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REVIEW

Fat and liver transplantation: clinical implications

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SUMMARY

Nonalcoholic steatohepatitis (NASH), with or without hepatocellular carcinoma, is a growing indication for liver transplantation (LT) worldwide, particularly in the Western world. Patients with NASH typically combine features of metabolic syndrome with cardiovascular comorbidities, which challenge pre-LT evaluation, surgical approaches, post-LT management, and outcomes. Post-LT survival in NASH patients is excellent, similar to that achieved with other indications, particularly in the absence of cardiovascular comorbidities. Although disease recurrence on the liver allograft is common, progression to advanced disease is uncommon, at least in the short term. Whether this holds true with longer follow-up remains to be determined. Owing to the increased prevalence of nonalcoholic fatty liver disease worldwide, along with a shortened organ pool donation in many countries, utilization of donor grafts with hepatic steatosis is now more common. Understanding the limitations of these grafts as well as potential mechanisms to improve graft quality and/or transplant outcome is clue for transplant centers. In this review, we will summarize current data on evaluation of NASH patients and whether it differs from that applied to other candidates, the natural history of NASH both pre- and post-transplantation, emphasizing on waiting list management and recurrence of the original disease in the new graft as well as post-transplant outcome. Finally, we will discuss the current use of steatotic liver donors and strategies to improve outcome when using this type of grafts.

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NASH before liver transplantation

Prevalence of NASH

The global prevalence of nonalcoholic fatty liver disease (NAFLD) is around 25% [1] with significant geographic variation, higher in South America (30%) and the Middle East (31%), and lower in Africa (13%). Given that liver biopsies are not performed in studies targeting the general population, the exact prevalence of nonalcoholic steatohepatitis (NASH) remains unknown. However, based on available liver biopsies from healthy population subgroups such as living donors, it is estimated that the global prevalence of NASH ranges from 1.5% to 6.5% [2].

The natural history of NAFLD has been described from population-based studies [3]. Approximately 25% of patients with NAFLD develop NASH and 5% progress to cirrhosis. Liver-related outcomes and long-term overall mortality are associated with liver fibrosis [4].

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Ultimately, severe liver disease outcomes, such as liver-related death or need of liver transplantation (LT), only occur in 1–2% of patients with NAFLD. In other words, liver-related events are a relatively uncommon cause of mortality among patients with NAFLD. However, because of its very high global prevalence, NASH is becoming the leading cause of liver disease and liver-related mortality globally.

Indeed, NASH is the most rapidly growing indication for LT alone or for simultaneous liver–kidney transplantation (LKT) in the United States, but not yet in Europe. In the United States, it is currently the second LT waiting list indication and the third cause for LT [5–8]. Similarly, NASH-related cirrhosis has become the most common non-hepatocellular carcinoma (HCC) indication for LT in patients aged 65 or older. In Europe, recent data from the European Liver Transplantation Registry (ELTR) have been communicated in the last International Liver Congress, showing also an increase in the frequency of LT for NASH from 1.2% in 2002 to 8.4% in 2016 [9].

Features and mortality of wait-listed NASH patients

Patients with NASH present some unique features. The prevalence of metabolic syndrome is more frequent in patients with NASH as compared to other etiologies. Waiting list patients with NASH are more frequently female (47% vs. 29%; $P < 0.001$) [7], more likely to be white (78.5%), and significantly older (5–10 years of difference). In addition, the prevalence of diabetes mellitus (DM) (43.6%) among NASH patients is higher than that in other indications. Finally, higher body mass index (BMI) (31.6 kg/m^2) and lower glomerular filtration rate (GFR) (55.2 ml/min) [10] have been described in LT NASH candidates.

