**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 55869

**Manuscript Type:** Review

**Clinical considerations in the management of non-alcoholic steatohepatitis cirrhosis pre- and post-transplant: A multi-system challenge**

Steggerda JA *et al*. Management of NASH cirrhosis pre- and post-transplant

Justin A Steggerda, Krishnaraj Mahendraraj, Tsuyoshi Todo, Mazen Noureddin

**Justin A Steggerda, Krishnaraj Mahendraraj, Tsuyoshi Todo,** Department of Surgery, Division of Transplantation, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

**Mazen Noureddin,** Division of Digestive and Liver Diseases, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

**Author contributions:** Steggerda JA and Noureddin M developed the concept and designed the research; Steggerda JA, Mahendraraj K, and Noureddin M participated in data acquisition; Steggerda JA, Mahendraraj K, Todo T, and Noureddin M participated in the drafting and editing of the manuscript; Steggerda JA and Noureddin M developed the tables and figures to accompany the manuscript.

**Corresponding author: Mazen Noureddin, MD, Doctor,** Division of Digestive and Liver Diseases, Comprehensive Transplant Center, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Suite 270, Los Angeles, CA 90048, United States. mazen.noureddin@cshs.org

**Received:** April 6, 2020

**Revised:** May 7, 2020

**Accepted:** July 15, 2020

**Published online:**

**Abstract**

Non-alcoholic steatohepatitis (NASH) is the most common chronic liver disease worldwide, and the fastest growing indication for liver transplantation in the United States. NASH is now the leading etiology for liver transplantation in women, the second leading indication for men, and the most common cause amongst recipients aged 65 years and older. Patients with end-stage liver disease related to NASH represent a unique and challenging patient population due the high incidence of associated comorbid diseases, including obesity, type 2 diabetes (T2D), and hypertension. These challenges manifest in the pre-liver transplantation period with increased waitlist times and waitlist mortality. Furthermore, these patients carry considerable risk of morbidity and mortality both before after liver transplantation, with high rates of T2D, cardiovascular disease, chronic kidney disease, poor nutrition, and disease recurrence. Successful transplantation for these patients requires identification and management of their comorbidities in the face of liver failure. Multidisciplinary evaluations include a thorough pre-transplant workup with a complete cardiac evaluation, control of diabetes, nutritional support, and even, potentially, consultation with a bariatric surgeon. This article provides a comprehensive review of the conditions and challenges facing patients with NASH cirrhosis undergoing liver transplantation and provides recommendations for evaluation and management to optimize them before liver transplantation to produce successful outcomes.

**Key words:** Liver transplantation; Non-alcoholic fatty liver disease; Obesity; Metabolic syndrome

Steggerda JA, Mahendraraj K, Todo T, Noureddin M. Clinical considerations in the management of non-alcoholic steatohepatitis cirrhosis pre- and post-transplant: A multi-system challenge. *World J Gastroenterol* 2020; In press

**Core tip:** Non-alcoholic steatohepatitis (NASH) is the most common chronic liver disease worldwide, and the fastest growing indication for liver transplantation (LT) in the United States. Patients with NASH represent a unique and challenging population due the high incidence of associated conditions (i.e. obesity, diabetes, and hypertension), which carry considerable risk of morbidity and mortality before and after LT due to cardiovascular disease and kidney disease. This article provides a comprehensive review of the conditions and challenges facing patients with NASH and provides recommendations for evaluation and management to optimize them before LT.

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) is a global epidemic and the most common cause of chronic liver disease worldwide[1]. NAFLD represents a spectrum of liver disease, starting with simple steatosis (NAFL) and progressing to non-alcoholic steatohepatitis (NASH) with inflammation and cellular injury in addition to fat accumulation[2]. Livers affected by NASH may ultimately develop fibrosis and progress to cirrhosis and liver failure requiring liver transplantation (LT)[3]. While chronic infection with hepatitis C virus (HCV) has long-been the leading indication for liver transplantation, the recent advent of direct antiviral agents has resulted in increased rates of disease resolution and decreased the need for LT[4-6]. Simultaneously, the increasing prevalence of obesity throughout the world has led to an increased incidence of NASH and NASH-related cirrhosis[1]. Importantly, NASH is now the leading indication for LT in women, the second leading indication for men, and the most common non-malignant indication amongst recipients aged 65 years and older[7,8].

NASH cirrhosis represents a growing challenge in transplantation with no effective treatment. Strongly associated with the metabolic syndrome, patients with NASH often have the associated comorbidities of obesity, type 2 diabetes (T2D), cardiovascular disease, and chronic kidney disease, amongst others[9-12]. This constellation of diseases, along with end-stage liver disease (ESLD), makes treating patients with NASH cirrhosis a challenging clinical endeavor. Furthermore, these conditions increase the risk of transplantation and may complicate post-LT immunosuppression and care.

To address this unique clinical challenge, here we present a comprehensive review article in which we discuss the difficulties in managing patients with NASH before and after LT, with consideration given to the interplay of disease physiologies and potential treatments where available.

**Pre-Transplant Considerations for Patients with NASH**

NASH is the fastest rising cause of ESLD amongst registrants on LT waitlists in the United States, with a 170% increase from 2004 to 2013[13]. The number of LT performed for NAFLD increased fourfold between 2002 and 2012[6]. During nearly the same time, the mean age of all LT recipients increased, and the increase in age amongst HCV-negative patients was associated with an increase in NASH cirrhosis[14]. NASH has become the most common indication for LT amongst patients ≥ 65 years old[8]. Recently, Parikh *et al*[15]. using national data to model the rise of NASH in LT in the United States, predicted a 55.4% increase in NASH-related waitlist additions by 2030. In concert with decreasing prevalence of HCV[16]. NASH will likely become the most common indication for both waitlisting and receipt of LT in the next 15 years[15,17]. In addition to aging, NASH has a predilection for the female gender. Our group recently showed that NASH is the leading indication for LT waitlist registration and transplantation for women[7].

***NASH and obesity***

NASH patients are a unique and complex population, with multiple comorbidities complicating their underlying liver disease (Figure 1). Obesity is a growing epidemic in the United States, with an estimated 38% of adults having a body mass index (BMI) > 30 kg/m2[18]. Obesity alone has been a point of contention in LT[19]. In the pre-model for end-stage liver disease (MELD) era, Nair *et al*[20] considered morbid obesity (BMI ≥40 kg/m2) an independent predictor of mortality in LT recipients. In contrast, Leonard *et al*[21] evaluated LT outcomes by recipient BMI after removing ascites and found no difference in survival. Nonetheless, obesity has been associated with increased rates of early graft dysfunction, longer hospital stays, and increased rates of infection in the United States and the United Kingdom[20,22,23]. In the pre-LT setting, Segev *et al*[24] found that obese patients were more likely to be turned down for organ offers and to receive fewer MELD exception points than were leaner individuals. There is a trend towards worse outcomes when BMI is > 40 kg/m2 and with concomitant diabetes[25,26]. Overall, the International Liver Transplantation Consensus Statement on ESLD due to NASH does not recommend against LT on the basis of obesity alone but supports careful patient selection in the presence of comorbidities[27].

NASH is the result of progression from NAFL and is often considered the hepatic manifestation of the metabolic syndrome[2]. The syndrome has been defined in a joint publication of the International Diabetes Foundation and the National Heart, Lung, and Blood Institute in the United States (Table 1). In addition to being associated with older aged and female patients, NASH is also commonly seen with obesity, hypertension, diabetes, renal disease and cardiovascular disease[28].

***Insulin resistance, metabolic syndrome and NASH***

Insulin resistance likely is the primary pathogenetic factor that ties metabolic syndrome and NAFLD/NASH together. In the liver, elevated serum glucose and insulin values increase the activity of carbohydrate response element binding protein and sterol regulatory-element binding protein 1c, which leads to impaired metabolism of liver lipid, increased lipid deposition, and further inhibition of insulin signaling within the liver[29-31]. Hepatic insulin resistance and steatosis may be the “first hit” in the development of NAFLD, sensitizing the liver to “second hits,” which lead to the development of inflammation, fibrosis, and necrosis that are characteristics of NASH[32,33]. The second hits are multifactorial—inflammatory cytokines, adipokines, mitochondrial dysfunction, oxidative stress, breakdown of the gut mucosal barrier with endotoxemia, and activation of Kuppfer cells and hepatic stellate cells[34-38].

Not surprisingly, diabetes is common amongst LT candidates with NASH. The incidence of diabetes amongst patients awaiting LT with NASH is more than 2-fold higher than any other causes, ranging from 46%-55%[13,39]. Hoehn *et al*[40] reported that NASH was the most common cause of ESLD amongst patients undergoing LT with diabetes. Furthermore, the severity of liver disease in NAFLD/NASH may be related to T2D. In a 2006 study examining the association between NAFLD and diabetes, 71% of patients with biopsy- proven NASH had diabetes, whereas only 46% of patients with simple steatosis had the disorder[41]. Importantly, pre-LT diabetes is associated with early postoperative complications, such as infection and adverse cardiovascular events[42].

Hypertension is another component of the metabolic syndrome seen commonly in LT candidates with NASH[43]. In an evaluation of listed patients, hypertension was present in 46% of those with NASH compared with 28% of those with HCV[39]. An independent association between NAFLD/NASH and hypertension has been reported[44,45]. While hypertension is not prevalent amongst individuals awaiting LT, pathogenetic mechanisms associated with arteriolar hypertension may contribute to the increased incidence of renal dysfunction and cardiovascular risk in patients with NASH[46].

***Renal dysfunction with NASH***

Patients with NASH commonly have multiple risk factors for chronic kidney disease (CKD). CKD, defined as decreased estimated glomerular filtration rate (eGFR) and/or overt proteinuria and/or abnormal albuminuria, is common in patients with NAFLD and NASH, with a prevalence of 20%-55%[47]. While the development of CKD in these patients is likely related in part to the end-organ effects of diabetes, hypertension, and insulin resistance, distinct pathogenetic mechanisms due to NASH per se are possible[48-51], as NAFLD and NASH have been independently associated with both the prevalence and incident of CKD, [52-54] where the risk of developing CKD has hazard ratios (HR) of 1.49-1.85.

The severity of CKD has been related also to the severity of liver disease. Yasui *et al*[55] examined 174 Japanese patients with NAFLD and found a higher rate of CKD with NASH than with simple steatosis (21% *vs* 6%, *p* = 0.007). Another study evaluated 80 patients with biopsy-proven NASH and found that eGFR decreased with increasing degrees of hepatic fibrosis[56]. Musso *et al*[57] presented the most comprehensive evaluation of NAFLD/NASH and CKD in a meta-analysis, which included 63,902 patients and 33 studies; that study found both an independent association between NAFLD and CKD in both diabetic and non-diabetic patients, and higher prevalence and incidence of CKD with NASH than with simple steatosis.

CKD may affect all patients with NAFLD and NASH, but it is especially problematic for patients awaiting LT. Park *et al*[43] evaluated waitlisted patients and found higher serum creatinine values and prothrombin times in patients with NASH than in those with other causes of ESLD and the same MELD score; this observation was confirmed by Wong *et al*[13],who found a lower eGFR amongst waitlisted patients with NASH than amongst those with other causes of ESLD. The presence of renal dysfunction and CKD prior to LT is a risk factor for post-LT CKD and is associated with worse graft and patient survival[58-60]. Fussner *et al*[58] reported that NASH and female gender were independently associated with CKD at 1 year after LT. Houlihan *et al*[61] reported similarly higher rates of stage III CKD in patients with NASH than in those with liver disease of other causes (31.2% *vs* 8.3%, *p* < 0.001) at 2 years after LT; however, they found no difference in 1-year or 5-year patient or graft survival. Importantly, however, patients with NASH are more likely than those with ESLD from other etiologies to require renal replacement therapy prior to transplantation, which carries a 150% increased risk of mortality before transplantation[62,63].

