



Cardiovascular involvement after liver transplantation: role of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

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Abstract

Patients submitted to liver transplantation (LT) are exposed to high risk of cardiovascular (CV) complications which are the main determinants of both short-term and long-term morbidity and mortality in LT. Non-alcoholic fatty liver disease (NAFLD) is a very frequent condition in general population and is associated with a high risk of cardiovascular disease (CVD) which represents the first cause of death of these patients. NAFLD is predicted to become the first indication to LT and nowadays is also frequently detected in patients submitted to LT for other indications. Thus, the risk of CVD in patients submitted to LT is forecasted to increase in the next years. In this review the extent of CV involvement in patients submitted to LT and the role of NAFLD, either recurring after transplantation or as *de novo* presentation, in increasing CV risk is analysed. The risk of developing metabolic alterations, including diabetes, hypertension, dyslipidemia and weight gain, all manifestations of metabolic syndrome, occurring in the first months after LT, is depicted. The different presentations of cardiac involvement, represented by early atherosclerosis, coronary artery disease, heart failure and arrhythmias in patients with NAFLD submitted to LT is described. In addition, the tools to detect cardiac alterations either before or after LT is reported providing the possibility for an early diagnosis of CVD and an early therapy able to reduce morbidity and mortality for these diseases. The need for long-term concerted multidisciplinary activity with dietary counseling and exercise combined with drug treatment of all manifestations of metabolic syndrome is emphasized.

Keywords

Orthotopic liver transplantation, cirrhotic cardiomyopathy, cardiovascular mortality, subclinical atherosclerosis, fatty liver



Introduction

Liver transplantation (LT), the only effective treatment for end stage liver disease, has spread in the past 50 years in Europe, plateauing in recent years, with about 7,300 LTs performed in Europe and 8,000 in the United States annually [1, 2]. Non-alcoholic fatty liver disease (NAFLD) [3] is becoming the leading cause of LT in the USA, and rate of LT caused by NAFLD is likely to further increase in next years as a consequence of metabolic syndrome (MS) diffusion and the absence of established therapies [2]. Survival rates from United Network for Organ Sharing registry at 1, 5 and 10 years are approximately 85%, 70% and 50% [1, 4], with the critical period for post LT outcome represented by the first year during which 46% of deaths occur, nearly 60% of which within 6 months [1]. More than 10% of LT recipients have cardiovascular disease (CVD) which together with hepatic and cancer, are the most common causes of death after LT [5]. Nowadays, despite the marked improvement in immunosuppressive therapies and organ preservation techniques [6] post-transplant death rate remains elevated because of CVD.

The aim of this review is to clarify the extent of cardiovascular (CV) involvement in post LT patients, defining the role of NAFLD in increasing CV risk. Indeed, as depicted in Figure 1, beyond being a cause of LT, NAFLD can reappear after LT (recurrent NAFLD) and even arise after LT in patients without steatosis before transplantation (NAFLD). Reported data in this review were identified by search and selection database of MEDLINE, Google Scholar, PubMed, Elsevier, by using the search term “LT” combined with “CV risk” and “NAFLD”. Relevant articles were selected. Review articles are cited to provide more details and references.

