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7901 Stoneridge Drive,  
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## Cardiovascular assessment in liver transplant for non-alcoholic steatohepatitis patients: What we do, what we should do

Yolanda Sanchez-Torrijos, Javier Ampuero, Manuel Romero-Gómez

Yolanda Sanchez-Torrijos, Javier Ampuero, Manuel Romero-Gómez, Unidad Intercentros de Aparato Digestivo, Hospitales Universitarios Virgen del Rocío - Virgen Macarena, 41013 Sevilla, Spain

Javier Ampuero, Manuel Romero-Gómez, Instituto de Biomedicina de Sevilla, 41013 Sevilla, Spain

Javier Ampuero, Manuel Romero-Gómez, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), 28029 Madrid, Spain

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**Correspondence to:** Javier Ampuero, MD, PhD, Unidad Intercentros de Aparato Digestivo, Hospitales Universitarios Virgen del Rocío - Virgen Macarena, Avenida Manuel Siurot s/n, 41013 Sevilla, Spain. [javi.ampuero@gmail.com](mailto:javi.ampuero@gmail.com)  
Telephone: +34-95-5015761  
Fax: +34-95-5015899

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) is increasing considerably due to the current lifestyle, which means that it is becoming one of the main indications for liver transplantation. On the other hand, there is a strong association between NAFLD and cardiovascular disease. This has been evidenced in many studies revealing a higher presence of carotid plaques or carotid intima-media thickness, leading to cardiovascular events and, ultimately, mortality. According to the liver transplant guidelines, screening for heart disease in transplant candidates should be performed by electrocardiogram and transthoracic echocardiography while a stress echocardiogram should be reserved for those with more than two cardiovascular risk factors or greater than 50 years old. However, there are no specific recommendations in NAFLD patients requiring a liver transplantation, despite its well-known cardiovascular risk association. Many studies have shown that these patients probably require a more exhaustive assessment and a global approach including other specialists such as cardiologists or nutritionists. Also, the incidence of cardiovascular disease is also increased in NAFLD patients in the post-transplantation period in comparison with other etiologies, because of the pre-existent risk factors together with the immunosuppressive therapy. Therefore, an early intervention on the lifestyle and the individualized selection of the immunosuppressive regimen could lead to a modification of the cardiovascular risk factors in NAFLD patients requiring a liver transplantation.

**Key words:** Cardiovascular risk; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Pre-transplant assessment; Liver transplantation

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**Core tip:** Non-alcoholic fatty liver disease is a growing condition due to the current lifestyle. It is considered the liver manifestation of the metabolic syndrome, so it is



strongly related to cardiovascular disease. Given that is one of the main indications of liver transplantation, it is essential to carry out an adequate assessment of the pre-transplant cardiovascular risk, as well as an individualized management of the patient in the post-transplantation period (due to the pre-existent cardiovascular risk factors and the immunosuppressive therapy).

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical-pathological condition that encompasses a wide range of liver damage not caused by chronic alcohol consumption, including steatosis, non-alcoholic steatohepatitis (NASH) and cirrhosis<sup>[1]</sup>. NAFLD is considered a hepatic manifestation of metabolic syndrome. Its prevalence has increased considerably over last years, especially in Western countries, due to the current lifestyle (diet, sedentary lifestyle, obesity)<sup>[2,3]</sup>. It has been calculated that up to 30% of the population shows NAFLD, representing up to the 70% in patients with type 2 diabetes mellitus (DM)<sup>[4]</sup>. On the other hand, the prevalence of NASH (characterized by the presence of inflammation) is around 3%-5%. In NASH patients, cardiovascular (CV) risk represents one of the leading causes of mortality due to the frequent association with dyslipidemia, DM and other features of metabolic syndrome<sup>[5]</sup>. In fact, NASH patients suffer more subclinical atherosclerosis, heart disease, and CV clinical events than those without it<sup>[6]</sup>. This latter, together with NASH has become the second cause of liver transplantation (LT) in the United States and Europe<sup>[7]</sup>, makes especially relevant the adequate cardiovascular assessment in LT setting.