Simultaneous liver and kidney transplantation (SLKT) is an option for patients with NASH cirrhosis and CKD. NASH is the fastest rising indication for SLKT in the United States, increasing from 6.3% of SLKT in 2002 to 19.2% in 2011[64]. In a comparison with patients undergoing SLKT for alcoholic cirrhosis, NASH, and HCV, Singal *et al*[65] found similar 5-year liver allograft survival but significantly worse renal allograft survival and a 1.5-fold increased risk of renal graft loss. Molnar *et al*[66] compared pre-LT eGFR and post-LT renal recovery in 4,088 NASH LT recipients from the United Network for Organ Sharing database. Over a median follow-up of 5 years, NASH patients with preserved renal function had a lower risk of death than did those with eGFR < 30 ml/min; however, similar rates of death and graft loss were seen for NASH patients with SLKT and as those with reduced renal function[66].

***Cardiovascular disease and NASH***

Increasing literature supports an increased risk of cardiovascular events in patients with NASH. Cardiovascular disease (CVD) is a leading cause of mortality in LT patients, accounting for 19%-42% of non-graft-related mortality[67,68]. In LT patients, CVD is associated with typical risk factors: diabetes, hypertension and renal dysfunction[67]. Additionally, recent research supports NAFLD and NASH as independent risk factors for the development of CVD[69,70].

The pathogenetic mechanisms for CVD in patients with NAFLD are multifactorial and incompletely understood. In addition to the typical risk factors—hyperlipidemia, hypertension and impaired glucose tolerance—characteristics unique to NAFLD, have been found independently associated with endothelial dysfunction[71-73]. Arterial stiffness may play a role and has also been associated with NAFLD[74-78]. Endothelial dysfunction is a separate but inter-related mechanism that is common with atherosclerosis and is regulated by multiple mechanisms[79]. As both a result and mediator of arterial changes, NAFLD has been associated with increased expression of biomarkers of endothelial dysfunction, such as sICAM-1 and plasminogen activator inhibitor-1 (PAI-1)[80,81]. PAI-1 is not just a marker of endothelial dysfunction, but is also prothrombotic and associated with increased risk of myocardial infarction[82,83]. Changes in cardiac function also are present in patients with NAFLD: Kim *et al*[78] showed that NAFLD was independently associated with left ventricular diastolic dysfunction. Insulin resistance is a primary contributor to cardiac dysfunction, being associated with myocyte growth, interstitial fibrosis, sodium retention and changes in sympathetic nervous system activation[84,85].

Unfortunately, much of the cardiac dysfunction in NAFLD is subclinical and difficult to diagnose. NAFLD has been associated with decreased myocardial perfusion reserve, which may make patients with NAFLD prone to subendocardial ischemia in the presence of hemodynamic compromise[86]. LT screening guidelines recommend that dobutamine stress echocardiography be performed, and, if abnormal, be followed with coronary angiography[87,88]. In a study of patients with NAFLD undergoing LT evaluation, 37% did not reach target heart rate during stress echocardiography[89]. Tests of cardiac function in NAFLD patients may not reveal the severity of disease: A meta-analysis of cardiac stress test results during LT evaluation revealed a pooled sensitivity of 21-28% and specificity of 82-91% for coronary artery disease[90]. Dobutamine stress echocardiography has poor predictive value for post-operative cardiovascular events, with a reported positive predictive value of 6.7% and negative predictive value of 83.5%[91]. Prolonged QT segment may be a marker for cardiac dysfunction in NAFLD, and changes in cardiac morphology may lead to the development of atrial fibrillation, which has been independently associated with NAFLD[92,93]. Importantly, atrial fibrillation is a risk factor for both intra-operative and post-operative cardiac events in LT[94].

 An early study by Kadayifci *et al*[95] reported an increased prevalence of coronary artery disease associated with NASH-related cirrhosis compared other causes of liver disease (21.6% *vs* 5%, *p* = 0.005 respectively). Similarly, Patel *et al*[96] found an increased risk of severe coronary artery stenosis, defined as stenosis > 70% on angiography, in patients with non-alcohol related ESLD. Carotid artery disease also is increased in patients with NASH[97]. Carotid intima-media thickness, a marker of atherosclerosis, is associated with increased risk for myocardial infarction, cerebrovascular accidents and peripheral vascular disease[98]. Two studies have found increased carotid intima-media thickness in patients with NAFLD[99,100].

An increased risk of CVD events with NAFLD before and after LT has been reported[101-105]. CVD has been found the reason for waitlist mortality more often in patients with NASH than in those with other kinds of ESLD[13], and Vanwagner *et al*[89] have reported that patients who underwent LT for NASH were more likely to die of a cardiovascular event within 1 year post-LT than were those who had LT for alcoholic cirrhosis (adjusted OR = 4.12, 95%CI: 1.91-8.90). The same group later reported a higher incidence of sudden cardiac death or acute heart failure in patients transplanted for NASH than in those transplanted for other causes of ESLD[106]. A systematic review and meta-analysis comparing patients with LT for NASH with those without NASH supported these findings, showing that the recipients who had NASH had higher rates of death due to CVD[107].

***Bariatric surgery and NASH***

Patients with NAFLD and obesity should pursue exercise and nutrition counseling. However, dieting, exercise, and behavioral therapy are poorly tolerated by those patients who have severe liver disease[108]. As obesity in patients with NASH cirrhosis might prohibit LT, bariatric surgery has been proposed as an option[109]. Weight loss surgery can reduce the burden of comorbidities in patients with NASH, resulting in weight loss and improvement in T2D, hypertension, and insulin resistance[110,111]. Bariatric surgery in this population should be sleeve gastrectomy rather than gastric banding or gastric bypass, as the latter procedures might make the anatomy difficult for LT. Sleeve gastrectomy results in excellent weight loss and additionally has the benefit of not being a malabsorptive procedure, which may otherwise impact absorption of immunosuppressive medications post-LT.

Optimal timing of bariatric surgery for patients with NASH has not been determined; various groups have reported successful outcomes when the surgery is performed prior to, concurrent with, or after LT[112]. Shimizu *et al*[113] performed bariatric surgery in 23 patients with cirrhosis (22 with Child’s A cirrhosis); 14 patients underwent laparoscopic roux-en-y gastric bypass and 8 underwent laparoscopic sleeve gastrectomy. Overall, mean weight loss was approximately 35 kg, diabetes resolved or improved in 87%, and hypertension resolved or improved in 69%. The rates of complication were similar between the 2 procedures (28.6% for bypass *vs* 37.5% for sleeve gastrectomy; *P* > 0.05). A case series from France of 109 patients with NASH who underwent bariatric surgery had similar improvement in BMI, but, more important, had improvement in features of NASH: less hepatocellular ballooning in 84.2% and reduction in lobular inflammation in 67.1%[114]. However, this study included mostly NASH patients without cirrhosis.

The presence of decompensated cirrhosis, however, may prohibit elective weight-loss surgery. For these patients, bariatric surgery at time of transplantation may be an option. Heimbach *et al*[115] published one of the first case series with this approach, on patients listed for LT with BMI > 35 kg/m2. Seven patients were unsuccessful in pre-LT weight loss and ultimately underwent simultaneous LT and sleeve gastrectomy, with a median MELD score of 32 and BMI at transplantation of 48 kg/m2. Post-LT, all 7 patients had resolution of diabetes and hypertension and achieved a BMI below 35 kg/m2. Only 1 patient had a complication related to the bariatric surgery procedure, a leak at the gastric staple line. Since this initial report, a few more small case series have been published with similar findings[116,117]. Zamora-Valdes *et al*[118] recently updated the long-term results from the initial study, reporting that patients who underwent combined transplantation and sleeve gastrectomy maintained weight loss and had a lower incidence of diabetes, hypertension, and hepatic steatosis at 3 years after LT than did those who had pre-LT weight loss without bariatric surgery. Bariatric surgery after transplantation remains an option for obese patients; however, this approach is more technically complicated because of adhesions and increased risk of immunosuppression-related complications[119-121].

***Other issues for LT in patients with NASH***

Over the past 5 years, the nutritional status of patients with ESLD has become increasingly recognized as an important factor in outcomes. Despite increased weight and BMI, many obese individuals are nutritionally depleted, with muscle wasting and fatty muscle infiltration, which can lead to sarcopenic obesity[122-124]. Carey *et al*[125] performed a multicenter study to better define sarcopenia in LT, finding that skeletal mass index was independently associated with waitlist mortality and identifying cutoffs to define sarcopenia (< 50 cm2/m2 for men and < 39 cm2/m2 for women). Carias *et al*[126] identified NASH as an independent predictor of sarcopenic obesity.

 Portal vein thrombosis (PVT) is a common complication of chronic liver disease and is a risk factor for graft loss in patients with cirrhosis[127-131]. Patients with NAFLD have been found at higher risk for venous thromboembolism, such as pulmonary embolus or deep vein thrombosis[132]. Patients with NASH cirrhosis are at increased risk also for pre-LT PVT[133]. Stine *et al*[134] reported that, amongst patients with NASH, those who are older than 60 years and have a BMI > 30 kg/m2, hypertension and diabetes, have an even higher risk of pre-LT PVT. Agbim *et al*[135] recently reported a 37% increased risk of graft loss and a 31% increased risk of death amongst patients who underwent LT for NASH cirrhosis with pre-LT PVT compared to those without PVT.

***Hepatocellular carcinoma with NASH***

In addition to cirrhosis, NASH is associated also with the development of hepatocellular carcinoma (HCC), with an estimated incidence of 2.6% per year[136]. NASH is the fastest rising cause of HCC in LT[137]. Data from two North American centers reveal that the proportion of LT for NASH-related HCC rose from 4% to 9% between 2004 and 2014[138]. In a separate evaluation of data on Scientific Registry of Transplant Recipients, Younossi *et al*[137] found that the proportion of LT candidates who had NASH-related HCC increased 7.7-fold between 2002 and 2016 (2.1% to 16.2%, *p* < 0.0001), while the proportions of HCC related to HCV and alcohol-related liver disease remained stable. Moreover, up to 38% of patients with NASH and NAFLD may develop HCC, even in the absence of cirrhosis[139,140]. Survival outcomes for patients transplanted with HCC due to NASH do not seem to differ from outcomes with transplantation for other causes of HCC[137].

 Like other comorbidities associated with NASH, insulin resistance, oxidative stress, and an inflammatory environment contribute to the development of HCC[141,142]. Furthermore, over 28000 somatic mutations have been identified in HCC[143]. Grohmann *et al*[144] have described an independent mechanism in which obesity contributes to development of HCC through activation of signal transducer and activators of transcription (STAT)-1 and STAT-3 signaling. Together, STAT-1 and STAT-3 create a pro-inflammatory environment and drive oncogenesis, respectively[145,146]. Undoubtedly, as obesity and NAFLD become more prevalent, more mechanisms contributing to the pathogenesis of NASH and HCC will be identified.