With regard to comorbidities, the incidence of severe coronary artery disease (CAD) (>70% diameter stenosis) has been reported to be higher in NASH patients [11], with low reliability in assessing severity and surgical risk in these patients when only noninvasive techniques are used. Based on these assumptions, many groups include an exhaustive cardiac workup pre-LT for NASH patients, including a stress echocardiography with dobutamine ± angiography. Unfortunately in cirrhotic patients undergoing pre-LT evaluation, stress echocardiography with dobutamine has also been reported to be frequently not conclusive and therefore not useful in predicting cardiovascular (CV) events [12]. As a result, many centers, particularly from the United States, have advocated angiography as a screening test in the pre-LT cardiac evaluation of NAFLD cirrhotic patients. While overall results from some of these largely retrospective studies have reported good outcomes, it remains unclear whether invasive coronarography was actually performed in asymptomatic patients with risk factors or alternatively on the basis of CAD history or symptoms. Hence, good results reported in these series may reflect in fact the low mortality risk in the larger proportion of recipients with untreated silent disease [13–15]. What truly lies behind this lack of uniformity in the cardiac evaluation of NASH cirrhotic patients is the lack of evidence that a specific algorithm in LT candidates, not only those with NASH, results in improved outcome measures. Indeed, both an adequate estimation of the performance of the broad range of cardiac testing modalities (i.e., coronary artery calcium score, coronary computed tomography angiography, cardiac magnetic resonance, contrast-enhanced dobutamine stress echocardiography) and risk stratification remain unclear. In a recent systematic review aimed at characterizing the incidence and risk factors for CV events post-LT, which included 29 studies representing 57 493 patients, both the definitions of CV outcomes and the predictive capacity of various cardiac imaging modalities were highly inconsistent. Incidence rates of CV events were widely variable: 1–41% for outcomes at 6 months or shorter and 0–31% for outcomes occurring longer than 6 months post-LT. In the multivariate analyses, only older age and a history of cardiac disease consistently predicted CV events post-transplant [16]. Given the lack of conclusive evidence, we suggest that NASH patients should undergo a CV evaluation similar to that carried out for other cirrhotic patients taking into account known risk factors for CAD. Until much evidence is accrued, a strategy might be to perform a noninvasive evaluation of CAD in selected patients, such as in those with DM or ≥2 traditional risk factors for CAD (age >45 years for male or >55 years for female, hypercholesterolemia, hypertension, tobacco use, and family history of early CAD) and in those with abnormal noninvasive results and high pretest probability of CAD, consider invasive angiography.

While the cumulative incidence of HCC has been reported to be lower in NASH patients (2–12%) as compared to other etiologies [17], with the increased incidence of NASH, it is anticipated that the burden of NASH-related HCC will rise in the near future. In addition, HCC diagnosis may be difficult in these patients, taking into account ultrasound limitations in steatotic livers. In any case, dynamic multislice imaging (CT scan or MRI) is

performed prior to LT in every patient, thus increasing HCC diagnosis rate.

Chronic kidney disease (CKD) is frequent among NASH patients, similar to arterial hypertension (AHT), DM, and atherosclerotic disease, and it has been directly attributed to NASH features independent of other cardio-renal comorbidities. Indeed, liver disease severity in NASH patients has been shown to be associated with a twofold increased risk and severity of CKD [18].

Few studies have evaluated whether the outcome of NASH wait-listed patients differs from that of other etiologies, and specifically whether the probability to receive a LT on-time is similar to that described for other etiologies. In one study, wait-listed patients with NASH were less likely to receive a liver compared to hepatitis C (HCV) patients [19]. Causes for dropout though were different, and while the presence of comorbidities was the main cause in the NASH population (72%), psycho-social reasons were mainly implicated in the HCV population (39%). Interestingly for patients with model for end-stage liver disease (MELD) lower than 15, MELD progression was lower (1.3 vs. 3.2 MELD points yearly; $P = 0.003$), and thus, the probability to receive a LT was lower (27% vs. 46%; $P < 0.001$) in the NASH population. Once the MELD score increased beyond 15, the probability to receive a LT was similar for both transplant indications. In essence, although there needs to be much insight into this topic, it seems that waiting list dropout and mortality related to systemic comorbidities are higher for NASH patients compared to other indications. In addition, a high prevalence of obesity and sarcopenia among patients with NASH cirrhosis has been described [20]. In turn, higher BMI has been associated with an increased risk of clinical decompensation [21], and sarcopenia is known to be associated with poor pretransplant outcomes [22].