## CV RISK IN NAFLD PATIENTS

Several studies have clearly demonstrated the link between NAFLD and CV risk. It is not surprising, considering that they share many risk factors derived from metabolic syndrome (such as obesity, insulin resistance, DM, sedentary lifestyle, hypertension, dyslipidemia) and genetics (PNPLA3, TM6SF2)<sup>[8]</sup>. Gut microbiota also plays an important role. In both mice and humans, a high-fat diet results in an increase of lipopolysaccharides in plasma (a cellular component of Gram-negative bacteria) by modifying the microbiota and, therefore, the intestinal permeability. That is the reason to increase TLR4 receptor expression, stimulating liver cells to produce inflammatory cytokines and creating a systemic pro-inflammatory status, which favors atherosclerosis<sup>[9,10]</sup>. According to CV risk, we can classify it in three steps: Subclinical

atherosclerosis, clinical events, and mortality.

Firstly, a higher prevalence of subclinical atherosclerosis has been well-documented (Table 1). In 2005, Brea *et al*<sup>[11]</sup> published that NAFLD patients showed an increased carotid artery intima-media thickness (CIMT) and a higher prevalence of carotid plaques (50% vs 25%) compared to healthy controls. Regarding NAFLD subjects, NASH patients showed greater subclinical atherosclerosis in comparison with those with simple steatosis and the CV risk was progressively increased according to liver fibrosis<sup>[11]</sup>. Later, Kim *et al*<sup>[12]</sup> identified that patients with NAFLD had a higher percentage of coronary artery calcification (by computerized tomography) independently of other known factors. More recently, Puchner *et al*<sup>[13]</sup> again assessed the link between NAFLD and advanced coronary arterial disease. After performing a coronariography by computerized tomography, they found that the presence of significant coronary stenosis (16% vs 5%), global carotid plaques (78% vs 24%) and high-risk carotid plaques (59% vs 19%) were more prevalent in individuals with NAFLD. All of these findings have been confirmed in a recent meta-analysis, as NAFLD patients showed a greater link with subclinical atherosclerosis regarding CIMT [OR 2.04 (95%CI: 1.65-2.51)] and the presence of carotid plaques [OR 2.82 (95%CI: 1.87-4.27)]<sup>[14]</sup>. Secondly, NAFLD patients suffer more CV events than the overall population. In 2016, Fracanzani *et al*<sup>[15]</sup> aimed to evaluate the incidence of CV and cerebrovascular events in patients with NAFLD, who had been monitored for 10 years. Patients presented a higher number of CV events than the control group (19% vs 10%), being the presence of carotid plaques [OR 5.08 (95%CI: 2.56-10.95)] and liver steatosis [OR 1.99 (95CI: 1.01-3.94)] the main risk factors<sup>[15]</sup>. As a consequence of the higher prevalence of subclinical atherosclerosis and clinical events, CV mortality is ultimately increased as well. In fact, CV-related death appears to be one of the leading causes of death in most of the studies in NASH patients (Table 2). Ekstedt *et al*<sup>[16]</sup> followed-up 229 patients during more than 30 years, concluding that CV disease was the first cause of mortality for NASH patients without cirrhosis.

Taking all together, the European Association for the Study of the Liver recommend screening for CV disease in patients with NAFLD, irrespective of the presence of other traditional risk factors<sup>[17]</sup>.

## CV EVALUATION PRE-LT

CV disease is a major cause of death in post-LT knowing that this risk is bigger in patients showing pre-LT risk factors (irrespective of the etiology). For example, coronary artery disease has been observed in as many as 60% of potential LT candidates and, obviously, its presence increases the CV morbi-mortality pre and post-surgery<sup>[18]</sup>. Therefore, it is essential an adequate CV assessment to prevent these complications and increase post-LT survival rates.

To be included on the liver transplant list, comprehensive evaluation must be performed to evaluate the

**Table 1** Methods to detect subclinical atherosclerosis<sup>[8]</sup>

Carotid ultrasound	CIMT	> 0.9 mm
CT coronary angiography	No. of calcifications in coronary arteries	≥ 1
Endothelial function	Flow-mediated vasodilation brachial artery	
	Carotid-femoral pulse wave velocity	> 12 m/s
Morpho-structural alteration	Electrocardiogram (left ventricular hypertrophy)	Sokolov-Lyon > 38 mm; cornell > 2444 mm*ms
Renal function	Slight increase in plasmatic creatinine	M: 1.3-1.5 mg/dL
		F: 1.2-1.4 mg/dL
	Low glomerular filtration	Creatinine clearance < 60 mL/min
	Microalbuminuria	30-300 mg/24 h
		Alb/Cr ≥ 22 (M) or ≥ 31 (F) mg/g Cr
Inflammatory biomarkers	TNF, IL-6, C-reactive protein	
Thrombogenic biomarkers	PAI-1, fibrinogen, factor VII	

