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Title: Changing trends of liver transplantation and mortality from non-alcoholic fatty liver disease

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***Cover Letter**

Dear Professor Mantzoro

Many thanks for inviting us to submit a review on “Changing trends of liver transplantation and mortality from non-alcoholic fatty liver disease”.

NAFLD is the leading global cause of liver disease with an estimated prevalence of 25% and is the fastest growing indication for liver transplantation. Our review outlines the current epidemiology, natural history and outcomes of NAFLD with a focus on pre- and post-liver transplant settings.

We hope that you will find this review interesting and of benefit for the readership of Metabolism.

Your sincerely

Emmanuel Tsochatzis

Highlights

- NAFLD is the leading global cause of liver disease with a prevalence of 25% and is the fastest growing indication for liver transplantation
- Metabolic syndrome complications and cardiovascular risk require rigorous assessment and management, in both pre- and post-live transplant settings.
- Liver transplant outcomes in well-selected NAFLD patients appear similar to non-NAFLD indications
- Liver donor steatosis from NAFLD is a foreseeable problem for potential living donor and deceased donor liver grafts

Changing trends of liver transplantation and mortality from non-alcoholic fatty liver disease

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Abbreviations
NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH non-alcoholic steatohepatitis; LT, liver transplantation; HCC, hepatocellular carcinoma; MELD, Model for End Stage Liver Disease; CTP, Child-Turcotte-Pugh

Summary

The rising tide of non-alcoholic fatty liver disease (NAFLD) associated with the obesity epidemic is a major international health concern. NAFLD is the leading global cause of liver disease with an estimated prevalence of 25% and is the fastest growing indication for liver transplantation (LT). The presence and severity of liver fibrosis is the only histologic predictor of clinical outcomes in this group. NAFLD poses several challenges in the peri-transplant setting including the management of multiple metabolic co-morbidities, post-transplant obesity and cardiovascular risk. However, post-LT outcomes in well-selected NAFLD patients appear similar to non-NAFLD indications, including in the setting of hepatocellular carcinoma (HCC). The rising prevalence of NAFLD may impact potential liver graft donors, which may in-turn adversely affect post-LT outcomes. This review outlines the current epidemiology, natural history and outcomes of NAFLD with a focus on pre- and post-liver transplant settings.

Introduction

Liver diseases currently affect 844 million persons globally and are responsible for two percent of annual deaths[1,2]. There have been dramatic changes in the landscape of hepatology over the past 3 decades, characterised by the identification of chronic hepatitis viruses and the comparatively recent introduction of potent direct-acting antiviral therapy. Concomitantly, liver transplantation (LT) has emerged as a highly successful therapeutic option in selected individuals with 5-year survival in excess of 85%[3]. As the transition to a "post-hepatitis C era" begins, the rising tide of non-alcoholic fatty liver disease (NAFLD) associated with the obesity epidemic has now become a key focus.

NAFLD is defined as over 5% liver steatosis in the absence of excess alcohol consumption or other concurrent causes of liver steatogenesis such as drugs, genotype 3 hepatitis C infection, Wilson disease, coeliac disease or disorders of lipoprotein metabolism. It can be sub-classified into simple steatosis without hepatocyte injury (NAFL, non-alcoholic fatty liver) or non-alcoholic steatohepatitis (NASH), which is a histologic diagnosis characterised by hepatocellular injury and inflammation with or without fibrosis[4]. The presence of advanced liver fibrosis is the sole histologic predictor of clinical outcomes in this group[5-7]. Recently, the term Metabolic Associated Fatty Liver Disease (MAFLD) has been proposed as an alternative to NAFLD with the aim of better pathophysiological characterisation of this condition[8,9].

