

Review

Cardiovascular events after liver transplantation: MACE hurtsMario H. Altieri^{1,†}, Hongqun Liu^{2,†}, Samuel S. Lee^{2,*}¹Division of Gastroenterology, Hepatology and Nutrition, CHU, 14000 Caen, France²Liver Unit, University of Calgary Cumming School of Medicine, Calgary, AB T2N 4N1, Canada*Correspondence: samlee@ucalgary.ca (Samuel S. Lee)

†These authors contributed equally.

Academic Editors: Ichiro Wakabayashi and Klaus Groschner

Submitted: 19 November 2021 Revised: 17 December 2021 Accepted: 4 January 2022 Published: 9 March 2022

Abstract

The curative therapy for patients with end-stage liver disease is liver transplantation. However, liver transplantation challenges the cardiovascular system, and is associated with major adverse cardiovascular events (MACE). Immediately after implantation of the liver graft, changes in cardiac preload and afterload increase the cardiac workload. Longer-term postoperatively, a more sedentary lifestyle and enhanced appetite increase obesity and body mass index. Immunosuppressants may also affect the cardiovascular system. All these factors that liver recipients encounter impact the function of the cardiovascular system. Cardiac events are the third-leading cause of death in liver recipients. This review describes the pertinent factors that predispose to development of MACE after liver transplantation, and how to predict these cardiovascular events in the post-transplant period. We review the roles of metabolic syndrome, renal dysfunction, non-alcoholic fatty liver disease, diagnostic tests such as imaging and biomarkers, and parameters such as systolic and diastolic dysfunction, and QT interval prolongation in cardiovascular events. We summarize the current literature on scoring systems to predict cardiovascular events.

Keywords: cardiovascular complications; liver transplantation; heart failure; cirrhotic cardiomyopathy; arrhythmias; ventricular dysfunction

1. Introduction

The dictionary defines Mace as either a fearsome medieval weapon, typically a heavy club with a metal head and spikes or a noxious chemical irritant spray invented in the 1960s to dispel unruly crowds. Being attacked by either type of Mace obviously hurts. That MACE is harmful also applies to the post-liver transplantation (LT) scenario. MACE in that setting is the abbreviation for major adverse cardiovascular events. It is common in patients with LT. A study [1] evaluated 319 LT patients and reported that 23% of patients had MACE within 30 days after LT. We hereby review this syndrome in the setting of LT, including the factors that predispose to MACE, why it is harmful, and how to predict its development post-transplant.

The definition of cirrhotic cardiomyopathy is cardiac dysfunction in patients with end-stage liver disease in the absence of previous heart conditions [2–4]. Patients with cirrhosis have systemic vasodilation which reduces ventricular afterload, thereby “auto-treating” the patient and abrogating the development of overt congestive heart failure [5,6]. However, when challenged, overt heart failure can manifest itself [7–9]. LT generates a great challenge to patients due to the large fluctuations in preload and afterload starting from the perioperative and persisting for several days after transplantation.

LT is a double-edged sword for patients with end-stage liver diseases. On one hand, LT is the one and only curative treatment for end-stage liver diseases of any etiology in-

cluding hepatocellular carcinoma (HCC). Kim and coworkers [10] reported that one year after LT, the indices of cardiac function were recovered. These included left ventricular ejection fraction (LVEF, $65.8 \pm 5.0\%$ vs $62.5 \pm 4.9\%$, $p < 0.05$), left ventricular end diastolic diameter (LVEDD, 49.5 ± 4.7 vs 46.0 ± 5.1 mm, $p < 0.01$), global longitudinal strain (GLS, -24.9 ± 2.4 vs -20.6 ± 3.4 , $p < 0.001$), global circumferential strain (GCS, -28.4 ± 3.6 vs -24.6 ± 4.2 , $p < 0.05$) and other parameters, such as E/A ratio, E/e' ratio, left ventricular mass index, and extracellular volume fraction (ECV), etc. Furthermore, the QTc interval had also normalized (475 ± 41 msec vs 429 ± 30 msec, $p < 0.001$; this value was 410.5 ± 8.6 in healthy controls) [10].

On the other hand, LT puts a significant stress on the cardiovascular system. Intravenous fluids add preload and an increase in systemic vascular resistance augments the afterload. The left ventricular overload worsens pre-existing cirrhotic cardiomyopathy. Therefore, LT places the patient in a hazardous position. Adverse cardiovascular events lead to a lower rate of patient and graft survival. A little less than half of the patients undergoing liver transplant have shown signs of cardiac dysfunction during the perioperative period, with 7% to 21% mortality from heart failure in the following months after transplant [11]. Since the candidates for liver transplant tend to be older and those with non-alcoholic fatty liver disease (NAFLD) are a growing population [12], MACE will be increased in transplant recipients resulting in a lower rate of patient and graft sur-



Table 1. Metabolic syndrome definition.

MetS criteria components IDF 2006; abdominal obesity + 2 or more components		NHLBI/AHA 2005; at least 3 components
Waist circumference	≥90 cm (man)	≥102 cm (man)
	≥80 cm (woman)	≥88 cm (woman)
Fasting blood glucose	≥100 mg/dL and/or diabetes treatment	≥100 mg/dL and/or diabetes treatment
Blood pressure	≥130 mmHg (SBP) and/or	≥140 mmHg (SBP) and/or
	≥85 mmHg (DBP) and/or hypertension treatment	≥90 mmHg (DBP) and/or hypertension treatment
Triglycerides	≥150 mg/dL and/or hypertriglyceridemia treatment	≥150 mg/dL and/or hypertriglyceridemia treatment
HDL	<40 mg/dL (man)	<40 mg/dL (man)
	<50 mg/dL (woman)	<50 mg/dL (woman)

IDF, International Diabetes Federation; NHLBI/AHA, National Heart, Lung, and Blood Institute/American Heart Association; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, high density lipoprotein.

vival. However, the cardiovascular risk is poorly characterized. The preoperative cardiovascular evaluation is a key component of the LT assessment process [13]. The present review looked to summarize the potential risk factors for cardiac events in patients after LT.

2. Metabolic syndrome

Metabolic syndrome (MetS) is a combination of insulin resistance, obesity, dyslipidemia, and high blood pressure. There are several definitions of MetS including WHO 1999, NCEP (National Cholesterol Education Program) ATPIII 2005 [14], National Heart, Lung, International Diabetes Federation (IDF) 2005, and Blood Institute/American Heart Association (NHLBI/AHA) 2005. The last two criteria are more popular (Table 1). These two criteria are composed of the same components. However, NHLBI/AHA are more restrictive about waist circumference and blood pressure.