CIMT: Carotid intima-media thickness; CT: Computerized tomography; M: Male; F: Female; TNF: Tumor necrosis factor; IL: Interleukin; PAI-1: Plasminogen activator inhibitor type 1.

**Table 2** Cardiovascular mortality in non-alcoholic fatty liver disease patients

Ref.	Year	NAFLD diagnosis	Follow-up	CV mortality	Cause of mortality
Dam-Larsen <i>et al</i> <sup>[48]</sup>	2004	Histology	20 yr	38%	1 <sup>st</sup>
Adams <i>et al</i> <sup>[49]</sup>	2005	Histology	8 yr	25%	2 <sup>nd</sup>
Ong <i>et al</i> <sup>[50]</sup>	2008	Ultrasound	9 yr	25%	1 <sup>st</sup>
Rafiq <i>et al</i> <sup>[51]</sup>	2009	Histology	29 yr	13%	1 <sup>st</sup>
Söderberg <i>et al</i> <sup>[52]</sup>	2010	Histology	28 yr	35%	1 <sup>st</sup>
Angulo <i>et al</i> <sup>[53]</sup>	2013	Histology	9 yr	38%	1 <sup>st</sup>
Stepanova <i>et al</i> <sup>[54]</sup>	2013	Histology	12 yr	28%	1 <sup>st</sup>
Ekstedt <i>et al</i> <sup>[16]</sup>	2015	Histology	26 yr	43%	1 <sup>st</sup>

CV: Cardiovascular; NAFLD: Non-alcoholic fatty liver disease.

peri-surgery risk that could prevent from good long-term results. Regarding to CV assessment, current recommendations include<sup>[19]</sup>: (1) to carry out an electrocardiogram and a trans-thoracic echocardiography to rule out underlying heart disease; (2) in patients with > 2 CV risk factors or those older than 50 years old, an ergometry or a stress echocardiogram with dobutamine to detect subclinical ischemic cardiopathy; and (3) whether a significant coronary artery disease is detected during the usual evaluation, a coronariography must be performed (if this latter results effective, the survival rate after LT is similar to those who do not have previous CV disease<sup>[20,21]</sup>). Sometimes, non-invasive methods to screen for CV disease have low sensitivity and specificity compared to other tests (*i.e.*, angiography)<sup>[22]</sup>. However, there is no sufficient evidence to recommend invasive tests to evaluate CV risk before LT in asymptomatic patients. Therefore, the American Heart Association and the American College of Cardiology Foundation<sup>[23]</sup> propose to perform a coronariography in CV high-risk candidates, defined as those who have > 2 CV risk factors (DM, age > 60 years, smokers, AHT, and dyslipidemia). On the other hand, they recommend non-invasive stress tests in those patients with low risk of CV disease<sup>[24]</sup>.

Given that CV risk factors before LT have a great impact, it has been proposed that the Framingham Risk Score (an algorithm to predict CV risk at 10 years including age, sex, smoking, DM, arterial hypertension, and dyslipidemia) could be useful for predicting post-LT CV risk in candidate patients. This strategy could lead

to performing individualized diagnostic and therapeutic tests depending on the score<sup>[25]</sup>.

Clinical guidelines for NAFLD patients recommend that CV risk must be carefully evaluated in LT setting because theoretically these subjects have more risk factors to suffer CV-related clinical events and mortality. Even more, some of them probably would require invasive tests but the best method remains unclear. The British guideline<sup>[26]</sup> proposes the evaluation of the functional capacity of the patient measured by the MET unit (energy expenditure during physical activity), guiding the following tests according to the result. Consequently, patients able to climb at least two flights of stairs (equivalent to 4 METs) and those who do not present CV risk factors, may not require further tests. On the other hand, those with a MET < 4 or showing at least one CV risk factors (myocardial infarction, heart failure, stroke/transient ischaemic attack, renal dysfunction, DM requiring insulin therapy) will need a stress echocardiogram or cardiopulmonary exercise test. Likewise, they recommend the simultaneous evaluation with a cardiologist in CV high-risk patients, especially those who have suffered a CV disease before LT<sup>[23]</sup>. Despite all this, pre-LT CV assessment in NAFLD patients is not routinely different to those patients who have cirrhosis for other etiologies.