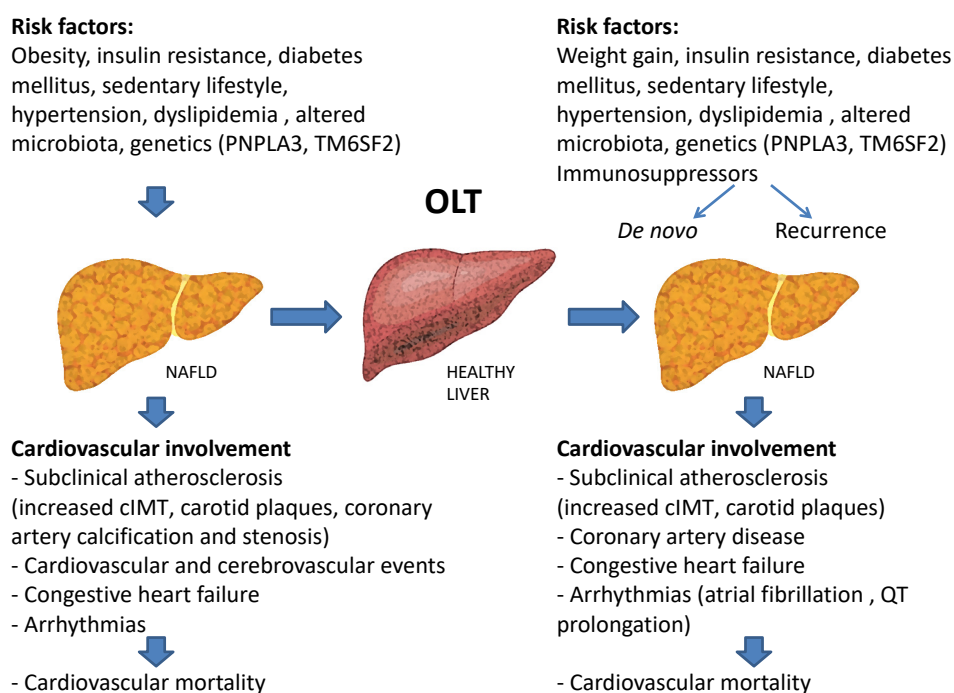


Figure 1. Risk factors for the development of NAFLD and cardiovascular damage before and after liver transplantation. Obesity, insulin resistance, diabetes mellitus, hypertension, dyslipidemia, sedentary lifestyle, altered microbiota and genetics [patatin-like phospholipase domain containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2)] favor the onset of NAFLD. NAFLD could progress into advanced liver disease requiring liver transplantation (LT). However, NAFLD can develop even after liver transplantation, sustained by the same pathogenetic factors of the pre-LT. Either in the pre-LT or post-LT period NAFLD exposes patients to high cardiovascular morbidity and mortality

NAFLD and CV risk

The link between NAFLD and CV disease is well established since both diseases share many metabolic risk factors such as obesity, insulin resistance, type 2 diabetes (T2DM), hypertension, dyslipidemia, as well as a sedentary lifestyle, genetic predisposition (PNPLA3 and TM6SF2 gene) [7-9] and gut microbiota impairment which favours either hepatic steatosis or inflammation and atherosclerosis [10, 11].

NAFLD is a risk factor for either subclinical or established CVD and mortality. In fact, a higher prevalence of subclinical atherosclerosis [12] represented by increased carotid artery intima-media thickness (cIMT)

and presence of carotid plaques [13], and coronary artery calcification and significant coronary stenosis at coronarography [14] have been demonstrated. Interestingly, there is a relation between severity of liver and CV damage, being a more advanced liver disease associated with a more serious vascular damage [11, 15]. In addition, NAFLD patients experience more CV events than the overall population. In 2016, Fracanzani et al. [16] evaluated the incidence of cardiac and cerebrovascular events in patients with NAFLD and in a control cohort, followed-up over a 10-year period, showing a higher prevalence of CV events in the NAFLD group [15]. In addition, NAFLD subjects are more likely to develop congestive heart failure and cardiac arrhythmias [mainly atrial fibrillation and corrected QT interval (QTc) interval prolongation] compared to the general population [17].

As a consequence, CV-related death appears to be the leading cause of mortality in patients with NAFLD, as demonstrated by Ekstedt et al. [18], who evaluated mortality from all causes in 229 patients over a period of 30 years.

Additionally, T2DM and morbid obesity, which are very prevalent in NAFLD, have been reported to impact on death/removal from the LT waiting list of patients with liver disease of different etiology [19]. On the basis of this evidence, screening for CV disease all patients with NAFLD, irrespectively of the presence of other traditional risk factors [20] is highly recommended by the European Association for the Study of the Liver [21].

Differences by gender

Recent literature data indicate a different gender-related presentation of NAFLD. The prevalence of NAFLD is higher in males compared to premenopausal women becoming comparable after menopause, when women tend to gain weight, to have a different distribution of fat, mainly visceral, with an increased risk to develop NAFLD and CVD [22, 23].

Data on the prevalence of CV complications are controversial and not conclusive. An independent male association with coronary artery calcifications has been described in general population [13]. A large Korean cross-sectional study reported that men had a higher prevalence of NAFLD, carotid plaque and cIMT values [24]. On the contrary data obtained from German and Austrian populations indicate a close association between NAFLD and CV events (myocardial infarction and coronary heart disease) regardless of gender [25, 26].

In postmenopausal women a correlation between NAFLD (evaluated by computer tomography) and prevalence of coronary artery calcifications has been described, however the association was lost after correction for the known CVD risk factors [27]. Finally, although not conclusive, literature data suggest that while in the general population female sex appears to be protective for ischemic CV events, in women with NAFLD is not [28]. Indeed, in a recent meta-analysis considering 108,711 patients with NAFLD (44% females) all-cause mortality was about 1.5 times higher in women than in men and CV events 2 times higher [29].

Future studies on the different ways of evaluating metabolic alterations in women compared to men are needed in consideration of the increased number of transplants performed in women. In fact, in recent years, non-alcoholic steatohepatitis (NASH) represents the leading cause of transplantation in the female population [30, 31].