Patients with MetS show increased incidence of cardiovascular events [15,16]. This scenario also applies to liver transplant recipients. Richards *et al.* [17] investigated weight gain and obesity post LT and found that the median weight gain at 1 and 3 years was 5.1 and 9.5 kg compared to the body weight before transplantation. By 1 and 3 years, 24% and 31% had become obese, respectively. The risk factors for liver recipients to develop MetS include: pre-transplant diabetes, pre-transplant obesity, more sedentary lifestyle, and drugs such as corticosteroids and immunosuppressants.

The prevalence of metabolic syndrome in the USA is about 30% as per the Adult Treatment Panel III (ATPIII) [15]. This prevalence is markedly increased in patients post LT. Anastacio and colleagues [18] analyzed 148 liver recipients and found that 50% of them had MetS according to IDF standards and 38.5% according to NHLBI/AHA criteria. Oommen *et al.* [19] demonstrated that the incidence of MetS was 31% before LT and a further 29% developed post LT. MetS predisposes the liver recipients to increased cardiovascular events. Compared with those without MetS, liver recipients with MetS are up to four times more likely

to have a cardiovascular event [20]. Therefore, physicians should pay more attention to this syndrome and try to prevent, diagnose, and treat metabolic syndrome in order to curb the risk of cardiovascular events [16] post LT.

3. Renal function and cardiovascular events after liver transplantation

Hepatorenal syndrome (HRS) is a serious complication of cirrhosis. About 30% of patients with end-stage liver disease (ESLD) develop HRS. Patients with HRS show comorbid profound circulatory and cardiac dysfunction. These patients have a greater risk of developing MACE as opposed to those without HRS (41/9% vs 22.0%, $p < 0.01$). When adjusted for MELD score, cardiovascular risk index, age, a positive stress test, and a history of coronary artery disease (CAD), HRS was still an independent predictor for MACE [1]. VanWagner *et al.* [21] evaluated the correlation of MACE and cardiac function. They found that on one hand, LT recipients with an early MACE had a mean of a higher creatinine (1.9 vs 1.6 mg/dL, $p < 0.0001$) and prevalence of chronic renal disease (19% vs 14%, $p = 0.0018$) compared to those without MACE. On the other hand, the frequency of MACE was higher in liver recipients with HRS than those without HRS (19.6% vs 14.6%, $p = 0.002$).

It is well known that renal failure is an independent risk factor for morbidity and cardiovascular mortality [22]. Soriano and coworkers [23] analyzed 57,946 patients who had type 2 diabetes and found that renal dysfunction (estimated GFR <60 mL/min/1.73 m²) is significantly correlated to a higher risk of major cardiac events. Brugts *et al.* [24] found that a 10 mL/min per 1.73 m² decrease in glomerular filtration rate was associated with a 32% higher risk of myocardial infarction. The correlation between renal dysfunction and cardiovascular events also applies to patients post LT. The major cardiac events include acute myocardial infarction, angina pectoris, unstable angina, cardiac failure, CAD, ischemic stroke, pulmonary edema, and sudden death. The study conducted by Saliba *et al.* [25] indicated that cardiac events occur in 7–28% of liver trans-

plant patients followed up to 24 months after transplantation. The risk of major cardiac events increases with deteriorating renal function after transplantation and this risk is inversely associated with glomerular infiltration rate (GFR) over the first 2 years after LT.

The risk factors for cardiac events in uremic patients with chronic kidney disease include anemia, hyperparathyroidism, hyperhomocysteinemia, high lipoprotein(a) levels, and low vitamin C [26]. All of these risk factors also exist in liver transplant recipients with renal dysfunction. Furthermore, some of the immunosuppressants, such as calcineurin inhibitors (CNIs), are nephrotoxic with long-term usage. Saliba *et al.* [25] divided their patients into 3 groups, and reported that patients receiving mammalian targets of rapamycin (mTOR) inhibitors with reduced or discontinued CNI had better renal function than the group continuing on CNI. Interestingly, both mTOR inhibitors with reduced or discontinued CNI groups had fewer major cardiac events compared with standard CNI therapy groups. These data further demonstrated that cardiac events become more likely as renal function deteriorates.

4. Nonalcoholic fatty liver disease (NAFLD)

NAFLD is subdivided into two types: simple fatty liver called non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The latter form may eventually lead to cirrhosis requiring LT. Although NAFLD represents the hepatic manifestation of metabolic syndrome, it is an independent risk factor for cardiovascular disease, independent of metabolic syndrome [27].

Patients with NASH-associated cirrhosis frequently have diabetes mellitus or dyslipidemia which are risk factors for CAD. The frequency of CAD in patients with NASH-cirrhosis is much higher than in other cirrhotic patients [28]. Given the aging population and obesity, the frequency of metabolic syndrome and NAFLD is increasing [29], NASH cirrhosis is also increasing which increases CAD prevalence in cirrhotic patients [30].

Charlton and colleagues [31] described a large increase in NASH as the indication for LT from 1.2% in 2001 to 9.7% in 2009 in the United States. Considering the future eradication of Hepatitis C virus and the application of Hepatitis B virus vaccination and therapy, NASH cirrhosis will be the most common indication for LT [32].

Patients with NASH have a higher chance to develop a comorbid MACE within one year after LT. VanWagner and colleagues [33] compared cardiovascular events post LT between NASH and alcohol-induced cirrhosis and found that after adjusting for previous history of CAD, previous history of metabolic syndrome, BMI, smoking, age, and sex, the MACE rate was still greater in the NASH group when compared to the alcohol group (26.4% vs 8.2%, $p < 0.01$). Another study also compared NASH and alcohol-induced cirrhotic patients who underwent LT. Although no statistically significant differences in post-transplant survival and cardiovascular mortality were found between the NASH

and alcohol groups, acute rejection and recurrent steatohepatitis were significantly more frequent in the NASH group [34].

The most common cardiac event in both groups was acute pulmonary edema (18.1% in NASH vs 16.2% in the alcohol group), followed by new-onset atrial fibrillation. More than 50% of the NASH patients with MACE had underlying risk factors for cardiovascular disease and metabolic syndrome, most frequently dyslipidemia or hypertension [33].