## CV RISK IN NAFLD POST-LT

Post-LT survival rates have been increasing over time,

**Table 3** Immunosuppressive drugs and metabolic side effects affecting post-liver transplantation cardiovascular risk<sup>[33]</sup>

Drug	Group	Side effects
Corticosteroids		Dyslipidemia ++ AHT +++ DM +++
Mycophenolate mofetil	<i>De novo</i> purine synthesis inhibitor	Renal impairment - Dyslipidemia - AHT - DM -
Cyclosporine Tacrolimus	Calcineurin inhibitors	Renal impairment - Dyslipidemia ++ AHT +++ DM ++
Sirolimus Everolimus	mTOR inhibitors	Renal impairment ++ Dyslipidemia +++ AHT - DM - Renal impairment -

(+): Positive association; (-): No association; AHT: Arterial Hypertension; DM: Diabetes mellitus.

due to the loss of the liver graft is less common and the short-term mortality is lower<sup>[27]</sup>. After the transplant, patients usually gain weight, and the incidence of metabolic syndrome is greater (as much as two-thirds of patients at 5 years) probably related to the lifestyle and the immunosuppressive treatment, respectively<sup>[28,29]</sup>. In this scenario, metabolic and CV complications are currently the main responsible for affecting the mid- and long-term survival.

Among non-liver-related 1-year mortality after the LT, CV disease is the second cause after tumors, followed by infections and kidney failure<sup>[30]</sup>. Madhwal *et al.*<sup>[31]</sup>, based on a meta-analysis including twelve observational studies, observed that CV events were present in 13.6% (95%CI: 9%-18%) of NAFLD patients within 10 years. Also, they noted that the incidence of CV disease was especially relevant in those who had additionally metabolic syndrome (four times higher of suffering a CV event)<sup>[31]</sup>. Precisely, NAFLD patients who required LT are older and have more prevalence of DM and obesity (as well as chronic kidney failure or previous CV disease) in opposition to the rest of etiologies<sup>[32]</sup>.

The prevalence of metabolic syndrome is around 50%-60% of the post-LT population<sup>[28,33]</sup>, influenced by the appearance of several risk factors. Obesity (BMI > 30 kg/m<sup>2</sup>) is approximately 24%-64% after LT<sup>[27]</sup>, due to the fact that the weight increases after the operation (reversion of cirrhosis and its hypercatabolic state, increase in appetite, absence of the chronic disease, effects of steroids) which means an increase in DM and dyslipidemia, as well as in vascular events and kidney disease<sup>[34]</sup>. On the other hand, DM (the most important risk factor of NAFLD) is diagnosed in 10%-64% of post-LT patients<sup>[28,35]</sup>, and is being considered more and more the main complication after LT. Its appearance is multifactorial, but the main modifiable factor (apart from lifestyle) is the choice and dose of the immuno-

suppressive therapy. Corticoids have diabetogenic effects producing resistance to insulin and increasing the gluconeogenesis, while the calcineurin inhibitors can directly damage the pancreatic cells (tacrolimus has a significantly higher risk than cyclosporine<sup>[36]</sup>). The immunosuppressive therapy is also responsible, at least in part, of the appearance of post-transplant AHT (40%-85%) and dyslipidemia (40%-66%)<sup>[37]</sup> (Table 3). All of this means that the liver disease can return after the LT (*de novo* NAFLD). Out of NASH patients who are transplanted, this entity reappears in 75%, being the post-LT hypertriglyceridemia, BMI and steroid treatment, the main risk factors<sup>[38]</sup> (causing a positive feedback for post-LT CV risk).