CVD post LT

Despite it is clear that CV complications determine either short-term or long-term morbidity and mortality in LT [9, 32, 33], studies exploring prevalence and risk factors for specific CV events after LT are lacking and often CV assessment is evaluated as composite including coronary artery disease (CAD), heart failure and arrhythmias without considering cirrhosis associated cardiomyopathy. Also in a recent systematic review of 29 studies including 57,493 patients, definitions of CV outcomes were highly inconsistent [34] and only 3 studies evaluated CV-related mortality [5, 9, 35].

We reported the most consistent data on the onset of CVD post LT and the role of NAFLD in this setting as depicted in Table 1.

Table 1. Evaluation of cardiovascular outcomes in transplanted patients with or without assessment of pre-LT steatosis, either receiving a graft with steatosis and/or with *de novo*/recurrent NAFLD post LT

Authors	Year	Type of study	Nation	Population	F-up after LT	CV endpoint	NAFLD	Results
Evaluation of CV outcomes in transplanted patients without data on pre-existing NAFLD								
Alves et al. [35]	2019	Cross-sectional	Brasil	79	1.4-6.3 years	cIMT	NA	<ul style="list-style-type: none"> • Prevalence of increased cIMT 54% • Independently associated with higher LDL, C-reactive protein and intake of saturated and trans fatty acids with diet • Prevalence of intraoperative/postoperative cardiac complications in 28%/8% (cases) and 5%/2% (controls) • Mortality for CV causes 9% cases, 0 controls
Bargehr et al. [53]	2018	Retrospective Case control	USA	717 -32 cases (AF) -63 controls	5-8 years	Intraoperative and postoperative cardiac complications (ventricular tachycardia, hemodynamic instability, cardiac arrest, death)	NA	<ul style="list-style-type: none"> • Prevalence of CV events 29%, with mortality in 88% of them (26% of the cohort) • Independently associated with pre-LT ECG abnormalities (prolonged QTc time, Q wave, ECG feature compatible with CAD) • Prevalence of HF 24% • Independently associated with pre-LT diastolic dysfunction • Incidence of systolic HF 7% • Independently associated with age and pulmonary hypertension
Josefsson et al. [44]	2014	Retrospective	UK	234	2-20 years	-CV events (arrhythmias, CAD) -Mortality from CV events	NA	
Dowsley et al. [43]	2012	Retrospective	USA	107	2.6 ± 1.4 months	HF	NA	
Eimer et al. [42]	2008	Prospective	USA	86	2 weeks-2 years	Systolic HF	NA	
Evaluation of CV outcomes in transplanted patients with data on pre-existing NAFLD but without analysis on the impact of NAFLD on CV assessment								
Memaran et al. [71]	2019	Cross-sectional	Germany	104 (children)	6.9 years	-Carotid-femoral pulse PWV -cIMT -LVMI	Pre-LT NASH 6%	<ul style="list-style-type: none"> • Prevalence of alterations in PWV, cIMT, and LVMI in 21.9%, 57.0%, and 11.1%. Data separated in NASH not available • PWV independently associated with diastolic BP and GFR; cIMT with age; LVMI with pre-LT BMI • Prevalence of systolic HF 6%. Data separated in NASH not available • Independently associated with pre-LT diastolic dysfunction
Sonny et al. [47]	2018	Case control	USA	1,284 -45 cases (LVEF < 45% within 6 months from LT) -180 controls	6 months	Systolic HF (LVEF < 45%)	-Pre-LT NASH case: 22% -Controls: 23%	

Table 1. Evaluation of cardiovascular outcomes in transplanted patients with or without assessment of pre-LT steatosis, either receiving a graft with steatosis and/or with *de novo*/recurrent NAFLD post LT (*continued*)