5. Diastolic dysfunction

Left ventricular diastolic dysfunction is the first manifestation of cirrhotic cardiomyopathy, because it usually appears before systolic dysfunction. The prevalence of diastolic dysfunction in cirrhotic patients is about 40% which is not correlated with the etiology and stage of liver disease, but with the degree of liver failure [35].

Conventional evaluation of cardiac diastolic function in cirrhotic patients include E/A ratio (peak velocity blood flow in early diastole, the E wave, to peak velocity flow in late diastole, the A wave), mitral valve deceleration time and isovolumic relaxation time [36]. However, these parameters are affected by heart rate and by loading conditions: E/A ratio is a dynamic index and affected by preload, the other two parameters, together with E/A ratio, exhibit a U-shaped relationship with diastolic function [2].

Therefore other echocardiographic parameters have been proposed, including septal mitral annular early diastolic velocity e' , E/e' ratio, left atrial volume index (LAVI) and tricuspid regurgitation (TR) velocity. e' (old term E_a) velocity is a relatively preload-independent marker of diastolic function, which reflects the status of intrinsic myocardial relaxation [37]. e' is specifically of importance in patients with endstage liver disease and volume overload.

Diastolic dysfunction is correlated with poorer prognosis. The one-year survival in cirrhotic patients without diastolic dysfunction is 95%, and with grade I dysfunction, 79%, and grade II, 39% [11]. Qurishi and colleagues [38] documented that diastolic dysfunction is a predictor for new-onset systolic heart failure post LT and diastolic heart failure is an independent predictive factor of mortality. Mittal *et al.* [39] found that 19% of liver transplant candidates had diastolic dysfunction and that these patients were at a higher risk of allograft rejection, graft failure, and mortality compared with those without diastolic dysfunction. Dowsley and coworkers [40] investigated the pre-transplant diastolic dysfunction and heart failure after transplant in 107 liver recipients. They found that pre-transplant elevation of E/e' ($p = 0.02$), increased left atrial volume index ($p = 0.05$), and lower mean arterial pressure ($p = 0.03$) were predictive factors of heart failure after transplant. Their study indicated that pre-transplant diastolic dysfunction is correlated with a greater risk of heart failure which may be associated with worse post-transplant survival [40].

6. Systolic dysfunction

The conventional systolic parameters applied to evaluate cardiac systolic function include blunted contractile response on stress testing and LV ejection fraction $<55\%$ [36]. However, beta-blockers, drugs that are commonly used in cirrhotic patients, may interfere with pharmacological challenge tests. Furthermore, the assessment of ejection fraction response cannot assess the impaired cardiac functional reserve, as hemodynamic changes also affect the ejection fraction response. Moreover, the vasodilatation in patients with advanced cirrhosis decreases afterload which also impacts the LVEF [2]. The newly proposed parameters from the 2020 Cirrhotic Cardiomyopathy Consortium for systolic function assessment in cirrhotic patients include LV ejection fraction $\leq 50\%$ and absolute global longitudinal strain (GLS) $<18\%$.

Strain measures tissue deformation, as strain rate = change in length/original length. The strain rate is defined as the percentage change in an object's dimension as compared to the original dimension in the heart [41]. In general, peak systolic strain is an index of local cardiac systolic function. It is less pressure-dependent and relatively volume-independent, and therefore better reflects the intrinsic cardiac contractile function. One of the new 2020 proposed cirrhotic cardiomyopathy criteria is a global longitudinal strain (GLS) absolute value $<18\%$ [2].

Systolic dysfunction post LT impacts the graft and patient survival. Interestingly, Jansen and coworkers [42] found that among patients on the waiting list for LT, left ventricular GLS $<14.9\%$ had a significantly lower transplant-free survival, especially in those with Child-Pugh class C.

Sonny and colleagues [43] defined systolic heart failure as LVEF $<45\%$ within 6 months after LT. They compared the patients with LVEF $<45\%$ to those with LVEF $>45\%$ and found that sepsis and multi-organ system failure were associated with systolic heart failure.

In terms of prediction of systolic heart failure, Sonny *et al.* [43] found that a greater preoperative LV ejection fraction reduced the probability of post-transplant systolic heart failure. On the contrary, any degree of diastolic dysfunction present in the preoperative echocardiogram increased the risk of post LT systolic heart failure. Multivariate analysis demonstrated that diastolic dysfunction was an independent predictor of postoperative systolic heart failure.

Sonny and coworkers concluded that systolic heart failure occurring within the first 6 months after LT increases the risk of mortality and/or graft failure during the first postoperative year. This data may suggest that the ability to cope with additive cardiovascular stress is limited by systolic heart failure.

Moon and colleagues [44] evaluated the predictive value of combined systolic and diastolic function on the outcomes of LT and found that the abnormality of LV stroke

volume index (LVSVI, a parameter of systolic function) plus E/e' ratio (an index of diastolic function) is an independent risk factor of a poorer prognosis after transplantation.

7. Electrocardiography

Josefsson *et al.* [45] from Sweden compared the ECG between cirrhotic patients and healthy controls and found that patients with transplants had 14 times the likelihood to suffer a cardiac event post LT compared with the general Swedish population.

Cirrhotics displayed a greater prevalence of ST segment depression, abnormal QRS axis deviation, a Q wave, prolonged QTc interval and abnormal T wave morphology ($p < 0.05$ for all compared with general Swedish population). These ECG features were compatible with CAD. Older age, cirrhosis severity, etiology, and arterial hypertension were linked to ECG abnormalities.

Kim *et al.* [46] analyzed 1430 liver recipients and found that 78 (5.5%) had ischemic change on ECG. The 1-year mortality of liver recipients with ischemic change on ECG was significantly higher than that of those without ischemic change (11.5% vs 4.0%; $p = 0.004$). The proportional hazard ratio of ischemic change on ECG was 2.91 (95% CI, 1.43–5.92; $p = 0.003$).

Among the ECG changes, QT interval corrected (QTc) prolongation is the most common abnormality in cirrhotic patients. The prevalence QTc prolongation is approximately 40% [47–49]. Zhao and colleagues [47] demonstrated that QTc interval prolongation is correlated with model for end-stage liver disease (MELD) score and Child-Pugh score, blood creatinine, prothrombin time, higher bilirubin, international normalized ratio, and albumin. However, they did not find any difference in in-hospital mortality compared to the groups with and without QTc prolongation [47]. Flaherty *et al.* [50] also reported that the prolonged QTc interval was not linked to mortality in LT recipients or an increased incidence of intraoperative cardiac events.