Mortality in NAFLD is predominantly due to cardiovascular disease and extra-hepatic cancers, followed by liver-related complications, namely decompensated cirrhosis and hepatocellular carcinoma (HCC)[10-12]. The presence of NAFLD *per se* might confer additional cardiovascular risk beyond that of traditional risk factors [13,14]. In the United States, NAFLD is the fastest growing indication for LT[15], the leading indication for female LT recipients[16] and the second leading indication overall behind chronic hepatitis C virus[17]. Similar trends are being observed in Europe[18] as well as Australia and New Zealand[19]. Several challenges may be faced when dealing with the patients with NAFLD in the peri-transplant setting including the management of multiple co-morbidities, post-transplant obesity and cardiovascular

risk[20] (Figure 1). This review aims to review the current state of NAFLD in the pre- and post-liver transplant setting.

Epidemiology of NAFLD

NAFLD is the leading cause of liver disease with an estimated global prevalence of 25%[21]. The highest reported prevalence is in the Middle East (32%), followed by South America (31%), Asia (27%), US (24%), Europe (23%) and then Africa (14%). The incidence varies from 28 per 1000 person-years in the West to 52 per 1000 person years in Asia. Both the prevalence and incidence of NAFLD are climbing, with the former increasing from 15% in 2005 to 25% in 2010 and the latter rising from 33% to 59% over the same period [21,22]. As the diagnosis of NASH requires liver biopsy, wider population data are not available, however NASH prevalence is estimated to range between 1.5% and 6.5% in the general population[23]. The true prevalence of NAFLD related advanced fibrosis and cirrhosis in the general population remains elusive.

The prevalence of NAFLD and NAFLD related fibrosis increases with age, however, data in the over 70 age group are sparse[21,24]. The peak age group appears to be between 45 and 64 years of age[24,25]. Sex differences also exist and encompass several factors of NAFLD pathobiology including body composition, oxidative stress, fatty acid oxidation, triglyceride synthesis, insulin resistance, bile acids and the intestinal microbiome[26]. In a recent international study of over 450 patients with NAFLD and liver biopsies, male sex and older age were associated with lower survival and greater risk of HCC[27]. The incidence of NAFLD is higher in men than pre-menopausal women, however, the incidence appears similar in men and post-menopausal women[26,28-30]. This may be due to a protective effect of oestrogen, which is supported by the finding that the prevalence of NAFLD is lower in post-menopausal women who take hormone replacement compared to those who do not[31].

The economic burden of NAFLD is substantial, with annual direct medical costs in the United States projected at US $103 billion (US $1613 per patient) according to a Markov model based study[32]. In the same study, the annual direct medical cost per patient estimates for Germany, France, Italy and the United Kingdom were €354,

€784, €1163 and £357, respectively. Total annual cost estimates were approximately 3- to 12-fold higher than direct medical costs due to the addition of societal costs, with the highest costs in the 45-65 age group[32]. However, accurate modelling is challenging in NAFLD due to the less predictable natural history compared to other aetiologies of chronic liver disease, resulting in variability in model outputs.

Natural history of NAFLD

Advanced fibrosis and cirrhosis

Liver fibrogenesis is the process of extra-cellular matrix deposition by activated hepatic stellate cells and portal myofibroblasts in response to repetitive and long-term inflammation. In NAFLD, liver inflammation is the product of several heterogenous insults or "multiple hits" in genetically predisposed individuals[33,34]. Specific genetic polymorphisms in *PNPLA3* (patatin-like phospholipase domain-containing protein) and *TM6SF2* (transmembrane 6 superfamily member 2) have been associated with NAFLD progression[35,36]. Factors that may promote liver inflammation and subsequent fibrosis include the development of obesity with peripheral and hepatocyte fat accumulation, insulin resistance, and changes in the intestinal microbiome, which are also influenced by epigenetics, dietary alterations, and the co-existence of other chronic liver diseases or fibrogenic drugs and toxins[33,34].