***NASH and the waitlist***

The combined effects of comorbidities yield a NASH population with complex systemic diseases. Unfortunately, this complexity compounds patients’ pre-transplant management. O’Leary *et al*[39] reported that NASH patients presenting for LT evaluation were more likely than others to be denied listing because of their comorbidities (72%). They also were more likely than patients with HCV to be removed from listing due to death or being “too ill” for transplantation (22% *vs* 16%, *p* = 0.006) and were less likely to receive a transplant (27% *vs* 46%, *p* < 0.001). Notably, when patients had MELD scores > 15, there was no difference in rate of transplantation, removal from waitlist, or progression of MELD score. Wong *et al*[13] found that NASH patients, compared with patients with alcoholic liver disease, had a lower rate of transplantation and increased mortality rate at 90-days from listing, but this discrepancy disappeared at 1-year after listing. More recently, in an examination of patients on the United Network for Organ Sharing waitlist from 2002 to 2016, Thuluvath *et al*[147] found that NASH patients also had a slightly higher unadjusted incidence of death or deterioration (29%) than did those with alcoholic liver disease (28%, *p* > 0.05); however, multivariable analysis showed that much of the difference could be attributed to factors associated with NASH (*i.e.*, older age and diabetes) and not to NASH independently. In light of these findings, no scoring system for pre-transplant mortality has been developed specifically for patients with NASH cirrhosis. To date, the MELD score is the most validated predictor of pre-transplant mortality regardless of etiology. Because of their older age, obesity, and multiple comorbidities, waitlisted NASH patients face numerous challenges: as waitlists for transplantation grow longer and the median MELD score at transplantation continues to rise, patients with NASH are at an ever-increasing risk for poor outcomes before reaching LT.

Older age and multiple comorbidities make patients with NASH who are undergoing LT evaluation a highly complex population. Proper pre-transplant evaluation includes a thorough assessment for diabetes, hypertension, renal dysfunction, and cardiovascular risk factors. Table 2 highlights our recommendations for each of these conditions. As with all patients undergoing LT, optimization of medical comorbidities is a necessity to achieve successful outcomes. We also recommend that obese patients undergo consultation with a nutritionist, an exercise therapist, and, if felt indicated, a bariatric surgeon. For obese patients with diabetes and/or hypertension who are not candidates for elective bariatric surgery, we recommend consideration of performing sleeve gastrectomy at the time of transplantation, but this consideration deserves scrutiny.

**Outcomes for LT in NASH Recipients**

***Overall survival***

Prognosis after LT for NASH is generally acceptable. A recent large-volume ten-year review from the Scientific Registry of Transplant Recipients (SRTR) found 1- and 3-year patient survival rates of 84% and 78% after LT for NASH compared with 87% and 78% for other indications[148]. No significant difference in 5-year graft loss or mortality was observed, suggesting that NASH itself is not an independent risk factor for mortality. In a meta-analysis of 16 studies on post-LT survival with NASH, most studies found no significant survival difference was found between NASH and other etiologies of liver disease[149]. Another study documented superior survival in NASH patients compared with LT recipients for other causes for transplantation, such as HCC, hepatitis C or alcoholic liver disease[150].

Mortality after LT for NASH patients is most common within the first few years after transplantation, with cardiovascular events being the primary cause[151-153]. Furthermore, the incidence of mortality from cardiovascular causes is 15% higher in NASH patients in the first year, but this difference is not sustained beyond the first postoperative year. Kennedy *et al*[154] reported long-term mortality in NASH patients after LT is primarily associated with malignancy (recurrent HCC and extrahepatic malignancy), cardiovascular complications, and infectious complications. A study by Bhati *et al*[155] also identified pre-transplant obesity (BMI > 30 kg/m2) and age of 60 years at the time of transplantation as predictors of post-LT mortality.

***Complications***

Despite lack of non-inferior survival data, the overall incidence of morbidity after LT appears to be higher for NASH recipients than others[156]. Metabolic syndrome develops in up to 50% of patients after LT for NASH; however, no significant difference between NASH and other etiologies of liver disease has been shown[149]. Nonetheless, it is postulated that LT recipients with NASH have a predisposing metabolic milieu that persists despite transplantation, and it may be further modulated by steroid-based immunosuppressive regimens. A strong correlation between metabolic syndrome and insulin resistance has been suggested, but this relationship has been poorly studied in the LT population.

Pre-existing diabetes is often cited as the leading cause of post-transplant morbidity, owing to impaired neutrophil function and increased susceptibility to infection with post-transplant hyperglycemia[156-158]. New onset diabetes after LT is associated with pre-transplant glucose intolerance, obesity, and family history, but the toxic effects of immunosuppressants on pancreatic B cells (particularly by calcineurin inhibitors) may play a role in its etiology[159,160]. Likewise, new onset obesity post-transplant occurs more often in NASH patients than in those with liver disease of other causes, and is closely linked to post-LT diabetes and *de novo* NASH[161,162]. In a study examining BMI change after LT, 22% of 320 recipients who were not obese pre-transplant became obese within 2 years after transplantation[163].

Several studies have reported a higher frequency of hypertension and dyslipidemia in post-LT patients with NASH than with other liver diseases and is often related to immunosuppression[164,165]. Among immunosuppressants, calcineurin-inhibitor based regimens were found closely linked with the development of these morbidities. Cyclosporine use was a risk factor for dyslipidemia and hypertension, whereas tacrolimus use was linked to post-LT diabetes by impairing insulin secretion, as discussed earlier[166,167].

In an examination of all post-operative morbidity, Dare *et al*[157] found similar rates of modified Clavien–Dindo grade 1 and 2 complications between NASH and non-NASH transplant recipients; however, NASH transplant recipients had increased rates of wound infections, bacteremia and pneumonia. Donor factors such as demographics, donation type (*e.g.,* donation after brain death or donation after circulatory death), BMI, cause of death, blood loss and transfusion requirement have not been found to be related to morbidity and mortality after transplantation amongst NASH recipients[168,169]. Reported early reoperation rates for bleeding or biliary complications are around 15%, and re-transplantation rates are under 10%[169,170].

***NASH recurrence and post-transplant de novo NASH***

The development of histologic NAFLD after LT has been well documented[171]. Metabolic syndrome after LT predisposes recipients to recurrent and/or *de novo* NAFLD and NASH[172]. The use of corticosteroids has also been implicated in the recurrence of NAFLD post-LT[173]. At 2 years post-LT, around 60%-80% of recipients develop NAFLD, with at least grade 2 steatosis or above (34%-66% by biopsy). More extensive liver disease, such as NASH with progressive fibrosis (METAVIR stage ≥ 2, defined as “more than septal formation”, including bridging fibrosis and cirrhosis), is rare however, occurring in only around 5% of recipients at 5 years post-LT[162,171]. In a review of LT in 227 patients with NASH-related or cryptogenic cirrhosis, the probability of developing histologic hepatic steatosis after LT was 8.2%, 24.9% and 32.9% at 1, 5 and 10 years, respectively, but with only 6% developing recurrent NASH during the study period[174].

Few studies have shown evidence of fibrosis beyond simple steatosis and early-stage NAFLD developing in the recipient allograft post-LT for NASH. In a recent single-center study, 88.2% of the 34 NASH recipients who had a liver biopsy post-LT had recurrent NAFLD, with 41.2% having evidence of recurrent NASH (median time from transplant of 47 mo)[155]. Subgroup analysis demonstrated that patients with NAFLD/NASH had a significantly higher rate of impaired fasting glucose and hypertriglyceridemia than did recipients without recurrent NAFLD. In the same study, 87.5% of 56 recipients being evaluated with transient elastography had NAFLD (median time 75 mo). In this cohort, 81% of those with NAFLD recurrence had diabetes, compared with 51% of those without recurrence.

Histologic NASH has been shown to develop in the transplanted livers of NASH patients and has been documented as early as 6 mo post-LT[175]. A major risk factor for the development of NASH is metabolic syndrome; one large seriesfound NASH in 34% of recipient livers in patients who had metabolic syndrome compared with 13% in recipient livers of patients who did not exhibit metabolic syndrome[120]. In the same study, hypertension and diabetes requiring insulin use were found to be significant risk factors for NASH recurrence—32% of hypertensive LT recipients developed NASH recurrence as opposed to 12% of those without hypertension; 37% of insulin users developed recurrence compared to 6% of non-users[120]. Notably, the mean time from transplantation to documented NASH recurrence in this study was 18.2 mo[120]. A separate study showed of NASH recipients showed 11% of allografts had progression from steatosis to steatohepatitis on serial biopsies post-LT with cumulative steroid exposure as a significant contributing factor to this progression[173].

More recently, the unique entities of *de novo* NAFLD and NASH developing in transplanted livers have been recognized. A retrospective series of 68 LT recipients (84% transplanted for hepatitis C) reported development of *de novo* NAFLD in 18%, and 9% developed *de novo* NASH after transplantation[176]. Development of *de novo* NAFLD/NASH could not be attributed to steatosis in the donor liver. Interestingly, a 10% increase in recipient BMI after LT correlated with a 35% increase in *de novo* NAFLD on biopsy. This study also found no significant effect of immunosuppressive regimens on the development of NAFLD. Conversely, a single-center retrospective review of 170 patients found that higher steroid dosage after LT contributed to the development of *de novo* metabolic syndrome in 33% of the study population, 50% of whom had *de novo* NAFLD within 1 year[177].

The most common risk factors for post-LT *de novo* NASH are metabolic syndrome, PNPLA3 genotype, alcoholic cirrhosis, and the use of immunosuppressive agents, including tacrolimus and steroids[153,162,178-180]. *De novo* NASH is most commonly recognized around 6 mo post-LT[178,179]. Furthermore, the incidence of *de novo* NASH has been shown to increase from 30% at 1 year to 47% at 10 years[180]. Importantly, no survival differences were found in patients with *de novo* NASH after LT who had more advanced fibrosis (F3 or F4 on transient elastography) compared to those with minimal or no fibrosis[153,178,180].

There are little data on re-transplantation for recurrent or *de novo* NASH after LT. One single-center study reported 30% (*n* = 6) of recipients with NASH recurrence underwent re-transplantation—three patients had graft failure from recurrence, two had hepatic artery thrombosis and one had concomitant autoimmune hepatitis[120].

***Management recommendations***

Management guidelines for post-LT patients with NASH are the same as those for non-transplant NASH patients, with emphasis on diet and exercise. Considering the propensity for NASH patients to develop metabolic syndrome after LT, careful attention should be placed on weight loss, strict glucose control and exercise[181]. Management of obesity and hyperglycemia is crucial in the pre-transplant phase, as postoperative weight gain and metabolic complications are exacerbated by debility and immunosuppression[152]. Considering the prevalence and mortality risk from cardiovascular complications post-LT for NASH, patients with cardiac comorbidities and risk factors should be diligently screened and managed in the pre-transplant phase[157].

**Conclusion**

NAFLD/NASH cirrhosis is an increasingly frequent indication for liver transplantation. The association of NAFLD/NASH with metabolic syndrome, cardiovascular disease and chronic kidney disease complicate the pre-and post-LT course and management. Physicians should appreciate the need for early optimization of transplant candidates to improve both pre- and post-transplantation survival. Multi-disciplinary teams which include dieticians, bariatric surgeons, endocrinologist, and other specialists could be important in the management of the unique problems facing this patient population.