NASH following liver transplantation

Post-transplant survival and outcomes

Post-transplant survival of NASH recipients at short and long term is similar to other etiologies, despite the increased presence of comorbidities and older age in NASH patients, as reported in several large cohorts. Post-LT survival rates are approximately 85–90% at 1 year, 80–85% at 3 years, and 75–80% at 5 years [7,23,24], which is similar to other indications when adjusted by age, sex, BMI, and renal disease. On the other hand, a higher early mortality, particularly in the first 30 days, has been reported in several studies, including a recent meta-analysis [24]. In that meta-analysis, which included nine publications before 2012, with 717 NASH patients and 3520 non-NASH patients, survival at 1 (OR: 0.77; 95% CI, 0.59–1.00; $P = 0.05$), 3 (OR: 0.97; 95% CI, 0.67–1.40; $P = 0.86$), and 5 (OR: 1.09; 95% CI, 0.77–1.56; $P = 0.63$) years post-transplant did not differ between the two groups. Cardiovascular disease and sepsis were the two most frequent causes of death in the NASH group, occurring at a significantly higher rate than in non-NASH recipients (OR: 1.65, 95% CI: 1.01–2.70, $P = 0.05$; and OR: 1.71, 95% CI: 1.17–2.50, $P = 0.006$, respectively). Interestingly, death because of graft loss occurred significantly less frequently in the NASH population [25–27]. A longer follow-up (10–20 years post-LT) will likely exhibit a greater rate of CV events in NASH individuals, as these tend to increase with age.

Many authors have investigated high-risk features that, in combination, might help to identify patients at significant higher risk of mortality for whom LT would be contraindicated. Some of these high-risk features were as follows: BMI >40, the combination of DM and obesity, age older than 60 years combined with a BMI >30, DM and AHT, or pretransplant hemodialysis. In some of these studies, these high-risk patients were found to have a 50% 1-year mortality [25] and a 15% 30-day mortality [28].

Particularly, obesity, with or without coexistence of NASH, has been associated with several negative outcomes. A higher rate of perioperative complications has been described in obese patients undergoing LT in most series: longer hospital and ICU stay, increased costs, higher rate of re-operations and use of blood products, higher rate of wound complications and dehiscence, and a higher rate of biliary complications and infections [29]. In a multicentric Australian cohort study ($n = 617$ patients) assessing the impact of pre-LT metabolic factors on post-LT survival, the authors found an additive effect of obesity and DM on 5-year survival [30]. Patients with concomitant diabetes and obesity had lower survival, whereas obese nondiabetic patients or diabetic nonobese patients had similar survival compared with nondiabetic, nonobese individuals. Other factors, such as AHT, dyslipidemia, and obesity and metabolic syndrome, had no independent effect on survival.

Few studies have addressed post-LT survival in NASH-related HCC. No significant differences in survival have been reported when compared to non-NASH HCC [31]. As with non-HCC NASH patients, those

with NAFLD and HCC were older at time of diagnosis and more likely to be white and male. Fewer patients with NAFLD-related HCC received a LT as compared to other HCC patients [32], probably due to a higher dropout rate in the context of more comorbidities, as mentioned before.

Donor steatosis

The pool of potential liver donor is now frequently populated by those with fatty liver disease, likely a result of increased obesity worldwide. Hepatic steatosis is seen on biopsy in 76% of potential liver donors with a BMI greater than 28 [33].