Authors	Year	Type of study	Nation	Population	F-up after LT	CV endpoint	NAFLD	Results
Roccaro et al. [62]	2018	Retrospective	USA	994	2-12 years	Major CV events (cardiac arrest, MI, stroke, PAD)	Pre-LT NASH 10%	<ul style="list-style-type: none"> • Prevalence of major CV events 12%, mortality from CV events 4%. Data separated in NASH not available. • Independently associated with post LT diabetes. • Increase in cIMT independently associated with glucose intolerance and diastolic hypertension.
Perito et al. [37]	2018	Cross-sectional	USA	88 (children)	11.2 ± 5.6 years	cIMT	Pre-LT NASH 17%	<ul style="list-style-type: none"> • Prevalence of hospitalization 32% and death from CV events 32% and 5%. Data separated in NASH not available. • Independently associated with T2DM, hypertension, pre-existing AF and HF, age > 65 years
VanWagner et al. [38]	2017	Retrospective	USA	1,024	10 years	Hospitalization or mortality from major CV events (MI, AF, HF, cardiac arrest, PE, TIA, stroke)	Pre-LT NASH 16%	<ul style="list-style-type: none"> • Prevalence of major CV events 3%. Data separated in NASH not available • Independently associate with NASH, age > 65 years, baseline AF and stroke
VanWagner et al. [32]	2016	Retrospective	USA	32,810	90 days	Major CV events (MI, AF, PE, HF, cardiac arrest, stroke)	Pre-LT NASH 9.7%	<ul style="list-style-type: none"> • Prevalence of CVD 30%. Data separated in NASH not available • Independently associated with age, diabetes, prior history of CVD and pre-LT serum troponin
Fussner et al. [39]	2015	Retrospective	USA	455	8-12 years	CVD (CAD, arrhythmias, congestive HF, symptomatic PAD)	Pre-LT NASH 10%	<ul style="list-style-type: none"> • Prevalence of death from CV events 1.1%. Data separated in NASH not available • Independently associated with age, intensive care unit status, ventilator status, MELD, portal vein thrombosis, donor BMI, and cold ischemia time
VanWagner et al. [9]	2014	Retrospective	USA	54,697	30 days	Mortality from CV events	Pre-LT NASH 5%	<ul style="list-style-type: none"> • Incidence of HF 10%. Data separated in NASH not available • Independently associated with pre-LT grade 3 diastolic dysfunction, diabetes, hypertension, BNP, pulmonary hypertension, QT > 450
Qureshi et al. [45]	2013	Prospective	USA	970	5.3 ± 3.4 years	HF	Pre-LT NASH 4.5%	<ul style="list-style-type: none"> • Prevalence of death 41%, from CV events 5%. Data separated in NASH not available • CV mortality independently associated with age, cryptogenic cirrhosis and ALD
Watt et al. [5]	2010	Retrospective	USA	798	12.5 (9-13) years	Mortality from all causes and CV causes	Pre-LT NASH 29%	

Table 1. Evaluation of cardiovascular outcomes in transplanted patients with or without assessment of pre-LT steatosis, either receiving a graft with steatosis and/or with *de novo*/recurrent NAFLD post LT (*continued*)

Authors	Year	Type of study	Nation	Population	F-up after LT	CV endpoint	NAFLD	Results
Evaluation of CV outcomes in transplanted patients with pre-existing NAFLD and with analysis on the impact of NAFLD on CV assessment								
Kwong et al. [29]	2020	Retrospective	USA	1,023	1-3 years	-Survival -CV events (AF, MI, HF, stroke)	Pre-LT NASH in 21%	<ul style="list-style-type: none"> No difference in survival at 1 and 3 year among NASH (91.3% and 83.3%) compared to non-NASH (90% and 81%) No difference in incidence of CV events between NASH and non-NASH patients Overall mortality 22%
Nagai et al. [95]	2019	Retrospective	USA	32,660 (6,344 NASH) (17,037 HCV) (9,279 ALD)	1-2 years	All cause and CV mortality	Pre-LT NASH 19%	<ul style="list-style-type: none"> Significantly higher mortality in NASH compared to HCV or ALD, adjusted for HCC presence (especially in age 50-59 years) Mortality from CV disease highest among patients with NASH (11.5%), compared to 7.0% in HCV and 9.6% in ALD Overall mortality 22%, 12% from CV causes ALD was an independent predictors of CV events, HCV of mortality No difference in prevalence of CV events at 3 years in patients with ALD (14.1%) and NASH (13.8%) No difference in survival between NASH and ALD patients (87.2% vs. 86.4%)
D'Avola et al. [98]	2017	Prospective	Spain	1,819	5 years	All cause and CV mortality	-Cryptogenetic cirrhosis 2.9% -Data on NASH NA	
Piazza et al. [104]	2016	Retrospective	Italy	143 (65 ALD) (78 NASH)	3 years	-All-cause mortality -CV events (sudden cardiac death, CAD, congestive HF, AF or arrhythmia, valvular heart disease, PAD, or stroke)	Pre-LT NASH 54%	
VanWagner et al. [8]	2012	Retrospective	USA	242 (115 NASH) (127 ALD)	5 years	-Survival -CV events (death from any cardiac cause, MI, acute HF, arrhythmia, stroke)	Pre-LT NASH in 47%	<ul style="list-style-type: none"> Increased CV events in NASH vs. ALD patients (26% vs. 8%) independently of confounding factors No difference in survival between two groups. The 1-, 3-, and 5- year patient survival were 81.3%, 73.3%, and 60.3% in the NASH group and 88.1%, 85.3%, and 68.8% in the ALD group Overall survival 96% No difference in survival among groups
Contos et al. [83]	2001	Prospective	USA	58 (30 NASH) (16 ALD) (12 PBC)	30 days	Survival	Pre-LT NASH 51%	