**References**

1 **Younossi Z**, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 11-20 [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]

2 **Loomba R**, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 686-690 [PMID: 24042449 DOI: 10.1038/nrgastro.2013.171]

3 **Cohen JC**, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; **332**: 1519-1523 [PMID: 21700865 DOI: 10.1126/science.1204265]

4 **Kwong A**, Kim WR, Mannalithara A, Heo NY, Udompap P, Kim D. Decreasing mortality and disease severity in hepatitis C patients awaiting liver transplantation in the United States. *Liver Transpl* 2018; **24**: 735-743 [PMID: 29125676 DOI: 10.1002/lt.24973]

5 **Gadiparthi C**, Cholankeril G, Perumpail BJ, Yoo ER, Satapathy SK, Nair S, Ahmed A. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. *World J Gastroenterol* 2018; **24**: 315-322 [PMID: 29391754 DOI: 10.3748/wjg.v24.i3.315]

6 **Wong RJ**, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* 2014; **59**: 2188-2195 [PMID: 24375711 DOI: 10.1002/hep.26986]

7 **Noureddin M**, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, Setiawan VW, Tran T, Ayoub WS, Lu SC, Klein AS, Sundaram V, Nissen NN. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. *Am J Gastroenterol* 2018; **113**: 1649-1659 [PMID: 29880964 DOI: 10.1038/s41395-018-0088-6]

8 **Kemmer N**, Neff GW, Franco E, Osman-Mohammed H, Leone J, Parkinson E, Cece E, Alsina A. Nonalcoholic fatty liver disease epidemic and its implications for liver transplantation. *Transplantation* 2013; **96**: 860-862 [PMID: 24247899 DOI: 10.1097/01.TP.0000436723.59879.01]

9 **Marchesini G**, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923 [PMID: 12668987 DOI: 10.1053/jhep.2003.50161]

10 **Ballestri S**, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, Roverato A, Guaraldi G, Lonardo A. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; **31**: 936-944 [PMID: 26667191 DOI: 10.1111/jgh.13264]

11 **Ryoo JH**, Suh YJ, Shin HC, Cho YK, Choi JM, Park SK. Clinical association between non-alcoholic fatty liver disease and the development of hypertension. *J Gastroenterol Hepatol* 2014; **29**: 1926-1931 [PMID: 24910023 DOI: 10.1111/jgh.12643]

12 **Sung KC**, Wild SH, Byrne CD. Development of new fatty liver, or resolution of existing fatty liver, over five years of follow-up, and risk of incident hypertension. *J Hepatol* 2014; **60**: 1040-1045 [PMID: 24445219 DOI: 10.1016/j.jhep.2014.01.009]

13 **Wong RJ**, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; **148**: 547-555 [PMID: 25461851 DOI: 10.1053/j.gastro.2014.11.039]

14 **Su F**, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, Reyes JD, Ioannou GN. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. *Gastroenterology* 2016; **150**: 441-53.e6; quiz e16 [PMID: 26522262 DOI: 10.1053/j.gastro.2015.10.043]

15 **Parikh ND**, Marrero WJ, Wang J, Steuer J, Tapper EB, Konerman M, Singal AG, Hutton DW, Byon E, Lavieri MS. Projected increase in obesity and non-alcoholic-steatohepatitis-related liver transplantation waitlist additions in the United States. *Hepatology* 2019; **70**: 487-495 [PMID: 28833326 DOI: 10.1002/hep.29473]

16 **Goldberg D**, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. *Gastroenterology* 2017; **152**: 1090-1099.e1 [PMID: 28088461 DOI: 10.1053/j.gastro.2017.01.003]

17 **Belli LS**, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, Morelli C, Donato F, Volpes R, Pageaux GP, Coilly A, Fagiuoli S, Amaddeo G, Perricone G, Vinaixa C, Berlakovich G, Facchetti R, Polak W, Muiesan P, Duvoux C; European Liver and Intestine Association (ELITA). Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *J Hepatol* 2016; **65**: 524-531 [PMID: 27212241 DOI: 10.1016/j.jhep.2016.05.010]

18 **Flegal KM**, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA* 2016; **315**: 2284-2291 [PMID: 27272580 DOI: 10.1001/jama.2016.6458]

19 **Barone M**, Viggiani MT, Avolio AW, Iannone A, Rendina M, Di Leo A. Obesity as predictor of postoperative outcomes in liver transplant candidates: Review of the literature and future perspectives. *Dig Liver Dis* 2017; **49**: 957-966 [PMID: 28801180 DOI: 10.1016/j.dld.2017.07.004]

20 **Nair S**, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002; **35**: 105-109 [PMID: 11786965 DOI: 10.1053/jhep.2002.30318]

21 **Leonard J**, Heimbach JK, Malinchoc M, Watt K, Charlton M. The impact of obesity on long-term outcomes in liver transplant recipients-results of the NIDDK liver transplant database. *Am J Transplant* 2008; **8**: 667-672 [PMID: 18294163 DOI: 10.1111/j.1600-6143.2007.02100.x]

22 **Hakeem AR**, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA, Ahmad N, Hidalgo EL, Prasad KR, Menon KV. Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. *Liver Transpl* 2013; **19**: 551-562 [PMID: 23408499 DOI: 10.1002/lt.23618]

23 **Singhal A**, Wilson GC, Wima K, Quillin RC, Cuffy M, Anwar N, Kaiser TE, Paterno F, Diwan TS, Woodle ES, Abbott DE, Shah SA. Impact of recipient morbid obesity on outcomes after liver transplantation. *Transpl Int* 2015; **28**: 148-155 [PMID: 25363625 DOI: 10.1111/tri.12483]

24 **Segev DL**, Thompson RE, Locke JE, Simpkins CE, Thuluvath PJ, Montgomery RA, Maley WR. Prolonged waiting times for liver transplantation in obese patients. *Ann Surg* 2008; **248**: 863-870 [PMID: 18948816 DOI: 10.1097/SLA.0b013e31818a01ef]

25 **Younossi ZM**, Stepanova M, Saab S, Kalwaney S, Clement S, Henry L, Frost S, Hunt S. The impact of type 2 diabetes and obesity on the long-term outcomes of more than 85 000 liver transplant recipients in the US. *Aliment Pharmacol Ther* 2014; **40**: 686-694 [PMID: 25040315 DOI: 10.1111/apt.12881]

26 **Conzen KD**, Vachharajani N, Collins KM, Anderson CD, Lin Y, Wellen JR, Shenoy S, Lowell JA, Doyle MB, Chapman WC. Morbid obesity in liver transplant recipients adversely affects longterm graft and patient survival in a single-institution analysis. *HPB (Oxford)* 2015; **17**: 251-257 [PMID: 25322849 DOI: 10.1111/hpb.12340]

27 **Tsochatzis E**, Coilly A, Nadalin S, Levistky J, Tokat Y, Ghobrial M, Klinck J, Berenguer M. International Liver Transplantation Consensus Statement on End-stage Liver Disease Due to Nonalcoholic Steatohepatitis and Liver Transplantation. *Transplantation* 2019; **103**: 45-56 [PMID: 30153225 DOI: 10.1097/TP.0000000000002433]

28 **Grundy SM**. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab* 2004; **89**: 2595-2600 [PMID: 15181029 DOI: 10.1210/jc.2004-0372]

29 **Uyeda K**, Repa JJ. Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. *Cell Metab* 2006; **4**: 107-110 [PMID: 16890538 DOI: 10.1016/j.cmet.2006.06.008]

30 **Jornayvaz FR**, Shulman GI. Diacylglycerol activation of protein kinase Cε and hepatic insulin resistance. *Cell Metab* 2012; **15**: 574-584 [PMID: 22560210 DOI: 10.1016/j.cmet.2012.03.005]

31 **Popov VB**, Lim JK. Treatment of Nonalcoholic Fatty Liver Disease: The Role of Medical, Surgical, and Endoscopic Weight Loss. *J Clin Transl Hepatol* 2015; **3**: 230-238 [PMID: 26623270 DOI: 10.14218/JCTH.2015.00019]

32 **Conlon BA**, Beasley JM, Aebersold K, Jhangiani SS, Wylie-Rosett J. Nutritional management of insulin resistance in nonalcoholic fatty liver disease (NAFLD). *Nutrients* 2013; **5**: 4093-4114 [PMID: 24152749 DOI: 10.3390/nu5104093]

33 **Brunt EM**, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, Bugianesi E, Sirlin CB, Neuschwander-Tetri BA, Rinella ME. Nonalcoholic fatty liver disease. *Nat Rev Dis Primers* 2015; **1**: 15080 [PMID: 27188459 DOI: 10.1038/nrdp.2015.80]

34 **Duseja A**, Chawla YK. Obesity and NAFLD: the role of bacteria and microbiota. *Clin Liver Dis* 2014; **18**: 59-71 [PMID: 24274865 DOI: 10.1016/j.cld.2013.09.002]

35 **Tilg H**, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology* 2010; **52**: 1836-1846 [PMID: 21038418 DOI: 10.1002/hep.24001]

36 **Miura K**, Seki E, Ohnishi H, Brenner DA. Role of toll-like receptors and their downstream molecules in the development of nonalcoholic Fatty liver disease. *Gastroenterol Res Pract* 2010; **2010**: 362847 [PMID: 21274430 DOI: 10.1155/2010/362847]

37 **Armstrong MJ**, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 1174-1197 [PMID: 24002776 DOI: 10.1002/hep.26717]

38 **Anstee QM**, Day CP. The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on PNPLA3 and TM6SF2. *Semin Liver Dis* 2015; **35**: 270-290 [PMID: 26378644 DOI: 10.1055/s-0035-1562947]

39 **O'Leary JG**, Landaverde C, Jennings L, Goldstein RM, Davis GL. Patients with NASH and cryptogenic cirrhosis are less likely than those with hepatitis C to receive liver transplants. *Clin Gastroenterol Hepatol* 2011; **9**: 700-704.e1 [PMID: 21570483 DOI: 10.1016/j.cgh.2011.04.007]

40 **Hoehn RS**, Singhal A, Wima K, Sutton JM, Paterno F, Steve Woodle E, Hohmann S, Abbott DE, Shah SA. Effect of pretransplant diabetes on short-term outcomes after liver transplantation: a national cohort study. *Liver Int* 2015; **35**: 1902-1909 [PMID: 25533420 DOI: 10.1111/liv.12770]

41 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

42 **Trail KC**, Stratta RJ, Larsen JL, Ruby EI, Patil KD, Langnas AN, Donovan JP, Sorrell MF, Zetterman RK, Pillen TJ. Results of liver transplantation in diabetic recipients. *Surgery* 1993; **114**: 650-6; discussion 656-8 [PMID: 8211678]

43 **Park CW**, Tsai NT, Wong LL. Implications of worse renal dysfunction and medical comorbidities in patients with NASH undergoing liver transplant evaluation: impact on MELD and more. *Clin Transplant* 2011; **25**: E606-E611 [PMID: 21958082 DOI: 10.1111/j.1399-0012.2011.01497.x]

44 **Aneni EC**, Oni ET, Martin SS, Blaha MJ, Agatston AS, Feldman T, Veledar E, Conçeicao RD, Carvalho JA, Santos RD, Nasir K. Blood pressure is associated with the presence and severity of nonalcoholic fatty liver disease across the spectrum of cardiometabolic risk. *J Hypertens* 2015; **33**: 1207-1214 [PMID: 25693058 DOI: 10.1097/HJH.0000000000000532]