Liver fibrosis is graded histologically from F0 (no fibrosis) to F4 (cirrhosis), with advanced (or bridging) fibrosis defined as F3. The presence of F3 or greater fibrosis signifies a higher risk of liver-related and cardiovascular mortality in NAFLD. Of the two NAFLD subtypes, NASH carries the greatest risk of fibrosis progression[37,38]. This was demonstrated in a meta-analysis of 411 patients in 11 paired liver biopsy studies that showed progression of one fibrosis stage occurs over 7 years in NASH and 14 years in NAFL. Furthermore, this study showed that 21% of patients with F0-F1 fibrosis at baseline progressed to F3/F4 fibrosis over a median of 5.9 years, suggesting the existence of a subgroup of "rapid progressors"[38].

A recent analysis of 475 patients with NASH and F3 fibrosis or compensated cirrhosis from two negative placebo-controlled studies of simtuzumab, a humanised anti-lysyl oxidase-like 2 (LOXL2) monoclonal antibody, further described the natural

history of progressive fibrosis in NASH[39]. Progression to cirrhosis occurred in 22% (48/217 F3 patients) and in those whom cirrhosis was already established, 19% (50/258) developed liver-related clinical events over a follow-up of only 96 weeks. The observed liver-related events included ascites (7%), hepatic encephalopathy (5%), variceal bleeding (3%), new onset varices (2%), hepatocellular carcinoma (<2%) and a single death (<1%). In the cirrhosis group, 68% had clinically significant portal hypertension at baseline, defined as hepatic venous pressure gradient (HVPG) measurement ≥10mmHg. The risk of clinical events increased by 15% for every 1 mmHg increase in HVPG. In a prior prospective study of 256 compensated NASH cirrhosis patients, 19% developed decompensation events over a follow-up of 27 months. In patients with HVPG <10mmHg, the event-free survival was 92% as opposed to 75% in those with HVPG of ≥10mmHg[40]. These findings suggest that HVPG has similar prognostic significance in NASH to other liver diseases.

Previous studies have reported variable rates of liver-related events in advanced fibrosis or cirrhosis due to NAFLD. For example, the PRELHIN study reported that 24% (4/17) of compensated cirrhosis and 13% (7/51) of F3 fibrosis patients developed liver-related clinical events over a median follow-up of 12.6 years[5]. Another study of 23 compensated NASH cirrhosis patients found that 39% developed decompensation events over median follow-up of 5 years, which was similar to HCV-related cirrhosis[41]. Furthermore, Hagstrom et al examined 646 biopsy-proven NASH patients with a mean follow-up of 19.9 years and found that the time to decompensation for 10 percent of the cohort was 11.8 years for F3 and 5.6 years for cirrhosis[7]. In a cohort of 437 patients with baseline liver biopsy, 32 patients (7.3%) decompensated or had a liver-related death after a follow-up of 9 years[42]. Predictors of such events were advanced fibrosis, increasing age and higher amount of collagen measured with morphometry (collagen proportionate area) but not NASH. Despite variations in time to decompensation, these studies all concur that fibrosis, rather than NASH, is the main predictor of liver-related outcomes. This is consistent with the paradigm that fibrosis is an impaired tissue response to sustained and repetitive liver inflammation from NASH and is therefore representative of long-standing liver damage on liver biopsy. Conversely, NASH might fluctuate in severity during the disease course and as a result, liver biopsy may

not accurately reflect the degree of disease activity over time[33]. A recent paired biopsy study of 446 patients found that clinical and histological (NAFLD activity score) markers of disease severity were associated with fibrosis progression and to a lesser extent, inversely associated with regression[43].

Recently, a multinational study of 458 patients over 5.5 years of median follow-up demonstrated that the clinical sequelae associated with NASH differ for F3 fibrosis and compensated cirrhosis[27]. The predominant clinical events of the 159 F3 fibrosis patients were vascular events and non-hepatic cancers with annual incidence of 0.9 and 1.2, respectively. In patients with Child-Turcotte-Pugh (CTP) score A5 cirrhosis, the major clinical events were decompensation, death or liver transplantation and HCC with annual incidence of 3.3, 2.1 and 1.8, respectively. The annual incidence of the same clinical events increased substantially in CTP A6 cirrhosis patients at 15.6 for decompensation, 11.1 for death or liver transplantation and 4.7 for HCC. These differences were reflected in 10-year transplant free survival rates of 94% for F3 fibrosis, 74% for CTP A5 and 61% for CTP A6. The predictors of the endpoints of death or transplantation, HCC and decompensation in cirrhosis patients were moderate alcohol consumption (up to 70 g/week for women and 140 g/week for men) and <33% steatosis.