However, a majority of the pertinent studies show that patients with the QTc interval prolongation have higher rates of cardiac events after LT [45,51]. Koshy and colleagues [51] found that the pre-transplant QTc was significantly longer in liver recipients who encountered cardiac arrest/ventricular arrhythmias within 30 days post LT. After adjustment of gender, MELD score, and age, QTc ≥ 480 ms remained the strongest predictor for the occurrence of cardiac arrest/ventricular arrhythmias; QTc ≥ 480 ms was associated with a 5-fold increase in the risk of cardiac arrest/ventricular arrhythmias [51]. Josefsson *et al.* [45] found that a prolonged QTc interval and Q wave are associated with post-transplant cardiac events. They revealed that the majority of patients suffering a post-transplant cardiac event have one or more ECG abnormalities. Total cardiac events were correlated with a Q wave, a prolonged QTc interval, and any ECG feature compatible with CAD. The oc-

Table 2. Risk factors for MACE post liver transplantation [1,33,56–58].

	With (%)	Without (%)	p value
Laish <i>et al.</i> [56] MetS	15.2	4.9	$p < 0.01$
Koshy <i>et al.</i> [1] HRS	36.5	18.4	$p < 0.01$
VanWagner <i>et al.</i> [33] NASH	26.4	8.2	$p < 0.01$
Zorzi <i>et al.</i> [57] CAC >400	27	7 (CAC = 0)	$p < 0.01$
Kim <i>et al.</i> [58] QTc >500 ms	20.1	12.5	$p < 0.01$

MACE, major adverse cardiovascular event; MetS, Metabolic syndrome; NASH, non-alcoholic steatohepatitis; CAC, coronary artery calcium; QTc, corrected QT interval.

currence of post-transplant acute coronary syndrome, and arrhythmias and peri-transplant heart failure [52] was also linked to prolonged QTc interval.

Atrial fibrillation and flutter are important predictors of early and late morbidity and mortality [53]. Rachwan and coworkers [53] analyzed 1011 liver recipients and found that the incidence of posttransplant atrial fibrillation or flutter was 10%. Pre-LT history of atrial fibrillation and a history of coronary artery disease were the predictors of atrial fibrillation and flutter. These patients had longer hospital stays, and mortality rates were higher during the LT admission, within 90-days and 1-year after transplantation. All these studies suggest that atrial fibrillation and flutter are important predictors for worse early and late post-transplant outcomes.

Other risk factors for cardiovascular events after liver transplantation include smoking history (47.3%), obesity (27.6%), diabetes mellitus (26.0%), hypertension (17.8%), family history (17.0%) or prior history of heart disease (6.0%), and hypercholesterolemia (7.2%) [54]. Van Wagner and colleagues also revealed that the following factors are associated with MACE: age, ethnicity, health care status, hospitalization status, socioeconomic status, recipient functional status at transplant, MELD score, cause of ESLD, complications of ESLD at LT such as hepatic encephalopathy, spontaneous bacterial peritonitis, etc. [55] (Table 2) (Ref. [1,33,56–58]).

8. Diagnostic methods

8.1 Magnetic resonance imaging (MRI)

Cardiovascular MRI (CMR) should play a significant role in the pre-transplantation evaluation. Reddy *et al.* [59] used MRI to detect CAD for patients who had no documented cardiac events in the past related to CAD. Their LT candidates were evaluated with these MRI modalities: stress CMR, late gadolinium enhancement, and *magnetic resonance* angiography. The sensitivity of CMR in detecting significant coronary stenosis was 50%, the specificity was 98%, and the accuracy 98%. A negative CMR stress examination was associated with 100% CAD event-free survival at 12 months [59].

CMRI-T2 may be an additional diagnostic tool in evaluating those transplant candidates who are at a high risk for post-transplant cardiac complications. In the study of Lewin and colleagues, post-transplant heart failure occurred exclusively in recipients with T2 less than 15 ms [60]. In the group with T2 10–14.9 versus T2 ≥ 20 ms (hazard ratio, 3.85; $p = 0.003$), survival was worse, but not for 15–19.9 versus T2 ≥ 20 ms, suggesting that individuals with T2 ≥ 15 ms may be suitable candidates for transplantation. This data suggests that CMR is well suited for the preoperative cardiac evaluation of patients with a relatively low prevalence of CAD [60].

8.2 Biomarkers

8.2.1 Troponin

Troponin is a complex of three regulatory proteins (troponin C, I and T) [61]. Cardiac troponin has been accepted as a biomarker of myocardial injury [62]. Following the development of sensitive troponin assays, cardiac troponin is now used for diagnosis of cardiac infarction, acute coronary syndrome (ACS) and non-ACS myocardial injury, as well as risk stratification and outcome assessment of these patients. Additionally, troponins can be used for the prediction of nonischemic myocardial injury, such as pulmonary embolism, congestive heart failure, and chronic kidney disease [63].

Park and coworkers [63] recently found that elevated troponin I is associated with adverse post-operative outcomes in patients after living donor LT. Their data showed that there was a significantly higher incidence of all-cause death or graft failure during hospital stay in recipients with high-sensitivity cardiac troponin I (hs-cTnI) > 0.04 ng/mL (1.9% vs 7.6%; $p < 0.05$) [63]. Coss and colleagues [64] detected the serum troponin I levels before LT and found that a troponin I level > 0.07 ng/mL is an independent risk factor for post-transplant cardiac events. Jankowski *et al.* [65] analyzed 79 cirrhotic patients who underwent LT. They found that cardiac troponin I (cTnI) > 0.215 ng/mL was the most promising and reliable predictor of death following LT.

However, Canbolat and colleagues [66] did not find a significant correlation between high cTnI and 30-day in-hospital and 1-year mortality. They defined myocardial injury as a cTnI level > 0.04 ng/mL. They found that although myocardial injury identified by serum cTnI elevation was common (57.4%) after living donor liver transplant, this elevation was not linked to 30-day in-hospital and 1-year mortality [66]. The role of cardiac troponin in the prediction of cardiac events in liver recipients needs further investigation.