Table 1. Evaluation of cardiovascular outcomes in transplanted patients with or without assessment of pre-LT steatosis, either receiving a graft with steatosis and/or with *de novo*/recurrent NAFLD post LT (*continued*)

Authors	Year	Type of study	Nation	Population	F-up after LT	CV endpoint	NAFLD	Results
Evaluation of CV outcomes in transplanted patients receiving liver graft with NAFLD								
Kulik et al. [79]	2017	Retrospective	Germany	1,205 [77 requiring re-LT, 39 due to primary non function (PNF) and 38 to vascular and biliary disease]	3 months-11 years	-In-hospital mortality in patients with re-LT -Survival in patients with re-LT	NAFLD in 69% of graft of with PNF	<ul style="list-style-type: none"> Overall survival 0.5 years in PNF and 5.3 years in patients with vascular and biliary disease In-hospital mortality was 53.8% vs. 26.4% PNF due to fatty liver allograft was the only independent factor associated with poor outcome.
Andert et al. [80]	2017	Retrospective	Germany	94	30 days-1 years	All cause mortality	Donor graft hepatic steatosis: < 30% (n = 27), 30%-60% (n = 41) > 60% (n = 26)	<ul style="list-style-type: none"> The 30-day survival rates were 100% in all groups. The 1-year patient survival rates were 94.4% in the group with steatosis < 30%, 87.9% 30%-60% and 90.9% in > 60% group (no difference among groups)
de Graaf et al. [76]	2012	Retrospective	Australia	291	3 months	Mortality	-NAFLD in 72% of graft -Data on pre-LT NASH NA	<ul style="list-style-type: none"> Increased prevalence of mortality in patients with steatosis graft compared to patients without steatosis graft and the higher the grade of steatosis the higher the mortality (steatosis grade 3 25%; grade 1 19%; absence 7%)
Evaluation of CV outcomes in transplanted patients with <i>de novo</i> /recurrent NAFLD								
Pisano et al. [36]	2020	Prospective	Italy	54	2 years	-Carotid IMT, plaques and PWV -Diastolic dysfunction (E/A) -EAT	-New onset steatosis 26% -Pre-LT NAFLD 19% -Graft with steatosis 20%	<ul style="list-style-type: none"> Prevalence of carotid plaques increased before and after LT from 52% to 67%; cIMT from 0.78 mm to 0.83 mm; E/A 1.1 to 0.86; EAT 5.9 mm to 8.1 mm Worsening of indices of early damage of carotid (IMT), diastolic dysfunction and EAT not different between patients with or without post LT steatosis
Bhati et al. [91]	2017	Retrospective	USA	103	5-15 years	-All cause and CV mortality -Survival	-Recurrent NAFLD 87-88% -Pre-LT NASH 47%, cryptogenetic cirrhosis 53%	<ul style="list-style-type: none"> Overall mortality 31%, CV mortality 6% 5, 10, and 15 years post-LT survival rates 86%, 71%, and 51%, respectively No difference in survival between patients with recurrent NAFL versus NASH as determined by biopsy
Hejllova et al. [85]	2016	Retrospective	Czech republic	548	15 years	Survival (comparison between grade 0-1 steatosis vs. 2-3 grade steatosis)	De novo NAFLD in 56% (17% grade 3)	<ul style="list-style-type: none"> Survival times did not differ between patients with significant steatosis and steatosis grades 0-1 CV mortality after the first year in patients with significant steatosis and steatosis grades 0-1 was 21.4% and 5.4% (NS)

Table 1. Evaluation of cardiovascular outcomes in transplanted patients with or without assessment of pre-LT steatosis, either receiving a graft with steatosis and/or with *de novo*/recurrent NAFLD post LT (*continued*)

Authors	Year	Type of study	Nation	Population	F-up after LT	CV endpoint	NAFLD	Results
Yalamanchili et al. [90]	2010	Retrospective	USA	2,052	1-10 years	Survival	- <i>De novo</i> NAFLD in 31% -Pre-LT NASH/criptogenetic cirrhosis in 12%	<ul style="list-style-type: none"> One-, 5-, and 10-year survival not different in patients transplanted for criptogenetic cirrhosis or NASH (86%, 71%, and 56%) vs. with other LT indications (86%, 71%, and 53%) Increased prevalence of CV death in patients transplanted for criptogenetic cirrhosis or NASH (21%) vs. with other LT indications (14%)
Dureja et al. [94]	2011	Cohort-study	USA	88	1-7 years	-All causes mortality and CV mortality -Survival	-Recurrent NAFLD 39% -Pre-LT NAFLD/criptogenetic cirrhosis 100%	<ul style="list-style-type: none"> Prevalence of mortality 27% (34% in patients with recurrent NAFLD vs. 24% not recurrent, NS) Survival and CV mortality, did not differ between those with and without NAFLD recurrence