There are limited data regarding the outcomes of NASH cirrhosis in comparison to other aetiologies. In a case-control study of 152 NASH cirrhosis patients compared to 150 patients with HCV cirrhosis, the NASH group had a lower mortality in CTP A disease, however, the mortality was equivalent in decompensated cirrhosis (CTP B and C)[44].

Similar to other aetiologies of chronic liver disease[45,46], regression of advanced liver fibrosis has also been observed in NAFLD. Data from the simtuzumab trials reported that 20% of patients with F3 fibrosis and 9% of those with compensated cirrhosis at baseline had fibrosis regression over 96 weeks[39]. Moreover, regression of fibrosis has been shown to occur in up to 40% of NAFLD after bariatric surgery according to a recent meta-analysis of 32 cohort studies[47]. The heterogeneity in fibrosis progression and potential fibrosis regression in NAFLD

suggests that the natural history is not necessarily linear, but may involve periods of stability, progression or regression[22].

Moving forward, since NAFLD is associated with a considerable disease burden but rarely results in advanced fibrosis, non-invasive testing pathways are required for risk stratification, in order to identify those patients at higher risk for liver-related events [48]. When such pathways are implemented in primary care, they can increase the detection of advanced fibrosis 4-fold[49] and the detection of cirrhosis 2-fold[50] compared to standard of care. Moreover, they are cost-effective[51,52] and reduce unnecessary secondary care referrals [53].

NAFLD associated hepatocellular carcinoma

HCC is a major concern in NAFLD related cirrhosis and to a lesser degree, in bridging fibrosis. In data from the Northeast of the UK, by 2010 NAFLD accounted for 35% of HCC cases, while metabolic risk factors were present in 66% of HCC cases irrespective of the underlying aetiology [54]. NAFLD was the third-most common cause of HCC in the US in an analysis from 2005 to 2009, with an increase of approximately 9% annually[55]. In this study, NAFLD related HCC patients were older and also found to be more likely to die from HCC as well as being more likely to have heart disease and have a shorter survival time than non-NAFLD patients with HCC. Furthermore, a recent retrospective analysis of the Veterans Health Administration Corporate Data Warehouse found that the risk of HCC in over 296,000 NAFLD patients was 7-fold higher than matched controls from the general population. The vast majority of the 490 HCCs occurred in those with cirrhosis, resulting in an annual incidence of 10.6 per 1000 person years[56]. However, approximately 13% did not have cirrhosis, which supports the concept that non-cirrhotic NAFLD patients may develop HCC. In a multicentre cohort of 145 patients with HCC on a background of NASH from Italy, only 50% of patients had cirrhosis [57]. Tumours that develop in the absence of cirrhosis have distinct morphological characteristics and are more often well differentiated [58].

An annual HCC incidence of 1.56% in NAFLD was found in an analysis of a Veterans Affairs healthcare system database in a recently published modelling study [59]. In terms of longer-term incidence, a recent meta-analysis of 25 studies calculates the incidence of HCC for cirrhosis as between 6.7% and 15% at 5 to 10

years[60]. These studies support HCC screening in NAFLD related cirrhosis, however the benefit in F3 fibrosis remains unclear[61]. There is no benefit to HCC surveillance in unselected patients with NAFLD.