8.2.2 Brain natriuretic peptide (BNP)

N-terminal pro-B-type natriuretic peptide (NT-ProBNP) and BNP are increased in cirrhotic patients and the levels are positively correlated with the severity of cirrhosis [67,68]. BNP is a marker of left ventricular func-

tion [69]. NT-ProBNP is thought to be highly sensitive to the detection of early systolic and diastolic dysfunction in noncirrhotic patients [70]. Lubien *et al.* [71] investigated 294 noncirrhotic patients. They used echocardiography to evaluate ventricular diastolic function and tried to explore the correlation between diastolic function and the plasma BNP levels. They found that patients with abnormal LV diastolic function had higher BNP concentration compared with controls (286 ± 31 vs 33 ± 3 pg/mL, $p < 0.001$). The predictive value of BNP on any diastolic dysfunction reached excellent levels (area under the receiver-operating characteristic curve (AUC = 0.92)). If the cutoff value of BNP was set to 62 pg/mL, the sensitivity was 85%, the specificity was 83%, and the accuracy was 84% for detecting diastolic dysfunction [71].

There is, however, relatively little study of diagnostic/prognostic value of natriuretic peptides as a marker of cardiac injury/dysfunction in cirrhosis. Bernal *et al.* [72] investigated the role of NT-proBNP in predicting cardiovascular events after LT and found that NT-proBNP levels >2000 pg/mL before transplantation had a significant correlation with the risk of cardiovascular events post LT (37% vs 9%, $p = 0.008$).

9. Prediction of cardiovascular events after liver transplantation

Many methods exist to evaluate the severity of chronic liver diseases such as the Model for End-Stage Liver Disease (MELD), the Child-Pugh system or others which predict the mortality of cirrhotic patients.

The majority of the models used in the prediction of the mortality in liver recipients are based on combinations of risk factors including recipient age, donor age, bilirubin, creatinine, ischemia time, prothrombin time, and others. These scoring systems are mostly based on MELD variables [73]. Ghobiral and coworkers [74] created a pre-transplant model to predict post-transplant survival for liver transplant patients, combining eight factors in the model to calculate the mortality index. Their formula is calculated as: mortality index after transplantation = 0.0084 donor age + 0.019 recipient age + 0.816 log creatinine + 0.0044 warm ischemia (in minutes) + 0.659 (if second transplant) + 0.10 log bilirubin + 0.0087 PT + 0.01 cold ischemia (in hours) [74]. The mortality scores accurately determined patient survival; the higher the score, the lower the survival rate. The survival of patients in the first quintile were 94%, 92%, and 83% at 6 months and 1 and 5 years, respectively; those in the fifth quintile were 71%, 67%, and 53% at 6 months and 1 and 5 years, respectively.

Brandao *et al.* [75] analyzed MELD and other predictors of survival post LT. Their multivariate analysis showed that recipient age ≥ 65 yr, MELD ≥ 21 , Child-Pugh C category, creatinine ≥ 1.5 mg/dL, bilirubin ≥ 7 mg/dL, hepatocellular carcinoma, platelet transfusion, and non-white donor skin color were predictors of mortality.

However, the prediction of major cardiac events post LT is still a new field, and there is no universally-accepted formula to calculate the risk scores.

Alexander and coworkers [76] used the sum of AHA/ACC risk factors (hypertension, left ventricular hypertrophy, diabetes mellitus, dyslipidemia, smoking, age >60 years, and prior cardiovascular disease) to predict CAD. They found that if the patients have ≥ 3 risk factors, they have a high chance to have severe CAD. The sensitivity was 75% and specificity was 77%. If patients have ≥ 3 risk factors, the risks of cardiac death, myocardial coronary and coronary revascularization were increased [76]. Using multivariate analyses, VanWagner *et al.* [55] listed cardiac morbidity-related factors to predict 1-year CAD complications. They included sex, age, race, education, working status, atrial fibrillation, respiratory failure on ventilator at transplant, pulmonary hypertension, hepatocellular carcinoma, hypertension, diabetes, and heart failure. This risk factor prediction method was called the CAR-OLT system. If the score is 13–15, the patients have low risk of cardiovascular complications, 16–30 have moderate, 31–36 have high and 37–40 have very high 1-year post liver transplant cardiovascular complications [55].

Assmann *et al.* [77] in 2002 created a scoring system for calculating the risk of acute coronary events called Prospective Cardiovascular Münster (PROCAM). (See Table 3, Ref. [1,55,78]) for comparison of CAR-OLT and PROCAM). They included 8 variables: smoking, LDL cholesterol, age, HDL cholesterol, family history of premature myocardial infarction, systolic blood pressure, triglycerides, and diabetes mellitus. They categorised the continuous variables and gave each variable at certain value a score. The points assigned to each patient add up to the PROCAM score. They estimated the risk of a coronary event according to the individual risk score in regular population.

Guckelberger and coworkers [79] in Berlin adopted this system to predict the risk of cardiovascular events for liver recipients. They followed the patients for 10 years, and tried to find the correlation of PROCAM score and cardiac events at the time points of 1 and 10 years. Although the patients with cardiovascular events had higher PROCAM scores (median 42, range 22–62) compared with those without events (median 39, 10–64), the difference was not statistically significant ($p = 0.087$) [79]. This suggests that PROCAM may be less reliable for the prediction of cardiac events after liver transplant. The Assmann group in 2007 updated the PROCAM score [80]. The same group in Berlin then used the new version of PROCAM to reassess the risk of cardiac events for liver recipients. The follow up period was for 0.5, 10 and 20 years [78]. However, the results were equivocal that the patients with higher PROCAM scores had higher risk of cardiac events after transplant. The observed cardiac events were not consistent with the predicted cardiac events according to the PROCAM score.

Table 3. Comparison of three main studies predicting cardiovascular events after liver transplantation [1,55,78].

	Cardiovascular risk and after LT. 313 consecutive patients followed up to 20 years [78]	Prediction of Perioperative Cardiovascular Events in LT [1]	Point based Prediction Model for Cardiovascular Risk in Orthotopic LT: the CAR-OLT Score [55]
	PROCAM	Study (PROCAM) European Systematic Coronary Risk Evaluation Project (SCORE)	CAR-OLT
Type of study	Retrospective	Retrospective	Retrospective
General objective	Comparison of a new version with an old version of the same prognostic score	Evaluation of pre-transplant HRS and perioperative MACE. Relationship between perioperative MACE and post-transplant survival	Creation of a prognostic score
Transplantation date	1988–1992	1988–1994	2002–2011
Follow up time	Up to 20 years	Up to 10 years	Up to 11 years
Number of patients	313	319	1024
Center	Single center Germany	Single center Australia	Single center USA
Methodology	Analysis of variance, post hoc tests	Data obtained at 6 months post-transplantation Framingham risk score calculated Multivariate analysis with stepwise backward or forward analysis Hosmer Limeshow test to assess adequacy of fit	Multivariate analysis with Akaike's adjustment criteria Hosmer Limeshow test to assess adequacy of fit
Number with complete values	161–to 6 months 167–to 10 years 138 to 20 years	319	1010
Limitations	Some variables missing, e.g., smoking history. Single center. retrospective design. Incomplete internal and external validation	Incomplete internal and external validation. Retrospective design	Single center. Retrospective design
Authors' conclusion	PROCAM is a useful tool for cardiovascular risk estimation for longterm follow-up after LT	SCORE and PROCAM were useful to predict cardiovascular events after transplant Calibrated PROCAM risk scores may be useful to calculate numbers needed to treat in setting up prospective intervention trials	The point-based CAR-OLTscore may be useful to predict MACE and to help stratify management strategies to improve CVD outcomes after transplant
Overall assessment	Too many limitations reduce reliability and validity of the authors' conclusions	Incomplete validation and missing data reduce the reliability and validity of the authors' conclusions	At present, best available predictive system but multicenter validation studies needed

