypertension and hepatic encephalopathy (76). Sepsis occurs in approximately 60% of patients and is the main cause of postoperative mortality after cardiac surgery through multi-system organ failure (10, 30). Gastrointestinal bleeding, low serum albumin, poor nutritional status and higher re-exploration rates are associated with increased rates of infection in liver disease (65). Blood transfusions after cardiac surgery are associated with an increased risk of infection at multiple sites, suggesting a system-wide immune dysfunction response (77). Sepsis is an important risk factor for mortality following cardiac surgery because it can produce a sepsis-induced cardiac dysfunction, which can ultimately enhance postoperative low cardiac output syndrome and limit fluid responsiveness (78). Screening for multi-resistant pathogens, early diagnosis of infection, early administration of antibiotics, and a careful prevention of nosocomial infections are among the strategies that may be recommended during the perioperative course of cardiac surgery.

Nutritional status

The correct functioning of the immune and metabolic response systems are both interdependent (66). Different factors lead to an insufficient nutritional reserve in patients with liver disease (i.e., poor nutritional intake, inappropriate absorption due to gastrointestinal dysfunction, persistent inflammation), and in consequence the response to surgical stress is metabolically inefficient (67). Preoperative serum albumin level can be used to assess nutritional status and underlying disease before cardiac surgery, with levels of serum albumin $<25\ g{\cdot}L^{-1}$ being independently associated with an increased risk of reoperation for bleeding (66, 68). Lower levels of hypoalbuminaemia are also associated with increased risk of infection after cardiac surgery, and guidelines do not recommend surgery in patients with albumin $<30–35\ g{\cdot}L^{-1}$ (68, 69). The lack of response (i.e., lack of improvement in albumin or prealbumin levels) to preoperative nutritional support may serve as a surrogate marker of poor hepatic reserve before cardiac surgery (69).

Cardiovascular function

Patients with liver disease suffer from cardiac dysfunction and poor cardiac reserve (32). Liver disease coexists with peripheral arterial vasodilatation due to reduced arterial compliance and activation of sodium and water retentive pathways that produce expansion and redistribution of blood volume in the splanchnic bed. Consequently, there is a resting hyperdynamic hemodynamic state with increased cardiac output in response to these alterations. These alterations progress in parallel with liver disease, leading to cardiac failure and cirrhotic cardiomyopathy. These are characterised by diastolic dysfunction with poorer inotropic and chronotropic response (31, 32). The assessment of preoperative cardiac function by means of echocardiography, even with dobutamine to evaluate stress responsiveness, could play a role in the preoperative evaluation and postoperative management in patients with liver disease undergoing cardiac surgery. A poor cardiac tolerance to stress echocardiography may indicate poor prognosis and higher probability of cardiac complications (e.g., low cardiac output syndrome) after cardiac surgery (31, 32). Brain natriuretic peptide, a marker of cardiac dysfunction useful in diagnosing heart failure, is correlated with the CTP score, occurrence of liver-related complications and 1-year mortality in patients with liver disease (63). Thus, stress echocardiography and brain natriuretic peptide may be used together to evaluate cardiac function preoperatively. In each cardiac surgery candidates, elevated preoperative or postoperative cardiac troponin could be associated with higher postoperative morbidity and mortality, especially in the case of urgent cardiac surgery due to acute myocardial ischaemia (61, 79).

Cardiovascular disease is also a common cause of morbidity and mortality in patients with liver disease (31). The histologic severity of liver injury and inflammation is associated with an increased cardiovascular risk and an atherogenic lipid profile

(62). If we exclude recurrent disease, graft loss resulting from technical complications, and malignancies, cardiac complications are among the most common complications after liver transplantation (34). Furthermore, liver allograft recipients have a greater risk of cardiovascular deaths and ischemic events than an age- and sex-matched population (80). A history of coronary artery disease, prior stroke, increased interventricular septal thickness, and postoperative sepsis are markers of adverse perioperative cardiac outcomes after liver transplantation, whereas use of perioperative beta-blockers was significantly protective (81). The same may be applied to patients with advanced liver disease undergoing CS in the absence of contraindications for beta-blocker administration, especially with the presence of diastolic dysfunction (32, 34).

Moderate to advanced heart failure can produce liver disease secondary to liver congestion (i.e., cardiac or congestive hepatopathy) (60). Advanced congestion, low cardiac output that causes hypoperfusion, and right-heart failure caused by severe tricuspid regurgitation or pulmonary hypertension (i.e., pulmonary artery systolic pressure >45 mmHg) are among its causes (82). Cardiac hepatopathy is usually partially or completely reversed when cardiac problems are corrected.

Haemodynamic postoperative management is key for cardiac complications, suggesting the need for a careful management of preload and fluid balance, which ultimately may influence postoperative renal and respiratory function (83). It is not surprising that higher central venous pressure is associated with higher short-term mortality in these patients (10). Addressing cardiovascular dysfunction after cardiac surgery is crucial, even during the follow-up after hospital discharge, since liver and heart failure are among the main causes of hospital readmission in patients who underwent cardiac surgery with liver disease (34).