Liver steatosis is associated with overall poorer recipient outcomes. Postreperfusion, steatosis induces microcirculatory and cellular changes in the liver graft, which potentially result in hepatocyte necrosis. Furthermore, the regeneration potential of steatotic livers is impaired [34,35]. Liver steatosis is typically classified quantitatively and qualitatively. The quantitative evaluation is based on the proportion of fat content of hepatocytes, mild (<30%), moderate (30–60%), or severe (>60%), with incremental risk of graft dysfunction after liver transplantation [36]. The qualitative classification is based on the number and size of the intracytoplasmic fat droplets and the location of the nucleus in the hepatocytes, differentiating micro- and macrovesicular steatosis. Macrovesicular steatosis is defined when a single large lipid vacuole fills the majority of the cytoplasm dislocating the cell nuclei to the periphery. Microsteatosis is considered by cytoplasmic accumulation of many, relatively small lipid droplets surrounding the nucleus without dislocating it. Micro- and macrosteatosis are most likely present simultaneously in the liver tissue in different degrees.

Hepatic steatosis is an independent risk factor for outcome post-LT, resulting in increased morbidity and mortality. This includes higher length of ICU admission, hospital stay, increased risk of primary nonfunction (PNF), and delayed graft nonfunction [37,38]. While most transplant surgeons routinely discard grafts with more than 60% because of high risk of graft failure, anecdotal reports with markedly severe graft steatosis have shown similar short and long-term post-transplant outcome to lean grafts when used in recipients with low MELD score [39]. Most published studies indicate a relatively low rate of PNF (between 0% and 4%) for grafts with moderate 30–60% macrosteatosis and no major effect on long-term outcome. However, a recent publication from Kulik *et al.* identified fatty liver as the cause of PNF in 70% of cases. Furthermore, fatty liver was the only predictive factor associated with inferior survival on multivariate analysis [40]. In the absence of large studies and present conflicting data, it is prudent to consider fatty grafts for low-risk recipients (lower MELD score, younger age, and shorter cold ischemic time).

In addition to the total amount of fat, the relevance of the type of steatosis, micro- or macrovesicular, on graft function and outcome is still unclear. Macrovesicular steatosis seems to be a benign, potentially reversible condition. It is mostly associated with obesity and alcohol consumption [41]. In contrast, microvesicular steatosis is considered a more serious condition often associated with impaired mitochondrial beta-oxidation and therefore a less favorable prognosis [42]. While some authors have suggested that livers with severe microsteatosis should not be utilized for LT [43], other including a recent study [44] did not show any negative impact of microsteatosis on post-LT outcomes.

It is important to highlight that assessment of graft steatosis is biased in most of the mentioned studies owing to the lack of a reliable, easy to perform, objective and reproductive modality for fat assessment. In many studies, fatty liver is assessed through visual evaluation and palpation at the time of procurement by the surgical team. This subjective modality of evaluation relies unfortunately on the experience of surgeons.

The gold standard to assess hepatic steatosis is a histological analysis by an experienced pathologist. Even in these cases, assessment of fat even on a liver biopsy may also be subject to several biases including sample size heterogeneity or modality of staining techniques (H&E versus more specific fat staining such as Sudan-III, toluidine blue, and oil red O staining) that can affect grading of steatosis. For example, it is reported that H&E staining of frozen section underestimates macrovesicular steatosis. Other bias includes significant interobserver variability among liver pathologists in reporting the percentage of fat content on biopsies [45]. All these factors may contribute to the discrepancies observed between studies, with low rate of PNF reported in some series despite marked steatosis.