We believe that the CAR-OLT scoring system is superior because they specifically examined the correlation between the score and cardiac events, whereas the two publications using the PROCAM system did not examine this. Because many factors are involved in MACE after liver transplant, further study is required.

10. Conclusions

MACE accounts for 7%–21% of mortalities of liver transplant recipients. The risk factors for post-transplant MACE include metabolic syndrome, NASH, and cardiovascular abnormalities before transplantation. An accurate, reliable method of prediction is needed to improve patient and graft survival. However, at present we believe that the CAR-OLT system represents the best method of predicting cardiovascular events post-transplantation.

Author contributions

SSL—conception and design; MHA and HL—collection and assembly of data, manuscript writing; All authors: Final approval of manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Koshy AN, Farouque O, Cailes B, Ko J, Han H, Weinberg L, *et al.* Prediction of Perioperative Cardiovascular Events in Liver Transplantation. *Transplantation*. 2020; 105: 593–601.
- [2] Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, *et al.* Redefining Cirrhotic Cardiomyopathy for the Modern Era. *Hepatology*. 2020; 71: 334–345.
- [3] Chahal D, Liu H, Shamatutu C, Sidhu H, Lee SS, Marquez V. Review article: comprehensive analysis of cirrhotic cardiomyopathy. *Alimentary Pharmacology & Therapeutics*. 2021; 53: 985–998.
- [4] Liu H, Yoon KT, Zhang J, Lee SS. Advances in cirrhotic cardiomyopathy. *Current Opinion in Gastroenterology*. 2021; 37: 187–193.
- [5] Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. *Seminars in Liver Disease*. 2008; 28: 59–69.
- [6] Yoon KT, Liu H, Lee SS. Cirrhotic Cardiomyopathy. *Current Gastroenterology Reports*. 2020; 22: 45.
- [7] Liu H, Lee SS. Diagnostic Criteria of Cirrhotic Cardiomyopathy: out with the Old, in with the New? *Hepatology*. 2021; 74: 3523–3525.
- [8] Ma L, Liu X, Wu Q, Hu X, Liu H, Zhang J, Lee SS. Role of Anti-Beta-1-Adrenergic Receptor Antibodies in Cardiac Dysfunction in Patients with Cirrhotic Cardiomyopathy. *Journal of Cardiovascular Translational Research*. 2021. (in press)
- [9] Honar H, Liu H, Zhang ML, Glenn TK, Keurs HEDJ, Lee SS. Impaired myosin isoform shift and calcium transients contribute to cellular pathogenesis of rat cirrhotic cardiomyopathy. *Liver International*. 2020; 40: 2808–2819.
- [10] Kim HM, Kim H, Lee J, Lee YB, Park E, Park J, *et al.* Myocardial structural and functional changes in patients with liver cirrhosis awaiting liver transplantation: a comprehensive cardiovascular magnetic resonance and echocardiographic study. *Journal of Cardiovascular Magnetic Resonance*. 2020; 22: 25.
- [11] Lyssy LA, Soos MP. Cirrhotic Cardiomyopathy. *StatPearls Publishing: Treasure Island (FL)*. 2021.
- [12] Fussner LA, Heimbach JK, Fan C, Dierkhising R, Coss E, Leise MD, *et al.* Cardiovascular disease after liver transplantation: when, what, and who is at Risk. *Liver Transplantation*. 2015; 21: 889–896.
- [13] Gallegos-Orozco JF, Charlton MR. Predictors of Cardiovascular Events after Liver Transplantation. *Clinics in Liver Disease*. 2017; 21: 367–379.
- [14] Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Current Hypertension Reports*. 2018; 20: 12.
- [15] Dommermuth R, Ewing K. Metabolic Syndrome: Systems Thinking in Heart Disease. *Primary Care*. 2018; 45: 109–129.
- [16] Thoenfer LB, Rostved AA, Pommergaard H, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: a systematic review and meta-analysis. *Transplantation Reviews*. 2018; 32: 69–77.
- [17] Roda E, Parini P, Bazzoli F, Mazzella G, Festi D, Aldini R. Advances in the therapy of cholestatic liver disease. *Hepato-Gastroenterology*. 1992; 39: 53–55.
- [18] Anastácio LR, Ferreira LG, Ribeiro HDS, Liboredo JC, Lima AS, Correia MITD. Metabolic syndrome after liver transplantation: prevalence and predictive factors. *Nutrition*. 2011; 27: 931–937.
- [19] Arun C, Oommen T, Kumar H, Nair V, Jayakumar R, Sudhindran S, *et al.* Incidence of new-onset diabetes and posttransplant metabolic syndrome after liver transplantation - a prospective Study from South India. *Indian Journal of Endocrinology and Metabolism*. 2020; 24: 165.
- [20] Fatourou EM, Tsochatzis EA. Management of metabolic syndrome and cardiovascular risk after liver transplantation. *The Lancet Gastroenterology & Hepatology*. 2019; 4: 731–741.
- [21] VanWagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M, *et al.* Factors Associated with Major Adverse Cardiovascular Events after Liver Transplantation among a National Sample. *American Journal of Transplantation*. 2016; 16: 2684–2694.
- [22] Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, *et al.* Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. *Circulation*. 2003; 108: 2154–2169.
- [23] Cea Soriano L, Johansson S, Stefansson B, Rodríguez LAG. Cardiovascular events and all-cause mortality in a cohort of 57,946 patients with type 2 diabetes: associations with renal function and cardiovascular risk factors. *Cardiovascular Diabetology*. 2015; 14: 38.
- [24] Brugts JJ, Knetsch AM, Mattace-Raso FUS, Hofman A, Witteman JCM. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. *Archives of Internal Medicine*. 2005; 165: 2659–2665.
- [25] Saliba F, Fischer L, de Simone P, Bernhardt P, Bader G, Fung J. Association between Renal Dysfunction and Major Adverse Cardiac Events after Liver Transplantation: Evidence from an International Randomized Trial of Everolimus-Based Immunosuppression. *Annals of Transplantation*. 2018; 23: 751–757.