45 **Vasunta RL**, Kesäniemi YA, Ylitalo AS, Ukkola OH. High ambulatory blood pressure values associated with non-alcoholic fatty liver in middle-aged adults. *J Hypertens* 2012; **30**: 2015-2019 [PMID: 22940679 DOI: 10.1097/HJH.0b013e3283576faf]

46 **Fargion S**, Porzio M, Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. *World J Gastroenterol* 2014; **20**: 13306-13324 [PMID: 25309067 DOI: 10.3748/wjg.v20.i37.13306]

47 **Targher G**, Chonchol MB, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis* 2014; **64**: 638-652 [PMID: 25085644 DOI: 10.1053/j.ajkd.2014.05.019]

48 **Kurella M**, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005; **16**: 2134-2140 [PMID: 15901764 DOI: 10.1681/ASN.2005010106]

49 **Weiner DE**, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The relationship between nontraditional risk factors and outcomes in individuals with stage 3 to 4 CKD. *Am J Kidney Dis* 2008; **51**: 212-223 [PMID: 18215699 DOI: 10.1053/j.ajkd.2007.10.035]

50 **Kendrick J**, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. *Nat Clin Pract Nephrol* 2008; **4**: 672-681 [PMID: 18825155 DOI: 10.1038/ncpneph0954]

51 **Kronenberg F**. Emerging risk factors and markers of chronic kidney disease progression. *Nat Rev Nephrol* 2009; **5**: 677-689 [PMID: 19935815 DOI: 10.1038/nrneph.2009.173]

52 **Targher G**, Chonchol M, Bertolini L, Rodella S, Zenari L, Lippi G, Franchini M, Zoppini G, Muggeo M. Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease. *J Am Soc Nephrol* 2008; **19**: 1564-1570 [PMID: 18385424 DOI: 10.1681/ASN.2007101155]

53 **Chang Y**, Ryu S, Sung E, Woo HY, Oh E, Cha K, Jung E, Kim WS. Nonalcoholic fatty liver disease predicts chronic kidney disease in nonhypertensive and nondiabetic Korean men. *Metabolism* 2008; **57**: 569-576 [PMID: 18328362 DOI: 10.1016/j.metabol.2007.11.022]

54 **Targher G**, Mantovani A, Pichiri I, Mingolla L, Cavalieri V, Mantovani W, Pancheri S, Trombetta M, Zoppini G, Chonchol M, Byrne CD, Bonora E. Nonalcoholic fatty liver disease is independently associated with an increased incidence of chronic kidney disease in patients with type 1 diabetes. *Diabetes Care* 2014; **37**: 1729-1736 [PMID: 24696459 DOI: 10.2337/dc13-2704]

55 **Yasui K**, Sumida Y, Mori Y, Mitsuyoshi H, Minami M, Itoh Y, Kanemasa K, Matsubara H, Okanoue T, Yoshikawa T. Nonalcoholic steatohepatitis and increased risk of chronic kidney disease. *Metabolism* 2011; **60**: 735-739 [PMID: 20817213 DOI: 10.1016/j.metabol.2010.07.022]

56 **Targher G**, Bertolini L, Rodella S, Lippi G, Zoppini G, Chonchol M. Relationship between kidney function and liver histology in subjects with nonalcoholic steatohepatitis. *Clin J Am Soc Nephrol* 2010; **5**: 2166-2171 [PMID: 20724519 DOI: 10.2215/CJN.05050610]

57 **Musso G**, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J, Barrera F, Hafliðadóttir S, Björnsson ES, Armstrong MJ, Hopkins LJ, Gao X, Francque S, Verrijken A, Yilmaz Y, Lindor KD, Charlton M, Haring R, Lerch MM, Rettig R, Völzke H, Ryu S, Li G, Wong LL, Machado M, Cortez-Pinto H, Yasui K, Cassader M. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; **11**: e1001680 [PMID: 25050550 DOI: 10.1371/journal.pmed.1001680]

58 **Fussner LA**, Charlton MR, Heimbach JK, Fan C, Dierkhising R, Coss E, Watt KD. The impact of gender and NASH on chronic kidney disease before and after liver transplantation. *Liver Int* 2014; **34**: 1259-1266 [PMID: 24262002 DOI: 10.1111/liv.12381]

59 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427 [PMID: 20486907 DOI: 10.1111/j.1600-6143.2010.03126.x]

60 **Ramachandran J**, Juneja R, John L, Dutta AK, Chen JW, Woodman RJ, Wigg AJ. Chronic kidney disease following liver transplantation: a South Australian experience. *Transplant Proc* 2010; **42**: 3644-3646 [PMID: 21094832 DOI: 10.1016/j.transproceed.2010.06.022]

61 **Houlihan DD**, Armstrong MJ, Davidov Y, Hodson J, Nightingale P, Rowe IA, Paris S, Gunson BK, Bramhall SB, Mutimer DJ, Neuberger JM, Newsome PN. Renal function in patients undergoing transplantation for nonalcoholic steatohepatitis cirrhosis: time to reconsider immunosuppression regimens? *Liver Transpl* 2011; **17**: 1292-1298 [PMID: 21761549 DOI: 10.1002/lt.22382]

62 **VanWagner LB**, Lapin B, Skaro AI, Lloyd-Jones DM, Rinella ME. Impact of renal impairment on cardiovascular disease mortality after liver transplantation for nonalcoholic steatohepatitis cirrhosis. *Liver Int* 2015; **35**: 2575-2583 [PMID: 25977117 DOI: 10.1111/liv.12872]

63 **Agopian VG**, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, Zarrinpar A, Petrowsky H, Farmer D, Yersiz H, Xia V, Hiatt JR, Busuttil RW. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. *Ann Surg* 2012; **256**: 624-633 [PMID: 22964732 DOI: 10.1097/SLA.0b013e31826b4b7e]

64 **Singal AK**, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. *Transplantation* 2014; **98**: 216-221 [PMID: 24621538 DOI: 10.1097/TP.0000000000000048]

65 **Singal AK**, Hasanin M, Kaif M, Wiesner R, Kuo YF. Nonalcoholic Steatohepatitis is the Most Rapidly Growing Indication for Simultaneous Liver Kidney Transplantation in the United States. *Transplantation* 2016; **100**: 607-612 [PMID: 26479282 DOI: 10.1097/TP.0000000000000945]

66 **Molnar MZ**, Joglekar K, Jiang Y, Cholankeril G, Abdul MKM, Kedia S, Gonzalez HC, Ahmed A, Singal A, Bhamidimarri KR, Aithal GP, Duseja A, Wong VW, Gulnare A, Puri P, Nair S, Eason JD, Satapathy SK; Global NAFLD Consortium. Association of Pretransplant Renal Function With Liver Graft and Patient Survival After Liver Transplantation in Patients With Nonalcoholic Steatohepatitis. *Liver Transpl* 2019; **25**: 399-410 [PMID: 30369023 DOI: 10.1002/lt.25367]

67 **Laryea M**, Watt KD, Molinari M, Walsh MJ, McAlister VC, Marotta PJ, Nashan B, Peltekian KM. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl* 2007; **13**: 1109-1114 [PMID: 17663411 DOI: 10.1002/lt.21126]

68 **Vogt DP**, Henderson JM, Carey WD, Barnes D. The long-term survival and causes of death in patients who survive at least 1 year after liver transplantation. *Surgery* 2002; **132**: 775-80; discussion 780 [PMID: 12407365 DOI: 10.1067/msy.2002.128343]

69 **Stepanova M**, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol* 2012; **10**: 646-650 [PMID: 22245962 DOI: 10.1016/j.cgh.2011.12.039]

70 **Lu H**, Liu H, Hu F, Zou L, Luo S, Sun L. Independent Association between Nonalcoholic Fatty Liver Disease and Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Int J Endocrinol* 2013; **2013**: 124958 [PMID: 23690766 DOI: 10.1155/2013/124958]

71 **Pastori D**, Loffredo L, Perri L, Baratta F, Scardella L, Polimeni L, Pani A, Brancorsini M, Albanese F, Catasca E, Del Ben M, Violi F, Angelico F. Relation of nonalcoholic fatty liver disease and Framingham Risk Score to flow-mediated dilation in patients with cardiometabolic risk factors. *Am J Cardiol* 2015; **115**: 1402-1406 [PMID: 25776455 DOI: 10.1016/j.amjcard.2015.02.032]

72 **Pugh CJ**, Spring VS, Kemp GJ, Richardson P, Shojaee-Moradie F, Umpleby AM, Green DJ, Cable NT, Jones H, Cuthbertson DJ. Exercise training reverses endothelial dysfunction in nonalcoholic fatty liver disease. *Am J Physiol Heart Circ Physiol* 2014; **307**: H1298-H1306 [PMID: 25193471 DOI: 10.1152/ajpheart.00306.2014]

73 **Thakur ML**, Sharma S, Kumar A, Bhatt SP, Luthra K, Guleria R, Pandey RM, Vikram NK. Nonalcoholic fatty liver disease is associated with subclinical atherosclerosis independent of obesity and metabolic syndrome in Asian Indians. *Atherosclerosis* 2012; **223**: 507-511 [PMID: 22748277 DOI: 10.1016/j.atherosclerosis.2012.06.005]

74 **Fotbolcu H**, Yakar T, Duman D, Karaahmet T, Tigen K, Cevik C, Kurtoglu U, Dindar I. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. *Cardiol J* 2010; **17**: 457-463 [PMID: 20865675 DOI: 10.1097/CRD.0b013e3181ebdb2f]

75 **Sunbul M**, Agirbasli M, Durmus E, Kivrak T, Akin H, Aydin Y, Ergelen R, Yilmaz Y. Arterial stiffness in patients with non-alcoholic fatty liver disease is related to fibrosis stage and epicardial adipose tissue thickness. *Atherosclerosis* 2014; **237**: 490-493 [PMID: 25463079 DOI: 10.1016/j.atherosclerosis.2014.10.004]

76 **Salvi P**, Ruffini R, Agnoletti D, Magnani E, Pagliarani G, Comandini G, Praticò A, Borghi C, Benetos A, Pazzi P. Increased arterial stiffness in nonalcoholic fatty liver disease: the Cardio-GOOSE study. *J Hypertens* 2010; **28**: 1699-1707 [PMID: 20467324 DOI: 10.1097/HJH.0b013e32833a7de6]

77 **Vlachopoulos C**, Xaplanteris P, Vyssoulis G, Bratsas A, Baou K, Tzamou V, Aznaouridis K, Dima I, Lazaros G, Stefanadis C. Association of serum uric acid level with aortic stiffness and arterial wave reflections in newly diagnosed, never-treated hypertension. *Am J Hypertens* 2011; **24**: 33-39 [PMID: 20508625 DOI: 10.1038/ajh.2010.111]

78 **Kim BJ**, Kim NH, Kim BS, Kang JH. The association between nonalcoholic fatty liver disease, metabolic syndrome and arterial stiffness in nondiabetic, nonhypertensive individuals. *Cardiology* 2012; **123**: 54-61 [PMID: 22986520 DOI: 10.1159/000341248]

79 **Tilg H**, Moschen AR. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. *Trends Endocrinol Metab* 2008; **19**: 371-379 [PMID: 18929493 DOI: 10.1016/j.tem.2008.08.005]

