Cardiovascular events after liver transplantation: MACE hurts

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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 including 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 ± 5.0% vs 62.5 ± 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-
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. Brugs 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 transplants.

### 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) ≥80 cm (woman)                       | ≥102 cm (man) ≥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              |
| Triglycerides           | ≥90 mmHg (DBP) and/or hypertension treatment     | ≥90 mmHg (DBP) and/or hypertension 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.
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 Ea) 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 1 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. Mital 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 ≤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 post-operative 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-
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 (CMRI) should play a significant role in the pre-transplantation evaluation. Reddy et al. [59] used CMRI 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 CMRI, late gadolinium enhancement, and magnetic resonance angiography. The sensitivity of CMRI in detecting significant coronary stenosis was 50%, the specificity was 98%, and the accuracy 98%. A negative CMRI 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 CMRI 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-
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]. Ghobrial 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/ACCF 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 | Prediction of Perioperative Cardiovascular Events in LT | Point based Prediction Model for Cardiovascular Risk in Orthotopic LT: the CAR-OLT Score [55] |
|---------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------|
| PROCAM                          | Study (PROCAM)                                          | CAR-OLT                                                                         |
|                                 | European Systematic Coronary Risk Evaluation Project     | Retrospective                                                                  |
|                                 | (SCORE)                                                 | Creation of a prognostic score                                                  |
| Type of study                   | 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            |
| 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                                 |
| Number with complete values     | 161–to 6 months                                         | 319                                                                             |
|                                 | 167–to 10 years                                         | 1010                                                                            |
|                                 | 138 to 20 years                                         |                                                                                 |
| 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-OLT score 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.

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Conflict of interest

The authors declare no conflict of interest.

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