PAD: peripheral artery disease; BMP: brain natriuretic peptide; MI: myocardial infarction; AF: atrial fibrillation; PE: pulmonary embolism; PWV: pulse wave velocity; LVMl: left ventricular mass index; HF: heart failure; LVEF: left ventricular ejection fraction; TIA: transient ischemic attack; NAFL: non-alcoholic fatty liver; BP: blood pressure; GFR: glomerular filtrate rate; NS: not statistically significant; NA: not available; LDL: low density lipoproteins; BNP: brain natriuretic peptide; ALD: alcoholic liver disease; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; PBC: primary biliary cholangitis; PNF: primary non function; E/A: E wave A wave ratio; EAT: epicardial adipose tissue

Early atherosclerosis post LT

The presence of early atherosclerosis assessed by either cIMT or by the presence of carotid plaques in patients undergoing LT has been recently documented not only in adults but also in pediatric patients. Indeed, endothelial damage has been demonstrated to onset very early after LT, with increase in carotid IMT and stiffness after 6 months from transplant [36, 37], both in children and adolescents [38]. In adults, presence of subclinical atherosclerosis was associated with an increased prevalence of features of MS, namely diabetes, hypertension and dyslipidemia [37].

CAD post LT

CAD is the most studied CVD in patients post LT because of its highly negative prognostic impact on patient's survival. In fact, a study following up patients post LT for 10 years showed an incidence of CAD, either with or without myocardial infarction, of approximately 40%, with increasing incidence over time (i.e. 15% at 3 years and 30% at 8 years post LT). In particular, among all patients who experienced CAD, 12% underwent a revascularization procedure in the first year after LT [39]. Interestingly, in subjects without pre-existing CVD, pre-transplant troponin I elevation (> 0.07 ng/mL) before LT was predictive of occurrence of CVD after LT [40], as well as of higher mortality in the first month post-transplant, possibly indicating that even subtle undiagnosed CAD (i.e. subclinical or microvascular), could predispose to future CV events [41].

Heart failure post LT

Heart failure after LT is often reported, with transient cardiac decompensation occurring in 7-43% of patients during postoperative period [42-49]. Cirrhotic cardiomyopathy (CCM), described as a cardiac dysfunction (systolic or diastolic) in patients with end-stage liver disease without prior heart disease, includes a hyperdynamic circulation, a blend of systolic and diastolic dysfunction, along with prolonged ventricular repolarization, and blunted inotropic and chronotropic response to stress [32]. CCM is possibly due to fibrosis and hypertrophy of the myocardium and to subendocardial oedema [50, 51].

Pre-transplant diastolic dysfunction seems to be linked with graft rejection and failure [47], post-transplant mortality [44, 47] and post-transplant systolic heart failure [44, 48]. Indeed, in the absence of an overt clinical manifestation it is often challenging to establish whether subclinical CV damage was already present before the transplant or whether it is a new onset. In addition, some cardiac alterations of patients with cirrhosis are due to coexisting obesity or diabetes, thus making the diagnosis of CCM even more confusing. The recent availability of new methods for the assessment of CCM in patients with end-stage liver disease modified the criteria for the diagnosis and follow-up of the patients before and after LT [52].

Dysrhythmia post LT

A prolonged QT interval is very frequently reported in the ECG of patients listed for LT [50], and it is associated with a high risk of sudden cardiac death (SCD), especially when the interval is more than 0.5 s. On the other hand, the prognostic role of prolonged QTc in cirrhotic patients not requiring LT is not defined [50]. However, QTc often normalizes after LT [50], whereas its persistent prolongation is associated with an increased rate of post LT fatal and non-fatal CV events [45, 53].

Among all tachyarrhythmias, atrial fibrillation, either before or after LT, is the most widely observed. Its prevalence in LT candidates ranges from 1.4% to 6% [33, 54] and it is associated with post LT increased CV complications, graft failure and mortality [33, 54, 55]. Interestingly increased long-term risk of atrial fibrillation has recently been described in NAFLD patients [56] and more severe the liver disease (i.e. NASH or cirrhosis) higher its prevalence. Few data are available on the development of atrial fibrillation after LT in patients with cirrhosis of which the etiology is not metabolic.

Assessment of CV risk post LT

In order to define the prognostic role of CV complications, CV risk assessment is essential in LT recipients, so that scores predictive of both early and late CV atherosclerotic complications are accumulating.

Among predictors of short term occurrence (i.e. within 1 year after LT) of CV events, the most widely used is the CV risk in orthotopic liver transplantation (OLT), which is based on pre-LT demographic, social, and clinical variables [57].