80 **Sookoian S**, Castaño GO, Burgueño AL, Rosselli MS, Gianotti TF, Mallardi P, Martino JS, Pirola CJ. Circulating levels and hepatic expression of molecular mediators of atherosclerosis in nonalcoholic fatty liver disease. *Atherosclerosis* 2010; **209**: 585-591 [PMID: 19896127 DOI: 10.1016/j.atherosclerosis.2009.10.011]

81 **Verrijken A**, Francque S, Mertens I, Prawitt J, Caron S, Hubens G, Van Marck E, Staels B, Michielsen P, Van Gaal L. Prothrombotic factors in histologically proven nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* 2014; **59**: 121-129 [PMID: 24375485 DOI: 10.1002/hep.26510]

82 **Mertens I**, Van Gaal LF. Obesity, haemostasis and the fibrinolytic system. *Obes Rev* 2002; **3**: 85-101 [PMID: 12120424 DOI: 10.1046/j.1467-789x.2002.00056.x]

83 **Thögersen AM**, Jansson JH, Boman K, Nilsson TK, Weinehall L, Huhtasaari F, Hallmans G. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation* 1998; **98**: 2241-2247 [PMID: 9826309 DOI: 10.1161/01.cir.98.21.2241]

84 **Wong CY**, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004; **110**: 3081-3087 [PMID: 15520317 DOI: 10.1161/01.CIR.0000147184.13872.0F]

85 **Di Bello V**, Santini F, Di Cori A, Pucci A, Palagi C, Delle Donne MG, Giannetti M, Talini E, Nardi C, Pedrizzetti G, Fierabracci P, Vitti P, Pinchera A, Balbarini A. Relationship between preclinical abnormalities of global and regional left ventricular function and insulin resistance in severe obesity: a Color Doppler Imaging Study. *Int J Obes (Lond)* 2006; **30**: 948-956 [PMID: 16446750 DOI: 10.1038/sj.ijo.0803206]

86 **Nakamori S**, Onishi K, Nakajima H, Yoon YE, Nagata M, Kurita T, Yamada T, Kitagawa K, Dohi K, Nakamura M, Sakuma H, Ito M. Impaired myocardial perfusion reserve in patients with fatty liver disease assessed by quantitative myocardial perfusion magnetic resonance imaging. *Circ J* 2012; **76**: 2234-2240 [PMID: 22664721 DOI: 10.1253/circj.cj-11-1487]

87 **Sehgal L**, Srivastava P, Pandey CK, Jha A. Preoperative cardiovascular investigations in liver transplant candidate: An update. *Indian J Anaesth* 2016; **60**: 12-18 [PMID: 26962249 DOI: 10.4103/0019-5049.174870]

88 **Zaky A**, Bendjelid K. Appraising cardiac dysfunction in liver transplantation: an ongoing challenge. *Liver Int* 2015; **35**: 12-29 [PMID: 24797833 DOI: 10.1111/liv.12582]

89 **Vanwagner LB**, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology* 2012; **56**: 1741-1750 [PMID: 22611040 DOI: 10.1002/hep.25855]

90 **Soldera J**, Camazzola F, Rodríguez S, Brandão A. Cardiac stress testing and coronary artery disease in liver transplantation candidates: Meta-analysis. *World J Hepatol* 2018; **10**: 877-886 [PMID: 30533188 DOI: 10.4254/wjh.v10.i11.877]

91 **Agrawal A**, Jain D, Dias A, Jorge V, Figueredo VM. Real World Utility of Dobutamine Stress Echocardiography in Predicting Perioperative Cardiovascular Morbidity and Mortality after Orthotopic Liver Transplantation. *Korean Circ J* 2018; **48**: 828-835 [PMID: 30088354 DOI: 10.4070/kcj.2017.0350]

92 **Targher G**, Valbusa F, Bonapace S, Bertolini L, Zenari L, Rodella S, Zoppini G, Mantovani W, Barbieri E, Byrne CD. Non-alcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes. *PLoS One* 2013; **8**: e57183 [PMID: 23451184 DOI: 10.1371/journal.pone.0057183]

93 **Käräjämäki AJ**, Pätsi OP, Savolainen M, Kesäniemi YA, Huikuri H, Ukkola O. Non-Alcoholic Fatty Liver Disease as a Predictor of Atrial Fibrillation in Middle-Aged Population (OPERA Study). *PLoS One* 2015; **10**: e0142937 [PMID: 26571029 DOI: 10.1371/journal.pone.0142937]

94 **Bargehr J**, Trejo-Gutierrez JF, Patel T, Rosser B, Aranda-Michel J, Yataco ML, Taner CB. Preexisting atrial fibrillation and cardiac complications after liver transplantation. *Liver Transpl* 2015; **21**: 314-320 [PMID: 25488693 DOI: 10.1002/lt.24060]

95 **Kadayifci A**, Tan V, Ursell PC, Merriman RB, Bass NM. Clinical and pathologic risk factors for atherosclerosis in cirrhosis: a comparison between NASH-related cirrhosis and cirrhosis due to other aetiologies. *J Hepatol* 2008; **49**: 595-599 [PMID: 18662837 DOI: 10.1016/j.jhep.2008.05.024]

96 **Patel S**, Kiefer TL, Ahmed A, Ali ZA, Tremmel JA, Lee DP, Yeung AC, Fearon WF. Comparison of the frequency of coronary artery disease in alcohol-related versus non-alcohol-related endstage liver disease. *Am J Cardiol* 2011; **108**: 1552-1555 [PMID: 21890080 DOI: 10.1016/j.amjcard.2011.07.013]

97 **Pais R**, Giral P, Khan JF, Rosenbaum D, Housset C, Poynard T, Ratziu V; LIDO Study Group. Fatty liver is an independent predictor of early carotid atherosclerosis. *J Hepatol* 2016; **65**: 95-102 [PMID: 27129836 DOI: 10.1016/j.jhep.2016.02.023]

98 **Belcaro G**, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L, Barsotti A. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. *Arterioscler Thromb Vasc Biol* 1996; **16**: 851-856 [PMID: 8673559 DOI: 10.1161/01.atv.16.7.851]

99 **Brea A**, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1045-1050 [PMID: 15731489 DOI: 10.1161/01.ATV.0000160613.57985.18]

100 **Fracanzani AL**, Burdick L, Raselli S, Pedotti P, Grigore L, Santorelli G, Valenti L, Maraschi A, Catapano A, Fargion S. Carotid artery intima-media thickness in nonalcoholic fatty liver disease. *Am J Med* 2008; **121**: 72-78 [PMID: 18187076 DOI: 10.1016/j.amjmed.2007.08.041]

101 **Moon SH**, Noh TS, Cho YS, Hong SP, Hyun SH, Choi JY, Kim BT, Lee KH. Association between nonalcoholic fatty liver disease and carotid artery inflammation evaluated by 18F-fluorodeoxyglucose positron emission tomography. *Angiology* 2015; **66**: 472-480 [PMID: 24904182 DOI: 10.1177/0003319714537872]

102 **Ekstedt M**, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; **61**: 1547-1554 [PMID: 25125077 DOI: 10.1002/hep.27368]

103 **Emre A**, Terzi S, Celiker E, Sahin S, Yazıcı S, Erdem A, Ceylan US, Asik M, Yesilcimen K. Impact of Nonalcoholic Fatty Liver Disease on Myocardial Perfusion in Nondiabetic Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2015; **116**: 1810-1814 [PMID: 26506122 DOI: 10.1016/j.amjcard.2015.09.021]

104 **Zeb I**, Li D, Budoff MJ, Katz R, Lloyd-Jones D, Agatston A, Blumenthal RS, Blaha MJ, Blankstein R, Carr J, Nasir K. Nonalcoholic Fatty Liver Disease and Incident Cardiac Events: The Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2016; **67**: 1965-1966 [PMID: 27102512 DOI: 10.1016/j.jacc.2016.01.070]

105 **Fracanzani AL**, Tiraboschi S, Pisano G, Consonni D, Baragetti A, Bertelli C, Norata D, Valenti L, Grigore L, Porzio M, Catapano A, Fargion S. Progression of carotid vascular damage and cardiovascular events in non-alcoholic fatty liver disease patients compared to the general population during 10 years of follow-up. *Atherosclerosis* 2016; **246**: 208-213 [PMID: 26803429 DOI: 10.1016/j.atherosclerosis.2016.01.016]

106 **VanWagner LB**, Wilcox JE, Colangelo LA, Lloyd-Jones DM, Carr JJ, Lima JA, Lewis CE, Rinella ME, Shah SJ. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. *Hepatology* 2015; **62**: 773-783 [PMID: 25914296 DOI: 10.1002/hep.27869]

107 **Wang X**, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 394-402.e1 [PMID: 24076414 DOI: 10.1016/j.cgh.2013.09.023]

108 **Ayloo S**, Armstrong J, Hurton S, Molinari M. Obesity and liver transplantation. *World J Transplant* 2015; **5**: 95-101 [PMID: 26421262 DOI: 10.5500/wjt.v5.i3.95]

109 **Takata MC**, Campos GM, Ciovica R, Rabl C, Rogers SJ, Cello JP, Ascher NL, Posselt AM. Laparoscopic bariatric surgery improves candidacy in morbidly obese patients awaiting transplantation. *Surg Obes Relat Dis* 2008; **4**: 159-64; discussion 164-5 [PMID: 18294923 DOI: 10.1016/j.soard.2007.12.009]

110 **Hafeez S**, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance? *J Obes* 2013; **2013**: 839275 [PMID: 23431426 DOI: 10.1155/2013/839275]

111 **Shouhed D**, Steggerda J, Burch M, Noureddin M. The role of bariatric surgery in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Expert Rev Gastroenterol Hepatol* 2017; **11**: 797-811 [PMID: 28712339 DOI: 10.1080/17474124.2017.1355731]

112 **Diwan TS**, Rice TC, Heimbach JK, Schauer DP. Liver Transplantation and Bariatric Surgery: Timing and Outcomes. *Liver Transpl* 2018; **24**: 1280-1287 [PMID: 30080949 DOI: 10.1002/lt.25303]

113 **Shimizu H**, Phuong V, Maia M, Kroh M, Chand B, Schauer PR, Brethauer SA. Bariatric surgery in patients with liver cirrhosis. *Surg Obes Relat Dis* 2013; **9**: 1-6 [PMID: 23201210 DOI: 10.1016/j.soard.2012.07.021]

114 **Lassailly G**, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, Raverdy V, Leteurtre E, Dharancy S, Louvet A, Romon M, Duhamel A, Pattou F, Mathurin P. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. *Gastroenterology* 2015; **149**: 379-88; quiz e15-6 [PMID: 25917783 DOI: 10.1053/j.gastro.2015.04.014]

115 **Heimbach JK**, Watt KD, Poterucha JJ, Ziller NF, Cecco SD, Charlton MR, Hay JE, Wiesner RH, Sanchez W, Rosen CB, Swain JM. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. *Am J Transplant* 2013; **13**: 363-368 [PMID: 23137119 DOI: 10.1111/j.1600-6143.2012.04318.x]

116 **Nesher E**, Mor E, Shlomai A, Naftaly-Cohen M, Yemini R, Yussim A, Brown M, Keidar A. Simultaneous Liver Transplantation and Sleeve Gastrectomy: Prohibitive Combination or a Necessity? *Obes Surg* 2017; **27**: 1387-1390 [PMID: 28281236 DOI: 10.1007/s11695-017-2634-5]