Clinical strategies to improve outcomes of steatotic grafts post-LT include ischemic preconditioning, hypothermic machine perfusion, and venous systemic oxygen persufflation. While some studies have shown both a decrease in preservation injury and post-transplant rejection in ischemic preconditioning groups [46,47], a larger randomized clinical trial failed to prove efficacy of this strategy on post-transplant preservation

injury [48]. Novel concepts to preservation approaches including hypothermic and normothermic–subnormothermic machine perfusion seem to offer promising approaches for both functional assessment and repair of fatty livers. Guarrera *et al.* reported in a matched cohort study the outcome of declined steatotic grafts, which were perfused with hypothermic machine perfusion (HMP) compared to the traditional cold storage preservation. HMP demonstrated lower IPF rates (19% vs. 30%), less biliary complications (13% vs. 43%), shorter hospital stay (14 vs. 20 days), and identical 1-year patient survival (84% vs. 80%) [49]. Similarly, studies with normothermic machine perfusion have shown some efficacy in defatting steatotic livers in rodent [50] and porcine animal models. In the latter model, a prolonged normothermic perfusion alone reduced liver fat content by 50%, without adjunction of any defatting cocktail [51]. Perfusion of declined human steatotic grafts has been performed recently by a few centers. These reports suggest feasibility of the technique to perfuse these livers. So far, no data on efficacy of defatting strategy of human liver grafts are available to prove the role of these perfusion strategies for this indication.

NASH recurrence post-LT: risk factors and natural history

Recurrence of steatosis and NAFLD in the liver allograft is relatively common, ranging from 30% to 100%. However, progression to advanced fibrosis and cirrhosis is rare (around 5% at 5 years post-LT). Need for retransplantation is also unusual.

Table 1 shows the results of the main studies reporting on recurrent NASH. In a study including 88 patients transplanted for NASH cirrhosis, after a 5-year follow-up, NAFLD recurrence occurred in 39% of patients, but severe recurrence was only present in three patients and advanced fibrosis in other three individuals. NAFLD recurrence significantly correlated with higher pretransplant ($P = 0.001$) and post-transplant ($P < 0.0001$) BMI, as well as with elevated post-LT triglyceride levels. Average steroid dose at 6 months post-LT was significantly higher in those with NAFLD recurrence [52]. Other risk factors that have been associated with NASH recurrence are DM and AHT. However, risk factors for progressive NASH leading to advanced fibrosis and cirrhosis have not been specifically identified.

In addition, risk factors for NAFLD increase over time in the post-LT setting in all transplant recipients

Table 1. Summary of studies assessing recurrence of NASH after liver transplantation.

Study	*N*	Steatosis	NASH (%)	Cirrhosis	Median Follow-up (months)	Survival rate
Dureja [52]	88 (NAFLD)	34 (39%)	25 (28.4)	3	82	79% (5-year)
Bhagat [69]	71 (cryptogenic cirrhosis with NAFLD phenotype)	NA	31 (33)	0	50	75% (5-year)
Ong [70]	51 (cryptogenic cirrhosis)	13 (25%)	8 (16)	0	26	NA
Contos [71]	30 (27 cryptogenic cirrhosis, 3 NAFLD)	30 (100%)	3 (10)	0	42	NA
Charlton [72]	16 (NAFLD)	9 (60%)	5 (33)	2 (12.5%)	28	81% (3-year)
Tanaka [73]	7 (NAFLD)	NA	1 (14)	0	64	100% (5-year)
Vallin [57]	11 (NAFLD)	7 (100%)	5 (71)	2	60	NA

regardless of transplant indication [53,54]. Approximately 65–70% of patients develop metabolic syndrome 5 years post-LT. Development of AHT, DM and dyslipidemia is well-known side effects of immunosuppressive therapy (calcineurin inhibitors, steroids). Most previously mentioned studies report 3–5 years post-LT follow-up, so long-term outcomes are still unclear.

de novo NASH: risk factors and natural history

de novo NAFLD post-LT likely results from an accumulation of metabolic risk factors, including hyperlipidemia, AHT, and DM with exposure to immuno suppressive drugs together with changes in lifestyle after LT. Table 2 summarizes the reports of studies focusing on *de novo* NASH.