In this scenario, several studies have evaluated whether patients with NAFLD show a higher risk of post-LT CV disease in comparison with other etiologies. Yalamanchili *et al.*<sup>[39]</sup> evaluated 2152 patients with liver cirrhosis, of which 12% had NAFLD or cryptogenic cirrhosis. Survival rate at 10 years after the LT was similar regardless of the etiology, but a significant increase was observed in CV mortality in NAFLD patients (21% vs 14%)<sup>[39]</sup>. VanWagner *et al.*<sup>[40]</sup> compared the incidence of CV events between NAFLD and alcohol after the LT. Authors observed an increase in CV-related 1-year mortality after LT in NAFLD group (26% vs 8%) and, more interestingly, the most of the CV events occurred in the peri-surgery period (70%)<sup>[40]</sup>. The same research group has recently determined a group of risk factors clearly associated with post-LT CV mortality: Age > 55 years old, male sex, DM, and kidney failure<sup>[32]</sup>. Wang *et al.*<sup>[41]</sup> performed a meta-analysis in NAFLD patients to estimate post-LT results regarding overall survival, CV mortality, sepsis and liver graft failure. Authors concluded that survival rates were similar in patients with or without NAFLD, as far as 5 years after LT. However, it was found that NAFLD patients were more likely to die because of CV complications [OR 1.65 (95%CI: 1.01-2.70)]<sup>[41]</sup>.

## RECOMMENDATIONS IN NAFLD LIVER TRANSPLANT

### *Pre-liver-transplantation recommendations*

Taking into account the information exposed before, the pre-LT CV assessment in patients with NAFLD should be more exhaustive than in the rest of etiologies. However, there are no specific recommendations probably due to there is no an ideal procedure regarding cost, availability, and reliability.

NAFLD is not considered a CV risk criterion to influence the decision of the selection of the CV evaluation in the pre-LT assessment. Consequently, many NAFLD patients only undergo a trans-thoracic echocardiogram or a computerized coronary tomography with calico-score. Some authors have proposed the stress echocardiography with dobutamine as an initial test in NAFLD candidates for LT because it shows a high negative predictive value to detect low-risk patients<sup>[42]</sup>. In high CV

risk patients (age > 55 years, male gender, DM, kidney failure), it probably should be the initial test.

NAFLD is a condition that, more than a specific treatment, needs a multidisciplinary approach whose aim is a dramatic change in the lifestyle<sup>[43]</sup>. Thus, it is crucial to have a systematic intervention of a nutritionist during the LT evaluation in NAFLD patients (overweight, obesity, unhealthy diet) to reinforce and maintain a healthy lifestyle after the LT<sup>[44]</sup>.

### Post-liver-transplantation recommendations

Given that liver transplant recipients have an increased risk of CV disease, an early and effective treatment is required, as well as changing of the other risk factors (lifestyle, treatment of co-morbidities, immunosuppressive therapy). One example is the obligation of starting the treatment to control AHT, dyslipidemia or DM as soon as possible<sup>[44]</sup>.

Regarding the immunosuppressive drugs, most of them can cause and enhance various CV risk factors. Mycophenolate mofetil is associated with an increased risk of CV disease in post-LT patients<sup>[45]</sup>. More recently, the use of mTOR inhibitors (sirolimus, everolimus) was associated to lower CV risk than calcineurin inhibitors<sup>[46]</sup>. Therefore, mTOR inhibitors could be considered for patients with metabolic syndrome and multiple CV risk factors, such as NAFLD patients. Nevertheless, these findings must be confirmed and validated in prospective cohorts. On the other hand, we should use a steroid-free regimen (or an early steroid withdrawal) preferably considering an, for example, a basiliximab-based induction therapy<sup>[26]</sup>.

A healthy diet and regular exercise are effective and complementary therapies<sup>[47]</sup>. Exercise is effective to lower the CV risk in non-transplant patients, but the connection between the benefits and the possible damage of regular exercise after LT has not been established. Also, there are no data concerning the impact of these exercise programs on the prevalence of metabolic syndrome or its individual components after LT.

## CONCLUSION

The increased CV risk in patients with NAFLD, compared to other etiologies of liver disease, has important implications both in pre- and post-LT. An adequate stratification of CV risk and an early detection of the different features of metabolic syndrome is required to prevent or decrease CV-related morbi-mortality. In this scenario, an active intervention on lifestyle and an individualized management of immunosuppression could be the most suitable strategies to maintain an adequate balance between risks and benefits.

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