117 **Tariciotti L**, D'Ugo S, Manzia TM, Tognoni V, Sica G, Gentileschi P, Tisone G. Combined liver transplantation and sleeve gastrectomy for end-stage liver disease in a bariatric patient: First European case-report. *Int J Surg Case Rep* 2016; **28**: 38-41 [PMID: 27677115 DOI: 10.1016/j.ijscr.2016.09.011]

118 **Zamora-Valdes D**, Watt KD, Kellogg TA, Poterucha JJ, Di Cecco SR, Francisco-Ziller NM, Taner T, Rosen CB, Heimbach JK. Long-term outcomes of patients undergoing simultaneous liver transplantation and sleeve gastrectomy. *Hepatology* 2018; **68**: 485-495 [PMID: 29457842 DOI: 10.1002/hep.29848]

119 **Lazzati A**, Iannelli A, Schneck AS, Nelson AC, Katsahian S, Gugenheim J, Azoulay D. Bariatric surgery and liver transplantation: a systematic review a new frontier for bariatric surgery. *Obes Surg* 2015; **25**: 134-142 [PMID: 25337867 DOI: 10.1007/s11695-014-1430-8]

120 **El Atrache MM**, Abouljoud MS, Divine G, Yoshida A, Kim DY, Kazimi MM, Moonka D, Huang MA, Brown K. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. *Clin Transplant* 2012; **26**: E505-E512 [PMID: 23061759 DOI: 10.1111/ctr.12014]

121 **Butte JM**, Devaud N, Jarufe NP, Boza C, Pérez G, Torres J, Pérez-Ayuso RM, Arrese M, Martínez J. Sleeve gastrectomy as treatment for severe obesity after orthotopic liver transplantation. *Obes Surg* 2007; **17**: 1517-1519 [PMID: 18219781 DOI: 10.1007/s11695-008-9432-z]

122 **Anand AC**. Potential Liver Transplant Recipients with Hepatitis C: Should They Be Treated Before or After Transplantation? *J Clin Exp Hepatol* 2017; **7**: 42-54 [PMID: 28348470 DOI: 10.1016/j.jceh.2017.01.116]

123 **Montano-Loza AJ**, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, Esfandiari N, Ma M, Baracos VE. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia Sarcopenia Muscle* 2016; **7**: 126-135 [PMID: 27493866 DOI: 10.1002/jcsm.12039]

124 **Vidot H**, Kline K, Cheng R, Finegan L, Lin A, Kempler E, Strasser SI, Bowen DG, McCaughan GW, Carey S, Allman-Farinelli M, Shackel NA. The Relationship of Obesity, Nutritional Status and Muscle Wasting in Patients Assessed for Liver Transplantation. *Nutrients* 2019; **11**: [PMID: 31487854 DOI: 10.3390/nu11092097]

125 **Carey EJ**, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, Dunn MA; Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl* 2017; **23**: 625-633 [PMID: 28240805 DOI: 10.1002/lt.24750]

126 **Carias S**, Castellanos AL, Vilchez V, Nair R, Dela Cruz AC, Watkins J, Barrett T, Trushar P, Esser K, Gedaly R. Nonalcoholic steatohepatitis is strongly associated with sarcopenic obesity in patients with cirrhosis undergoing liver transplant evaluation. *J Gastroenterol Hepatol* 2016; **31**: 628-633 [PMID: 26399838 DOI: 10.1111/jgh.13166]

127 **Amitrano L**, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J Hepatol* 2004; **40**: 736-741 [PMID: 15094219 DOI: 10.1016/j.jhep.2004.01.001]

128 **Gayowski TJ**, Marino IR, Doyle HR, Echeverri L, Mieles L, Todo S, Wagener M, Singh N, Yu VL, Fung JJ, Starzl TE. A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. *J Surg Res* 1996; **60**: 333-338 [PMID: 8598664 DOI: 10.1006/jsre.1996.0053]

129 **Englesbe MJ**, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. *Liver Transpl* 2010; **16**: 999-1005 [PMID: 20677291 DOI: 10.1002/lt.22105]

130 **Rana A**, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, Guarrera JV, Brown RS Jr, Emond JC. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant* 2008; **8**: 2537-2546 [PMID: 18945283 DOI: 10.1111/j.1600-6143.2008.02400.x]

131 **Steggerda JA**, Kim IK, Todo T, Malinoski D, Klein AS, Bloom MB. Liver Transplant Survival Index for Patients with Model for End-Stage Liver Disease Score ≥ 35: Modeling Risk and Adjusting Expectations in the Share 35 Era. *J Am Coll Surg* 2019; **228**: 437-450.e8 [PMID: 30594593 DOI: 10.1016/j.jamcollsurg.2018.12.009]

132 **Di Minno MN**, Tufano A, Rusolillo A, Di Minno G, Tarantino G. High prevalence of nonalcoholic fatty liver in patients with idiopathic venous thromboembolism. *World J Gastroenterol* 2010; **16**: 6119-6122 [PMID: 21182227 DOI: 10.3748/wjg.v16.i48.6119]

133 **Stine JG**, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. *Liver Transpl* 2015; **21**: 1016-1021 [PMID: 25845711 DOI: 10.1002/lt.24134]

134 **Stine JG**, Shah PM, Cornella SL, Rudnick SR, Ghabril MS, Stukenborg GJ, Northup PG. Portal vein thrombosis, mortality and hepatic decompensation in patients with cirrhosis: A meta-analysis. *World J Hepatol* 2015; **7**: 2774-2780 [PMID: 26644821 DOI: 10.4254/wjh.v7.i27.2774]

135 **Agbim U**, Jiang Y, Kedia SK, Singal AK, Ahmed A, Bhamidimarri KR, Bernstein DE, Harrison SA, Younossi ZM, Satapathy SK. Impact of Nonmalignant Portal Vein Thrombosis in Transplant Recipients With Nonalcoholic Steatohepatitis. *Liver Transpl* 2019; **25**: 68-78 [PMID: 30091296 DOI: 10.1002/lt.25322]

136 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]

137 **Younossi Z**, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, Eguchi Y, Wong VW, Negro F, Yilmaz Y, Romero-Gomez M, George J, Ahmed A, Wong R, Younossi I, Ziayee M, Afendy A; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. *Clin Gastroenterol Hepatol* 2019; **17**: 748-755.e3 [PMID: 29908364 DOI: 10.1016/j.cgh.2018.05.057]

138 **Sadler EM**, Mehta N, Bhat M, Ghanekar A, Greig PD, Grant DR, Yao F, Sapisochin G. Liver Transplantation for NASH-Related Hepatocellular Carcinoma Versus Non-NASH Etiologies of Hepatocellular Carcinoma. *Transplantation* 2018; **102**: 640-647 [PMID: 29319620 DOI: 10.1097/TP.0000000000002043]

139 **Paradis V**, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, Bedossa P, Belghiti J. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology* 2009; **49**: 851-859 [PMID: 19115377 DOI: 10.1002/hep.22734]

140 **Stine JG**, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, Argo CK. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther* 2018; **48**: 696-703 [PMID: 30136293 DOI: 10.1111/apt.14937]

141 **Marengo A**, Rosso C, Bugianesi E. Liver Cancer: Connections with Obesity, Fatty Liver, and Cirrhosis. *Annu Rev Med* 2016; **67**: 103-117 [PMID: 26473416 DOI: 10.1146/annurev-med-090514-013832]

142 **Font-Burgada J**, Sun B, Karin M. Obesity and Cancer: The Oil that Feeds the Flame. *Cell Metab* 2016; **23**: 48-62 [PMID: 26771116 DOI: 10.1016/j.cmet.2015.12.015]

143 **Schulze K**, Imbeaud S, Letouzé E, Alexandrov LB, Calderaro J, Rebouissou S, Couchy G, Meiller C, Shinde J, Soysouvanh F, Calatayud AL, Pinyol R, Pelletier L, Balabaud C, Laurent A, Blanc JF, Mazzaferro V, Calvo F, Villanueva A, Nault JC, Bioulac-Sage P, Stratton MR, Llovet JM, Zucman-Rossi J. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet* 2015; **47**: 505-511 [PMID: 25822088 DOI: 10.1038/ng.3252]

144 **Grohmann M**, Wiede F, Dodd GT, Gurzov EN, Ooi GJ, Butt T, Rasmiena AA, Kaur S, Gulati T, Goh PK, Treloar AE, Archer S, Brown WA, Muller M, Watt MJ, Ohara O, McLean CA, Tiganis T. Obesity Drives STAT-1-Dependent NASH and STAT-3-Dependent HCC. *Cell* 2018; **175**: 1289-1306.e20 [PMID: 30454647 DOI: 10.1016/j.cell.2018.09.053]

145 **Hong F**, Jaruga B, Kim WH, Radaeva S, El-Assal ON, Tian Z, Nguyen VA, Gao B. Opposing roles of STAT1 and STAT3 in T cell-mediated hepatitis: regulation by SOCS. *J Clin Invest* 2002; **110**: 1503-1513 [PMID: 12438448 DOI: 10.1172/JCI15841]

146 **D'Amico S**, Shi J, Martin BL, Crawford HC, Petrenko O, Reich NC. STAT3 is a master regulator of epithelial identity and KRAS-driven tumorigenesis. *Genes Dev* 2018; **32**: 1175-1187 [PMID: 30135074 DOI: 10.1101/gad.311852.118]

147 **Thuluvath PJ**, Hanish S, Savva Y. Waiting List Mortality and Transplant Rates for NASH Cirrhosis When Compared With Cryptogenic, Alcoholic, or AIH Cirrhosis. *Transplantation* 2019; **103**: 113-121 [PMID: 29985186 DOI: 10.1097/TP.0000000000002355]

148 **Charlton MR**, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249-1253 [PMID: 21726509 DOI: 10.1053/j.gastro.2011.06.061]

149 **Andrade ARCF**, Cotrim HP, Bittencourt PL, Almeida CG, Sorte NCAB. Nonalcoholic steatohepatitis in posttransplantation liver: Review article. *Rev Assoc Med Bras (1992)* 2018; **64**: 187-194 [PMID: 29641680 DOI: 10.1590/1806-9282.64.02.187]

150 **Afzali A**, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012; **18**: 29-37 [PMID: 21932374 DOI: 10.1002/lt.22435]

151 **Albeldawi M**, Aggarwal A, Madhwal S, Cywinski J, Lopez R, Eghtesad B, Zein NN. Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl* 2012; **18**: 370-375 [PMID: 22140067 DOI: 10.1002/lt.22468]

152 **Everhart JE**, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, Hoofnagle JH. Weight change and obesity after liver transplantation: incidence and risk factors. *Liver Transpl Surg* 1998; **4**: 285-296 [PMID: 9649642 DOI: 10.1002/lt.500040402]

153 **Lim LG**, Cheng CL, Wee A, Lim SG, Lee YM, Sutedja DS, Da Costa M, Prabhakaran K, Wai CT. Prevalence and clinical associations of posttransplant fatty liver disease. *Liver Int* 2007; **27**: 76-80 [PMID: 17241384 DOI: 10.1111/j.1478-3231.2006.01396.x]