A study reviewing more than 400 LT recipients transplanted for indications other than NASH found a 31% incidence of steatosis and a 5% risk of *de novo* NASH. Several independent risk factors for *de novo* NAFLD were identified including patient obesity at the time of liver biopsy, tacrolimus-based immunosuppression, DM, hyperlipidemia, AHT, alcoholic liver disease as indication for LT, and donor graft steatosis >5% or more of hepatocytes [55].

In another study by Seo *et al.* [56]. where 68 LT recipients of several etiologies with pretransplant and post-transplant biopsies were included, the incidence of *de novo* steatosis was 18% while that of NASH was 9%.

A study by Vallin *et al.* [57]. comparing recurrent (n = 11) and *de novo* (n = 80) NAFLD with liver biopsies at 1-, 3-, and 5-years post-LT found that *de novo* NAFLD was present in 67%, 69%, and 78%, respectively, versus 100% of NAFLD patients with recurrent NAFLD. Severe fibrosis and steatohepatitis were also more frequent in patients with recurrent NAFLD at all three time periods. Consequently, recurrent NAFLD seems a more concerning entity than *de novo* NAFLD, as suggested by these studies.

Impact of NASH recurrence on graft and patient survival

While NAFLD can be caused by the metabolic syndrome and its components, it is also an independent risk factor for renal dysfunction and CV disease post-LT. A comparative study between 48 NASH and 48 non-NASH patients found that NASH was an independent risk factor for developing CKD, after adjusting for BMI, tacrolimus levels, DM, AHT, and HCC. After 2 years post-LT, 31% of the NASH patients (15/48) had developed stage IIIb CKD compared to only 8% of the non-NASH patients (4/48) (P = 0.009) [58]. In a study examining risk factors for CV disease in the post-transplant setting in almost 800 LT recipients, NASH patients had a significantly higher risk of suffering a CV event at 1 and 3 years after LT (15% and 19%, $P < 0.05$), as compared to other etiologies [59]. Individuals with post-transplant DM and AHT also had an increased risk of CV events in this study. In contrast to these systemic effects, no study so far has reported a negative impact of NASH on graft survival on the long term.

Therapeutic strategies

As in the pretransplant setting, several preventive and therapeutic strategies involving a multidisciplinary approach are encouraged in the management of post-transplant NASH. These strategies include a judicious use of immunosuppressive therapy, lifestyle measures and pharmacological control of CV risk factors, namely AHT, DM, dyslipidemia, overweight–obesity, and smoking.

Regarding the use of immunosuppressive therapy, calcineurin inhibitors (CNI) and steroids can cause AHT, DM, and dyslipidemia [53,60,61]. In addition, CNI can cause a decrease in GFR. Tacrolimus trough levels under 10 ng/ml within the first month post-LT have been associated with a decreased risk of renal failure [62], and currently, a trend toward even lower trough levels (5–7 ng/ml) is increasingly being recommended in most centers.

Table 2. Summary of studies assessing the incidence of *de novo* NASH after liver transplantation.

Study	*N*	Steatosis (%)	NASH (%)	Cirrhosis	Median Follow-up (months)	Survival rate
Lim [74]	30	12 (40)	4 (13)	0	44	NA
Dumortier [55]	599	131 (31)	5 (4)	3 (2.3%)	40	NA
Seo [56]	68	12 (18)	6 (9)	0	28	NA
Vallin [57]	80	50 (78)	11 (17)	3	60	NA