Conversely, scores for the assessment of the risk of late atherosclerotic complications tailored for LT recipients are missing, so that currently those applied in the general population are used, including the Framingham general CVD score (FRS) [58], the pooled cohort equations (PCEs) [59], the Reynolds Risk Score [60], the Prospective Cardiovascular Münster Study (PROCAM) [61] and the Systematic Coronary Risk Evaluation Project (SCORE) [62]. On the contrary, no validated scores for the prediction of heart failure after LT are available.

Along with risk scores, also the presence of metabolic comorbidities may help clinicians in stratifying CV risk in LT recipients. In fact, T2DM, especially if persistent after LT, has been demonstrated a key prognostic factor for CV morbidity, with an incidence of major CV events of 13% and 27% at 5 and 10 years [63].

Unfortunately, clear guidelines about CV follow-up after LT are missing, as well as about evaluation of subclinical CV changes. Usually, the follow-up consists of a clinical and biochemical control performed semesterly or annually and referral to a specialist only in the presence of hypertension or diabetes. If on one hand the onset CV events after LT has been widely studied, on the other hand only few studies and a meta-analysis [37, 64-72] demonstrated an increase in subclinical atherosclerosis after solid organ transplantation.

Steatosis, LT and CVD

Patients who undergo LT can receive a liver graft with steatosis, can develop steatosis which was absent before LT (steatosis) and can have recurrence of steatosis in the new liver (patients with NAFLD pre-LT).

Liver graft with steatosis

Given the increased prevalence of NAFLD worldwide, along with a shortened organ pool donation in many countries, utilization of donor grafts with hepatic steatosis is now more common [73]. Hepatic steatosis is seen in the biopsies of a consistent percentage of potential liver donors, reaching up to 75% if overweight is present [74].

As a consequence of reperfusion, alterations in microcirculation and hepatocytes are induced by steatosis in the graft, with consequent necrosis and impaired regenerative processes [75, 76]. As a result, hepatic steatosis in donor livers exposes recipients to increased morbidity and mortality. Necessity of intensive care unit, longer hospitalization, as well as increased risk of graft failure [77-79], especially for steatosis in more than 60% of the graft [79-82], is usually observed. Viceversa, presence of moderate steatosis seems to affect significantly neither the long-term liver-related outcome [83] nor the CV outcome [37].

De novo steatosis

The term *de novo* NAFLD indicates the occurrence of steatosis in the transplanted livers of patients who did not have steatosis before LT, its prevalence ranging from 25% to 60% [37, 84-86] depending on follow-up duration and populations studied. Interestingly, prevalence of *de novo* steatosis increases over time (30% at 1 year up to nearly 50% after 10 years) with 5-10% progressing towards NASH and 2.5% to cirrhosis [85-89].

Risk factors for *de novo* steatosis

Risk factors for *de novo* steatosis include presence in LT recipients of sarcopenia and features of MS (especially insulin resistance, hypertension and obesity), tacrolimus based immunosuppressive therapy, hepatitis C virus and genetic predisposition as the genotype [83-85], as well as hypoadiponectinemia and high levels of free fatty acids [90]. Indeed, in transplanted patients who develop *de novo* steatosis, CV events are common with nearly 40% of transplant recipients experiencing an event within 10 years, one-third occurring within the first year.

Recurrence of steatosis

Recurrent NAFLD is the onset of steatosis in the graft of a patient needing LT for the liver complications of hepatic steatosis in a dysmetabolic setting, with a recurrence rate of 30-60% within 1-5 years after LT, and with progression towards NASH of 10-33% and advanced fibrosis of 5-10% [91]. Other data report a higher prevalence, with a recurrence rate as high as 90-100% [84, 92]. Differences in the prevalence of steatosis recurrence are likely related to the diagnostic methodology to assess steatosis, the time from transplant, and presence of pre and post-transplant risk factors.

In addition, patients who need a liver transplant because of metabolic cirrhosis are likely to have recurrence of NAFLD, and classically they present features of MS and pre-existing CV disease [91, 93], thus being exposed to higher CV risk by default [94, 95].

De novo and recurrent NAFLD are indeed two distinct entities. In particular, patients with recurrent NAFLD present higher prevalence of obesity and diabetes compared with patient with *de novo* NAFLD, are more likely to progress to advanced forms of NAFLD, suggesting a more aggressive course of the disease [87], likely because of a longer exposure to metabolic alterations. In addition, it has been reported that steatosis resolves in one-fifth of patients with *de novo* and only rarely in those with recurrent NAFLD [87]. However, data on the impact of recurrent NAFLD on long-term outcomes are conflicting, some showing a similar overall survival in patients with and without recurrent NAFLD [84, 91, 95], even in the presence of NASH [92], others an increase in mortality, mainly if patients had developed NASH [83, 92, 96].