154 **Kennedy C**, Redden D, Gray S, Eckhoff D, Massoud O, McGuire B, Alkurdi B, Bloomer J, DuBay DA. Equivalent survival following liver transplantation in patients with non-alcoholic steatohepatitis compared with patients with other liver diseases. *HPB (Oxford)* 2012; **14**: 625-634 [PMID: 22882200 DOI: 10.1111/j.1477-2574.2012.00497.x]

155 **Bhati C**, Idowu MO, Sanyal AJ, Rivera M, Driscoll C, Stravitz RT, Kohli DR, Matherly S, Puri P, Gilles H, Cotterell A, Levy M, Sterling RK, Luketic VA, Lee H, Sharma A, Siddiqui MS. Long-term Outcomes in Patients Undergoing Liver Transplantation for Nonalcoholic Steatohepatitis-Related Cirrhosis. *Transplantation* 2017; **101**: 1867-1874 [PMID: 28296807 DOI: 10.1097/TP.0000000000001709]

156 **Siddiqui MS**, Sterling RK. Posttransplant metabolic syndrome. *Int J Hepatol* 2012; **2012**: 891516 [PMID: 23227347 DOI: 10.1155/2012/891516]

157 **Dare AJ**, Plank LD, Phillips AR, Gane EJ, Harrison B, Orr D, Jiang Y, Bartlett AS. Additive effect of pretransplant obesity, diabetes, and cardiovascular risk factors on outcomes after liver transplantation. *Liver Transpl* 2014; **20**: 281-290 [PMID: 24395145 DOI: 10.1002/lt.23818]

158 **Ronald A**, Ludwig E. Urinary tract infections in adults with diabetes. *Int J Antimicrob Agents* 2001; **17**: 287-292 [PMID: 11295410 DOI: 10.1016/s0924-8579(00)00356-3]

159 **Moon JI**, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: Long-term follow up. *Transplantation* 2006; **82**: 1625-1628 [PMID: 17198248 DOI: 10.1097/01.tp.0000250361.60415.96]

160 **Øzbay LA**, Møller N, Juhl C, Bjerre M, Carstens J, Rungby J, Jørgensen KA. Calcineurin inhibitors acutely improve insulin sensitivity without affecting insulin secretion in healthy human volunteers. *Br J Clin Pharmacol* 2012; **73**: 536-545 [PMID: 21988494 DOI: 10.1111/j.1365-2125.2011.04118.x]

161 **Kouz J**, Vincent C, Leong A, Dorais M, Räkel A. Weight gain after orthotopic liver transplantation: is nonalcoholic fatty liver disease cirrhosis a risk factor for greater weight gain? *Liver Transpl* 2014; **20**: 1266-1274 [PMID: 25044355 DOI: 10.1002/lt.23951]

162 **Dumortier J**, Giostra E, Belbouab S, Morard I, Guillaud O, Spahr L, Boillot O, Rubbia-Brandt L, Scoazec JY, Hadengue A. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". *Am J Gastroenterol* 2010; **105**: 613-620 [PMID: 20040915 DOI: 10.1038/ajg.2009.717]

163 **Charlton M**, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, Detre K, Hoofnagle J. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998; **28**: 823-830 [PMID: 9731579 DOI: 10.1002/hep.510280333]

164 **Ozbay LA**, Møller N, Juhl C, Bjerre M, Carstens J, Rungby J, Jørgensen KA. The impact of calcineurin inhibitors on insulin sensitivity and insulin secretion: a randomized crossover trial in uraemic patients. *Diabet Med* 2012; **29**: e440-e444 [PMID: 23003106 DOI: 10.1111/dme.12028]

165 **Bianchi G**, Marchesini G, Marzocchi R, Pinna AD, Zoli M. Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl* 2008; **14**: 1648-1654 [PMID: 18975273 DOI: 10.1002/lt.21588]

166 **Trotter JF**, Wachs ME, Trouillot TE, Bak T, Kugelmas M, Kam I, Everson G. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. *Liver Transpl* 2001; **7**: 401-408 [PMID: 11349259 DOI: 10.1053/jlts.2001.23916]

167 **Canzanello VJ**, Textor SC, Taler SJ, Schwartz LL, Porayko MK, Wiesner RH, Krom RA. Late hypertension after liver transplantation: a comparison of cyclosporine and tacrolimus (FK 506). *Liver Transpl Surg* 1998; **4**: 328-334 [PMID: 9649648 DOI: 10.1002/lt.500040404]

168 **Malik SM**, deVera ME, Fontes P, Shaikh O, Ahmad J. Outcome after liver transplantation for NASH cirrhosis. *Am J Transplant* 2009; **9**: 782-793 [PMID: 19344467 DOI: 10.1111/j.1600-6143.2009.02590.x]

169 **van den Berg EH**, Douwes RM, de Meijer VE, Schreuder TCMA, Blokzijl H. Liver transplantation for NASH cirrhosis is not performed at the expense of major post-operative morbidity. *Dig Liver Dis* 2018; **50**: 68-75 [PMID: 28935188 DOI: 10.1016/j.dld.2017.08.022]

170 **Heuer M**, Kaiser GM, Kahraman A, Banysch M, Saner FH, Mathé Z, Gerken G, Paul A, Canbay A, Treckmann JW. Liver transplantation in nonalcoholic steatohepatitis is associated with high mortality and post-transplant complications: a single-center experience. *Digestion* 2012; **86**: 107-113 [PMID: 22846254 DOI: 10.1159/000339344]

171 **Maor-Kendler Y**, Batts KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, Charlton MR. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. *Transplantation* 2000; **70**: 292-297 [PMID: 10933151 DOI: 10.1097/00007890-200007270-00009]

172 **Liu A**, Galoosian A, Kaswala D, Li AA, Gadiparthi C, Cholankeril G, Kim D, Ahmed A. Nonalcoholic Fatty Liver Disease: Epidemiology, Liver Transplantation Trends and Outcomes, and Risk of Recurrent Disease in the Graft. *J Clin Transl Hepatol* 2018; **6**: 420-424 [PMID: 30637220 DOI: 10.14218/JCTH.2018.00010]

173 **Contos MJ**, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, Fisher RA, Ham J, Sanyal AJ. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2001; **7**: 363-373 [PMID: 11303298 DOI: 10.1053/jlts.2001.23011]

174 **Yalamanchili K**, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. *Liver Transpl* 2010; **16**: 431-439 [PMID: 20373454 DOI: 10.1002/lt.22004]

175 **Bhagat V**, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; **15**: 1814-1820 [PMID: 19938128 DOI: 10.1002/lt.21927]

176 **Seo S**, Maganti K, Khehra M, Ramsamooj R, Tsodikov A, Bowlus C, McVicar J, Zern M, Torok N. De novo nonalcoholic fatty liver disease after liver transplantation. *Liver Transpl* 2007; **13**: 844-847 [PMID: 17029282 DOI: 10.1002/lt.20932]

177 **Sprinzl MF**, Weinmann A, Lohse N, Tönissen H, Koch S, Schattenberg J, Hoppe-Lotichius M, Zimmermann T, Galle PR, Hansen T, Otto G, Schuchmann M. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. *Transpl Int* 2013; **26**: 67-74 [PMID: 23126674 DOI: 10.1111/j.1432-2277.2012.01576.x]

178 **Singal AK**, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827afb3a]

179 **Finkenstedt A**, Auer C, Glodny B, Posch U, Steitzer H, Lanzer G, Pratschke J, Biebl M, Steurer M, Graziadei I, Vogel W, Zoller H. Patatin-like phospholipase domain-containing protein 3 rs738409-G in recipients of liver transplants is a risk factor for graft steatosis. *Clin Gastroenterol Hepatol* 2013; **11**: 1667-1672 [PMID: 23872669 DOI: 10.1016/j.cgh.2013.06.025]

180 **Hejlova I**, Honsova E, Sticova E, Lanska V, Hucl T, Spicak J, Jirsa M, Trunecka P. Prevalence and risk factors of steatosis after liver transplantation and patient outcomes. *Liver Transpl* 2016; **22**: 644-655 [PMID: 26707008 DOI: 10.1002/lt.24393]

181 **Laish I**, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. *Liver Transpl* 2011; **17**: 15-22 [PMID: 21254340 DOI: 10.1002/lt.22198]

182 **Alberti KGMM**, Eckel RH, Grundy, SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT, Loria CM, SmithJr SC; A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Harmonizing the Metabolic Syndrome. *Circulation* 2009; **120**: 1640–1645 [DOI: 10.1161/CIRCULATIONAHA.109.192644]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** AASLD, No. 179755; American Society of Transplant Surgeons, No. 13200.

**Peer-review started:** April 6, 2020

**First decision:** April 26, 2020

**Article in press:**

**Specialty type:** gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Inchingolo r, Tsukanov v **S-Editor:** Ma YJ **L-Editor: E-Editor:**

**Figure Legends**



**Figure 1 Optimizing patients with non-alcoholic steatohepatitis cirrhosis for liver transplantation.** Patients with non-alcoholic steatohepatitis cirrhosis represent a unique and challenging population. Comorbid conditions which may complicate pre- and post-transplant care are presented along with considerations for optimization. BMI: body mass index; LT: liver transplantation; NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; ESLD: end-stage liver disease; CKD: chronic kidney disease; SLKT: Simultaneous liver and kidney transplantation.

**Table 1 Metabolic syndrome criteria**

|  |
| --- |
| **Metabolic syndrome criteria** |
| **Characteristic** | **Description** |
| Waist Circumference | ≥ 88 cm in females≥ 102 cm in males |
| Triglycerides | ≥ 150 mg/dLOn drug treatment for elevated triglycerides |
| HDL | ≤ 40 mg/dL for men≤ 50 mg/dL for womenOn drug treatment for low HDL |
| Hypertension | Systolic blood pressure ≥ 130 mmHgDiastolic blood pressure ≥ 85 mmHgOn anti-hypertensive drug treatment for history of hypertension |
| Diabetes | Elevated fasting glucose ≥ 100 mg/dLOn drug treatment for elevated glucose |

Patients must exhibit 3 of the 5 components to have the diagnosis with metabolic syndrome. Based on consensus statement from International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity[182]. HDL: High-density lipoprotein.

**Table 2 Recommendations for pre-transplant evaluation in patients with non-alcoholic steatohepatitis cirrhosis**

|  |
| --- |
| **Evaluation and therapy for liver transplant candidates with non-alcoholic steatohepatitis** |
| Hypertension | Target blood pressure 130/80Initiate anti-hypertensive medical therapy |
| Diabetes | Blood glucose controlMonitor insulin resistanceHemoglobin A1c optimization |
| Hyperlipidemia | Initiate statin therapy as appropriate  |
| Renal dysfunction | Renal ultrasoundMeasure GFR by quantitative methodConsider simultaneous liver/kidney transplantation |
| Cardiovascular disease | Identify cardiovascular risk factors—hypertension, diabetes, hyperlipidemiaComprehensive cardiac evaluation to include EKG, DSEStrong consideration for coronary angiography, in addition to OR in place of DSECarotid artery duplex |
| Obesity | Consultation with nutritionist or dietician and exercise therapistConsider consultation with bariatric surgeonConsider pre-transplant or simultaneous LT + bariatric surgery if fail weight loss strategies with concurrent comorbid conditions |

GFR: Glomerular filtration rate; EKG: Electrocardiography; DSE: Dobutamine stress echocardiogram; LT: liver transplantation.