Trends in liver transplantation

Liver transplantation for NAFLD is performed in selected patients for either decompensated cirrhosis or HCC. In decompensated cirrhosis, the threshold for transplant benefit varies amongst organ sharing jurisdictions but generally is the equivalent of a Model for End-stage Liver Disease (MELD) score or MELD-sodium score of 15 or greater. Similarly, acceptable waitlisting criteria for hepatocellular carcinoma vary internationally, with the original Milan criteria considered the minimum standard[62,63]. The implications for NAFLD in the setting of liver transplantation are summarised in Table 1.

NAFLD is the fastest growing indication for liver transplantation according to data from several transplant registries, including those from the US[17], Europe[18] and Australia and New Zealand[19]. It is also the fastest growing indication for simultaneous liver-kidney transplantation in the US[64]. A recent analysis of the United Network for Organ Sharing/Organ Procurement and Transplant Network (UNOS/OPTN) database from 2004 to 2016 found that NASH is now the leading indication for LT in females, increasing by 91% over the study period. In men, NASH increased by 120% over the same period and was only second to alcohol related liver disease in terms of indication[16].

Transplantation for NAFLD related HCC is also rapidly increasing. In the US, patients undergoing LT for NAFLD associated HCC increased 4-fold from 2002 to 2012, which was higher than any other aetiology of HCC[65]. This trend has continued in a more recent analysis of the US Scientific Registry of Transplant Recipients from 2002 and 2016, which has shown that NASH is the fastest rising cause of HCC on the LT waiting list increasing from 2.1% to 16.2%, or almost 8-fold. Concurrently, the prevalence of HCC in LT candidates with NASH increased almost 12-fold, which was higher than other aetiologies[15]. In Australia and New Zealand, similar trends have occurred with NASH associated HCC increasing from 4% to 14% from 2004 to 2017 in transplant recipients[19]. Analysis of the European Liver

Transplant Registry from 2002 to 2016 revealed that HCC was more common in patients transplanted for NASH compared to other aetiologies at 39% and 29%, respectively[18].

Pre-transplant evaluation of NAFLD

NAFLD is strongly associated with the metabolic syndrome components of central obesity, hypertension, dyslipidaemia at type II diabetes mellitus (DM) and therefore transplant candidates with NAFLD are considered at increased cardiovascular risk[20]. However, the specific contribution of NAFLD as an independent risk factor for cardiovascular events and whether specialised pre-LT evaluation is required in patients with NAFLD remains unclear. A meta-analysis of 16 observational studies found that NAFLD was associated with a 64% increased risk of fatal or non-fatal cardiovascular events, however, traditional cardiovascular risk factor could not be controlled for in the analysis[66]. Conversely, a European study of four large primary care databases involving over 17 million adults found that there was no association between NAFLD and the risk of myocardial infarction or stroke after adjustment for age, sex and smoking status as well as the metabolic risk factors of hypertension, type II DM, total cholesterol level and statin use[67]. The authors concluded that cardiovascular assessment is important in NAFLD, however, it should be conducted in the same way as in the general population. In terms of post-LT cardiovascular outcomes, a retrospective study of 242 patients found that 26% of NASH patients had adverse cardiovascular events within 1 year of LT, versus 8.2% in the comparator group of alcohol related liver disease ($p<0.001$). Although there was increased risk of cardiovascular events after controlling for established cardiac risk factors in the NASH group, there was no difference in overall mortality[68]. Potential LT recipients with NAFLD therefore should be assessed on the presence of traditional cardiovascular risk factors and undergo formal cardiology assessment based on local protocols. No current gold-standard exists for pre-LT cardiovascular assessment in general or that apply specifically to patients with NAFLD. Generally, this involves electrocardiography, echocardiography, cardiac stress testing and possible invasive angiography[20]. If coronary revascularisation is required, then factors such as the duration of dual antiplatelet or anticoagulation therapy need to be balanced against the potential for clinical deterioration on the waiting list.