- [26] Saritas T, Floege J. Cardiovascular disease in patients with chronic kidney disease. *Herz*. 2020; 45: 122–128
- [27] Munteanu MA, Mircea PA. From NAFLD to Cardiovascular Disease. is it (still) the Metabolic Syndrome? *Clujul Medical*. 2014; 87: 80–86.
- [28] Howell WL, Manion WC. The low incidence of myocardial infarction in patients with portal cirrhosis of the liver: a review of 639 cases of cirrhosis of the liver from 17,731 autopsies. *American Heart Journal*. 1990; 60: 341–344.
- [29] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016; 64: 73–84.
- [30] Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akkas Z, Zein N, *et al.* Prevalence of Nonalcoholic Steatohepatitis-Associated Cirrhosis in the United States: an Analysis of National Health and Nutrition Examination Survey Data. *The American Journal of Gastroenterology*. 2017; 112: 581–587.
- [31] Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and Outcomes of Liver Transplantation for Nonalcoholic Steatohepatitis in the United States. *Gastroenterology*. 2011; 141: 1249–1253.
- [32] Shirazi F, Wang J, Wong RJ. Nonalcoholic Steatohepatitis Becomes the Leading Indication for Liver Transplant Registrants among US Adults Born between 1945 and 1965. *Journal of Clinical and Experimental Hepatology*. 2020; 10: 30–36.
- [33] Vanwagner LB, Bhawe M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology*. 2012; 56: 1741–1750.
- [34] Bhagat V, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transplantation*. 2009; 15: 1814–1820.
- [35] Carvalho F, Rodrigues C, Adrego T, Viana J, Vieira H, Seco C, *et al.* Diastolic Dysfunction in Liver Cirrhosis: Prognostic Predictor in Liver Transplantation? *Transplantation Proceedings*. 2016; 48: 128–131.
- [36] Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: Implications for liver transplantation. *Liver Transplantation*. 2017; 23: 826–835.
- [37] Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *Journal of the American College of Cardiology*. 1997; 30: 1527–1533.
- [38] Qureshi W, Mittal C, Ahmad U, Alirhayim Z, Hassan S, Qureshi S, *et al.* Clinical predictors of post-liver transplant new-onset heart failure. *Liver Transplantation*. 2013; 19: 701–710.
- [39] Mittal C, Qureshi W, Singla S, Ahmad U, Huang MA. Pre-transplant Left Ventricular Diastolic Dysfunction is Associated with Post Transplant Acute Graft Rejection and Graft Failure. *Digestive Diseases and Sciences*. 2014; 59: 674–680.
- [40] Dowsley TF, Bayne DB, Langnas AN, Dumitru I, Windle JR, Porter TR, *et al.* Diastolic dysfunction in patients with end-stage liver disease is associated with development of heart failure early after liver transplantation. *Transplantation*. 2012; 94: 646–651.
- [41] Abraham TP, Dimaano VL, Liang H. Role of tissue Doppler and strain echocardiography in current clinical practice. *Circulation*. 2007; 116: 2597–2609.
- [42] Jansen C, Cox A, Schueler R, Schneider M, Lehmann J, Praktikjo M, *et al.* Increased myocardial contractility identifies patients with decompensated cirrhosis requiring liver transplantation. *Liver Transplantation*. 2018; 24: 15–25.
- [43] Sonny A, Govindarajan SR, Jaber WA, Cywinski JB. Systolic heart failure after liver transplantation: Incidence, predictors, and outcome. *Clinical Transplantation*. 2018; 32: e13199.
- [44] Moon YJ, Kim JW, Bang YS, Lim YS, Ki Y, Sang BH. Prediction of all-cause mortality after liver transplantation using left ventricular systolic and diastolic function assessment. *PLoS ONE*. 2019; 14: e0209100.
- [45] Josefsson A, Fu M, Björnsson E, Kalaitzakis E. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis. *BMC Gastroenterology*. 2014; 14: 65.
- [46] Kim K, Park Y, Moon Y, Jung K, Kang J, Hwang G. Preoperative Myocardial Ischemia Detected with Electrocardiography is Associated with Reduced 1-Year Survival Rate in Patients Undergoing Liver Transplant. *Transplantation Proceedings*. 2019; 51: 2755–2760.
- [47] Zhao J, Qi X, Hou F, Ning Z, Zhang X, Deng H, *et al.* Prevalence, Risk Factors and in-hospital Outcomes of QTc Interval Prolongation in Liver Cirrhosis. *The American Journal of the Medical Sciences*. 2016; 352: 285–295.
- [48] Henriksen JH, Fuglsang S, Bendtsen F, Christensen E, Møller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. *Journal of Hepatology*. 2002; 36: 513–520.
- [49] Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, *et al.* Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998; 27: 28–34.
- [50] Flaherty D, Kim S, Zerillo J, Park C, Joseph T, Hill B, *et al.* Preoperative QTc Interval is not Associated with Intraoperative Cardiac Events or Mortality in Liver Transplantation Patients. *Journal of Cardiothoracic and Vascular Anesthesia*. 2019; 33: 961–966.
- [51] Koshy AN, Ko J, Farouque O, Cooray SD, Han H, Cailles B, *et al.* Effect of QT interval prolongation on cardiac arrest following liver transplantation and derivation of a risk index. *American Journal of Transplantation*. 2020; 21: 593–603.
- [52] Josefsson A, Fu M, Allayhari P, Björnsson E, Castedal M, Olausson M, *et al.* Impact of peri-transplant heart failure & left-ventricular diastolic dysfunction on outcomes following liver transplantation. *Liver International*. 2012; 32: 1262–1269.
- [53] Rachwan RJ, Kutkut I, Hathaway TJ, Timsina LR, Kubal CA, Lacerda MA, *et al.* Postoperative Atrial Fibrillation and Flutter in Liver Transplantation: an Important Predictor of Early and Late Morbidity and Mortality. *Liver Transplantation*. 2020; 26: 34–44.
- [54] Robertson M, Chung W, Liu D, Seagar R, O'Halloran T, Koshy AN, *et al.* Cardiac Risk Stratification in Liver Transplantation: Results of a Tiered Assessment Protocol Based on Traditional Cardiovascular Risk Factors. *Liver Transplantation*. 2021; 27: 1007–1018.
- [55] VanWagner LB, Ning H, Whitsett M, Levitsky J, Uttal S, Wilkins JT, *et al.* A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: the CAR-OLT score. *Hepatology*. 2017; 66: 1968–1979.
- [56] Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. *Liver Transplantation*. 2011; 17: 15–22.
- [57] Zorzi A, Brunetti G, Cardaioli F, D'Arcangelo F, Fabris T, Gambato M, *et al.* Coronary artery calcium on standard chest computed tomography predicts cardiovascular events after liver transplantation. *International Journal of Cardiology*. 2021; 339: 219–224.
- [58] Kim K, Kwon H, Jung K, Sang B, Moon Y, Kim B, *et al.* Markedly prolonged QTc interval in end-stage liver disease and risk of 30-day cardiovascular event after liver transplant. *Journal*