Renal function

Liver disease is related with renal dysfunction, the so called hepatorenal syndrome. This is associated with tissue and microcirculatory dysfunction in the heart and in the peripheral vascular bed (64). Oliguria could be a clinical sign of AKI, a common postoperative complication associated with higher short- and long-term mortality in cardiac surgery (33). Renal failure could lead to positive fluid balance, resulting in vital organs oedema and failure (83). Low urine output in the first 24 h following cardiac surgery is a valuable predictor of long-term outcome in patients with liver disease undergoing cardiac surgery (36). Patients with liver disease suffer from renal dysfunction more frequently after cardiac surgery than patients without liver disease (70). AKI has an incidence as high as 80% in cirrhotic patients after cardiac surgery, with up to 40% of these patients needing renal replacement therapies (30). We suggest that optimising haemodynamic status, avoiding nephrotoxic drugs that may enhance or cause renal failure, and avoiding positive fluid balance as much as possible are among the strategies to improve perioperative renal function (33, 71).

Pulmonary function

Ascites and fluid overload may cause or worsen pulmonary function due to atelectasis and heart failure. In patients with liver disease, severe pulmonary complications (i.e., those that cause respiratory insufficiency) occurs in up to 30% of cases (30).

Typical pulmonary complications in advanced liver disease include hepatopulmonary syndrome, portopulmonary hypertension and hepatic hydrothorax (72). Whereas hepatopulmonary syndrome and portopulmonary hypertension represent pulmonary vascular diseases, the development of hepatic hydrothorax is associated with the presence of ascites and phrenic nerve lesions. For severe hepatopulmonary syndrome and refractory hepatic hydrothorax, liver transplantation is the treatment of choice (45). Specific medical therapy is indicated in severe portopulmonary hypertension (e.g., intravenous prostanoids, oral endothelin receptor antagonists and phosphodiesterase-5 inhibitors) (45, 46, 72). All these complications need to be screened, especially in patients with a history of respiratory failure and moderate or advanced liver disease. Avoiding positive fluid balance and optimising right heart function may be helpful to reduce respiratory complications. Early physiotherapy should also be performed in order to avoid atelectasis (46).

Pathophysiological considerations for intraoperative management

Cardiac surgery involves a systemic inflammatory response mostly due to CPB, transfusions and surgical trauma. These together lead to poor hepato-splanchnic perfusion that can cause intestinal mucosal injury, therefore predisposing to endotoxemia and proinflammatory cytokine release (47). Extracorporeal CPB circuit stimulates inflammation by activation of the intrinsic coagulation pathway, worsening the coagulopathy of liver disease (48). Furthermore, the perioperative risks associated with all major cardiac surgery procedures are enhanced in the presence of liver disease due to the higher immunologic and metabolic demands that the surgical procedure imposes to the liver (2, 8, 10, 13, 14–25). The non-physiologic and non-pulsatile CPB flow could lead to ischaemia-reperfusion liver injury in association to low cardiac output episodes. A decrease in liver perfusion by about 20% and in arterial blood flow by 20%–45% through vasoconstriction during CPB could result in an imbalance in oxygen supply (49).

Perioperative strategies should focus on minimising CPB duration (<100 min) and minimising transfusion requirements. High perfusion flow rates (≥ 2.3 L/min) might have a beneficial effect on liver function and overall organ perfusion (50–52). As a consequence, there is a potential benefit when revascularisation surgery is performed off-pump and when aortic valve replacement is performed by means of transcatheter techniques (84). Albumin could be used as priming solution for CPB in order to improve bleeding-related complications (85). Emergent procedures should be avoided in order to optimise patients with liver disease as much as possible. This is especially true in patients with liver disease and infective endocarditis, who are prone to an increased risk of bacteraemia associated with invasive procedures and immune dysfunction (86).

Conclusions

Liver disease remains a major risk factor during the perioperative course of cardiac surgery. The pathophysiological characteristics of severe liver disease predispose to increased rates of complications and higher short- and long-term mortality when cardiac surgery is performed in these patients. All the different pathophysiological considerations of liver disease should be carefully evaluated prior to the performance of cardiac surgery in patients with liver disease. Liver scores (i.e., MELD and CTP) may be useful for the assessment of perioperative risk in those patients.

Optimize perfusion (e.g., Perfusion flow rates ≥2.3 L/min) and minimize surgical-related inflammation (e.g., minimise CPB and operation time as much as possible) are both key for avoiding perioperative liver dysfunction. The choice of less invasive and aggressive surgical techniques (e.g., transcatheter techniques) and the minimisation of surgical injury (e.g., off-pump revascularisation) may have a beneficial effect on the outcome of these patients. Close monitorization of coagulation and platelet function (e.g., TEG), and avoid hypothermia as much as possible, are both important to avoid bleeding and optimize transfusion policy. Fluid management avoiding positive fluid balance as much as possible may be useful to improve perioperative cardiovascular, renal, and even pulmonary and coagulopathy (i.e., hemodilution) status of these patients. All these considerations, together with a close attention for the prevention of nosocomial infections, preoperative optimization of physical status and early postoperative physiotherapy, as well as a plan to improve preoperative nutritional status and an early postoperative nutrition therapy, may be helpful to improve perioperative outcomes and prevent potential complications (see detailed recommendations on **Table 5**). Even though evidence comes mainly from small studies, some recommendations could be given for their perioperative management, even to improve preoperatively liver function.

Author contributions

JCLD, AP and GL performed research, selected manuscripts and wrote the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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