Although there are no concordant data on the increase in overall mortality in NAFLD transplant patients compared to those of other etiologies, CV complications after LT are higher in NAFLD patients. In fact, a higher incidence of major cardiac and cerebrovascular events was reported in NAFLD subjects related to age, pre-transplant T2DM and other features of MS and a history of post-transplant CAD [10, 97].

Furthermore, *de novo* and recurrent steatosis are related to weight gain post LT. Weight gain is observed in almost all patients after 3 months from LT, with patients with pre-transplant NAFLD gaining more weight than non-NAFLD patients [98]. Moreover, new onset obesity was found related with a higher incidence of CV disease [99].

Genetic, LT and CVD

The interplay between metabolic and genetic factors in the CVD of patients with NAFLD is known [100] conversely the relevance of genetic factors in CV complications post OLT is still not defined. A dated paper which analyzed the role of the C677T-methylenetetrahydrofolate reductase (MTHFR)-polymorphism on vascular complications in 47 liver transplant recipients reported that this polymorphism was significantly associated with an increased incidence of vascular complications [101]. However, the sample size was small and no other study confirmed these results. In addition, recently variants in the MTHFR gene have been recently demonstrated as not associated with fatty liver disease making unlikely the role of this variant in post OLT CVD [102]. As previously mentioned, genetic factors, including the major genetic determinant of NAFLD, and the *TM6SF2* E167K polymorphisms, as well as the membrane-bound *O*-acyltransferase domain-containing 7 (*MBOAT7*) genetic variant facilitate NAFLD occurrence before transplant [103].

It is very likely that the same polymorphisms will increase the risk of CVD after OLT. In a small study performed in China it was reported that the coexistence of obesity and positivity for I148M GG was strongly associated with *de novo* NAFLD occurrence post OLT [104]. Thus, even if longer follow up was not available to assess the risk of CVD in positive patients it can be expected that similarly to patients with NAFLD, transplanted subjects are at higher risk for CVD. It is possible that genetic polymorphisms may even play a major role given the presence of multiple environmental factors, after OLT, increasing CV risk. It will be interesting to define whether carriers of polymorphisms known to facilitate NAFLD occurrence but protect from CVD, such as the *TM6SF2* E167K, will reduce the risk of CVD post OLT [100].

In summary, given the epidemic of NAFLD and consequently the fastest growing indication to LT, some authors have evaluated whether NAFLD and NASH *per se* constitute an increased risk of CVD but results are

contrasting. Piazza et al. [105] found that NASH is not an independent risk factor for CVD in transplanted patients and a recent meta-analysis including 4,237 transplanted patients, 717 with NASH, from 9 studies [106] confirmed these data. In contrast, another meta-analysis pooling data from 16 observational studies, demonstrated that NAFLD was a risk factor for fatal and nonfatal CV events, and the more advanced the liver disease the higher the risk [107].

Thus, findings are far from being conclusive. While there is a general agreement that the metabolic alterations prevalent in NAFLD patients have an impact on death/removal during the LT waiting list, survival, CV events and renal failure rates were similar in NASH and non-NASH patients undergoing LT [30].

Conclusions

In conclusion, NAFLD represents one of the main indications for LT, it is often present also in patients in whom the indication for LT recognizes other etiologies and can develop after transplantation. Therefore, NAFLD seems to confer an increased risk of CV morbidity and mortality, mainly when associated with T2DM and MS.

Patients referred to LT for NAFLD-related complications need aggressive management of risk factors before LT to reduce waiting list morbidity/mortality and to reduce post LT CV damage related to *de novo* development or recurrent NAFLD, weight gain and MS.

Prevention of CVD morbidity and mortality requires long-term concerted multidisciplinary activity with dietary counseling and exercise associated with therapy for hypertension, T2DM and dyslipidemia.

Abbreviations

CAD: coronary artery disease

CCM: cirrhotic cardiomyopathy

cIMT: carotid artery intima-media thickness

CV: cardiovascular

CVD: cardiovascular disease

LT: liver transplantation

MS: metabolic syndrome

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

OLT: orthotopic liver transplantation

PNPLA3: patatin-like phospholipase domain containing 3

T2DM: type 2 diabetes

TM6SF2: transmembrane 6 superfamily member 2

Declarations

Author contributions

RL and GP revised the literature, focusing on full text paper regarding CV involvement in post LT patients and role of NAFLD in increasing the CV risk and wrote the draft of the manuscript. SF and ALF were involved in the critical revision of the manuscript to its final form and contributed to the review for important intellectual content.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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