of Gastroenterology and Hepatology. 2021; 36: 758–766.

- [59] Reddy ST, Thai NL, Oliva J, Tom KB, Dishart MK, Doyle M, *et al.* Cardio-hepatic risk assessment by CMR imaging in liver transplant candidates. *Clinical Transplantation*. 2018; 32: e13229.
- [60] Lewin SM, Kallianos K, Nevah MI, Zhao S, Fix OK, Brooks GC, *et al.* Cardiac MRI T2* in Liver Transplant Candidates: Application and Performance of a Novel Imaging Technique to Identify Patients at Risk for Poor Posttransplant Cardiac Outcomes. *Transplantation Direct*. 2018; 4: e363.
- [61] Marston SB, Redwood CS. Modulation of Thin Filament Activation by Breakdown or Isoform Switching of Thin Filament Proteins. *Circulation Research*. 2003; 93: 1170–1178.
- [62] Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J. Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and their Impact on Clinical Care. *Clinical Chemistry*. 2017; 63: 73–81.
- [63] Park J, Lee SH, Han S, Kim KY, Kim GE, Park M, *et al.* Elevated High-Sensitivity Troponin i during Living Donor Liver Transplantation is Associated with Postoperative Adverse Outcomes. *Transplantation*. 2018; 102: e236–e244.
- [64] Coss E, Watt KDS, Pedersen R, Dierkhising R, Heimbach JK, Charlton MR. Predictors of cardiovascular events after liver transplantation: a role for pretransplant serum troponin levels. *Liver Transplantation*. 2011; 17: 23–31.
- [65] Jankowski K, Trzebicki J, Bielecki M, Łągiewska B, Kurnicka K, Koczaj-Bremer M, *et al.* Prognostic value of perioperative assessment of plasma cardiac troponin I in patients undergoing liver transplantation. *Acta Biochimica Polonica*. 2017; 64: 331–337.
- [66] Canbolat IP, Adali G, Akdeniz CS, Bozkurt B, Ferah O, Bulutcu F, *et al.* Postoperative Myocardial Injury does not Predict Early and 1-Year Mortality after Living Donor Liver Transplantation. *Transplantation Proceedings*. 2019; 51: 2478–2481.
- [67] Wang L, An X, Wu X, Zhang S, Yang R, Han C, *et al.* Doppler myocardial performance index combined with plasma B-type natriuretic peptide levels as a marker of cardiac function in patients with decompensated cirrhosis. *Medicine*. 2018; 97: e13302.
- [68] Pentiuk N, Mostovoy Y, Motsiuk V, Demchuk A, Nekrut D. NT-proBNP level in patients with liver cirrhosis: relation to portal hypertension and cardiovascular changes. *Georgian Medical News*. 2019; 26–32. (In Russian)
- [69] Parekh N, Maisel AS. Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function and diastolic heart failure. *Current Opinion in Cardiology*. 2009; 24: 155–160.
- [70] Hammerer-Lercher A, Neubauer E, Müller S, Pachinger O, Puschendorf B, Mair J. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide in diagnosing left ventricular dysfunction. *Clinica Chimica Acta*. 2001; 310: 193–197.
- [71] Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, *et al.* Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. 2002; 105: 595–601.
- [72] Bernal V, Pascual I, Lanas A, Esquivias P, Piazzuelo E, Garcia-Gil FA, *et al.* Cardiac function and aminoterminal pro-brain natriuretic peptide levels in liver-transplanted cirrhotic patients. *Clinical Transplantation*. 2012; 26: 111–116.
- [73] Liu H, Lee SS. Predicting cardiovascular complications after liver transplantation: 007 to the rescue? *Liver Transplantation*. 2011; 17: 7–9.
- [74] Ghobrial RM, Gornbein J, Steadman R, Danino N, Markmann JF, Holt C, *et al.* Pretransplant model to predict posttransplant survival in liver transplant patients. *Annals of Surgery*. 2002; 236: 315–313.
- [75] Brandão A, Fuchs SC, Gleisner AL, Marroni C, Zanotelli ML, Cantisani G. MELD and other predictors of survival after liver transplantation. *Clinical Transplantation*. 2009; 23: 220–227.
- [76] Alexander S, Teshome M, Patel H, Chan EY, Doukky R. The diagnostic and prognostic utility of risk factors defined by the AHA/ACCF on the evaluation of cardiac disease in liver transplantation candidates. *BMC Cardiovascular Disorders*. 2019; 19: 102.
- [77] Assmann G, Cullen P, Schulte H. Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10-Year Follow-up of the Prospective Cardiovascular Münster (PROCAM) Study. *Circulation*. 2002; 105: 310–315.
- [78] Schoening W, Neidel N, Buescher N, Andreou A, Pascher A, Seehofer D, *et al.* Cardiovascular risk and events after liver transplantation. Experiences from 313 consecutive transplants with a follow-up of 20 years. *Clinical Transplantation* 2015; 29: 343–350.
- [79] Guckelberger O, Byram A, Klupp J, Neumann UP, Glanemann M, Stockmann M, *et al.* Coronary event rates in liver transplant recipients reflect the increased prevalence of cardiovascular risk-factors. *Transplant International*. 2005; 18: 967–974.
- [80] Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Münster (PROCAM) study. *European Journal of Clinical Investigation*. 2007; 37: 925–932.