Thus, a tailored immunosuppression regime in these high-risk NASH patients might be appropriate. This strategy might involve steroid-sparing regimes as well as low dose of CNI. Steroid-free regimes have demonstrated to have important benefits in a meta-analysis [63,64], particularly in terms of decreased risk of development of *de novo* DM and decreased cholesterol levels. AHT and hyperlipidemia are higher with cyclosporine-based immunosuppression than tacrolimus, but the incidence of post-transplant DM and metabolic syndrome are similar with cyclosporine and tacrolimus [65]. In a retrospective study, tacrolimus-based immunosuppression was associated with a lower risk of CV events [66]. However, tacrolimus has also been associated with development of *de novo* steatosis, as mentioned earlier [55]. When sparing doses of CNI, mycophenolate mofetil (MMF) and mammalian target of rapamycin (mTOR) inhibitors may be used. Although mTOR inhibitors can cause significant dyslipidemia, it does not seem to result in increased rate of CV events [67] and can be managed pharmacologically. MMF has also been described in association with increased post-LT CV risk [59], possibly due to the increased use of MMF in CNI-sparing regimes in high-risk patients (renal insufficiency, presence of diabetes), rather than a direct effect of MMF. Accordingly, to avoid an increased number of undesirable side effects from immunosuppressive therapy, the least effective dose should be our target.

Pharmacological therapies for NASH in the post-LT setting have not been investigated. Several agents are being studied in the nontransplanted NASH population (pioglitazone, obeticholic acid, vitamin E) with promising results, although none are currently approved. Therefore, the sole pharmacotherapy for NASH transplant recipients is aggressive treatment of DM, AHT, and hyperlipidemia.

Bariatric surgery has been used before, during, and after LT in some case series, with few number of patients included (around 60 patients in total). Its global efficacy in terms of weight loss is similar to that achieved in the general population (approximately 54% at 1 year and 66% at 2 years), but higher rates of complications have been reported [68]. Mortality during follow-up is around 10%, with a reoperation rate of about 12%, but no early postoperative deaths have been reported. The most popular techniques are restrictive procedures as sleeve gastrectomy and gastric banding, to avoid malabsorption of immunosuppressive agents that could derive from malabsorptive techniques and inability to access the biliary tree in Roux-en-Y procedures. As mentioned, different approaches in timing bariatric surgery and LT have been attempted. In published series, most patients undergoing pretransplant bariatric surgery were Child–Pugh A, and in many cases, diagnosis of cirrhosis was made incidentally during surgery. Thus, if pretransplant bariatric surgery is attempted, it must be performed at early stages, particularly before the onset of significant portal hypertension with development of collaterals. The performance of bariatric surgery during LT is less frequent, but open sleeve gastrectomy at the time of LT is increasingly being performed in some centers, although reports are still limited to case series. This approach is difficult to generalize to most centers owing to logistic reasons, because a hepatic and a bariatric surgeon must be available during the procedure. Laparoscopic sleeve gastrectomy is the most frequent procedure performed after transplantation, in more than half of cases reported. Performing bariatric surgery after LT allows for a better patient selection, but significant morbidity has been reported in published series. The average time lapse between LT and bariatric surgery has been reported to be 1-6 years in the different published series.

Conclusions

Nonalcoholic fatty liver disease is the most common etiology of chronic liver disease in developed countries and is becoming one of the leading indications for LT in the United States and other developed countries. NAFLD liver transplant candidates present a high risk of developing CV events before and after transplantation, and a thorough CV evaluation is recommended prior to inclusion in the waiting list, particularly in those with a history of prior CV disease and in those with several known CV risk factors. However, whether the addition of NAFLD to established CV risk factors and risk equations improves CV risk prediction, and thus type of assessment, is still unclear.

Post-LT outcomes are favorable and similar to other indications in terms of patient and graft survival. Disease recurrence is frequent after LT, but progression to advanced stages of fibrosis and cirrhosis, at least in the short–medium term, is rare, suggesting a slow disease progression. Studies with longer follow-up and prospective cohorts are needed to confirm these findings.

Finally, the obesity epidemic is also altering the donor population, with an increasing presence of steatotic grafts, which are associated with poorer post-LT outcomes. Several strategies may be implemented to optimize the quality of these grafts.

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Conflicts of interest

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