The evaluation and management of non-cardiac medical comorbidities pre-LT in NAFLD is challenging. Patients should be routinely screened for hypertension, diabetes and dyslipidaemia and optimised by a multidisciplinary medical team[20]. Renal dysfunction is variably present pre-LT and is often multifactorial from pre-existing comorbidities or due to hepatorenal syndrome. Pre-transplant renal dysfunction has been shown to increase the risk of post-LT mortality and cardiovascular disease. In a retrospective study of 671 LT recipients, each 5-unit reduction in estimated glomerular filtration rate (using MDRD4) was associated with a 2% higher hazard of all-cause mortality and 5% higher hazard ratio of cardiovascular mortality[69]. LT candidates with NAFLD and renal dysfunction should also be medically optimised, use early renal-sparing immunosuppression regimens post-LT and considered for simultaneous liver and kidney transplantation (SLKT) if indicated.

Obesity is a common and complex issue for LT candidates with NAFLD. Between 2002 and 2011, 33% of LT recipients in the US were classified as obese using body mass index (BMI)[70] compared to 20% in the period between 1988 and 1996[71]. However, a BMI-based definition of obesity is less useful in patient with decompensated cirrhosis due to factors including fluid status, altered fat distribution and sarcopenia [72]. Correcting for ascites when calculating BMI reclassified between 11-20% patients to a lower BMI classification of obesity in a study of over 1300 LT recipients[73]. Moreover, corrected BMI did not predict patient or graft survival. These findings are supported by a large analysis of 57,255 LT recipients from the UNOS database where post LT survival did not differ between class 1, 2 or 3 obesity and diabetes, rather than obesity predicted poor post-transplant survival[74]. Similarly, a study of over 80,000 LT recipients from the Scientific Registry of Transplant Recipients (SRTR) database also found that obesity did not impact post-LT mortality, unlike presence of diabetes[75]. The presence of sarcopenia[76,77], sarcopenic obesity[78,79] and subcutaneous adiposity in females[80] all appear to be better predictors of pre- and post-LT mortality but require standardisation of definitions and measurement modalities before being adopted in clinical practice. Therefore, class 1 to 3 obesity is not currently recommended as a contraindication to LT, however, careful selection based on comorbidities is advised[20].

Management of morbid obesity pre-LT in potential bariatric surgery candidates is also challenging. Weight gain is common after LT, with approximately one-third of recipients developing obesity [81]. The timing of bariatric surgery requires careful consideration. In patients with low MELD scores and without portal hypertension, bariatric surgery can potentially be considered pre-transplant. Recently, a single-centre experience of 29 patients with sleeve gastrectomy performed at the time of LT compared to lifestyle intervention in 36 patients found that weight loss was more effective and durable over the 3-year follow-up in the combined sleeve gastrectomy group[82]. In addition, metabolic syndrome complications were lower in this group. This approach may have benefit in patients who are at short-term higher risk of metabolic or cardiovascular problems post-LT. Bariatric surgery may also be performed post-transplant in those who at greater risk of intraoperative complications.

Post- transplant outcomes

The post-LT outcomes of patients with NAFLD are similar to non-NAFLD patients. This is supported by several large registry studies from the US[30,83,84] and the European Liver Transplant Registry (ELTR)[18], which are summarized in Table 2. The ELTR analysis of 68,950 LT recipients from 2002 to 2016 found that survival for LT recipients transplanted for NASH without HCC at 1, 5 and 10 years was 84%, 73% and 62% respectively compared to 86%, 75% and 63%, respectively in non-NASH non-HCC patients. In those transplanted for HCC, NASH 1-, 5- and 10-year survival was 89%, 69% and 47% respectively, compared with 87%, 68% and 53%, respectively in non-NASH recipients. Survival was lower in patients transplanted for HCC compared to those with non-HCC indications for transplantation. Interestingly, cardiovascular mortality was no different in NASH patients and indeed was the second most common cause of death, after infection in both NASH and non-NASH patients. NASH patients were less likely to die from extra-hepatic malignancy or recurrent primary liver disease than non-NASH patients. There are again similar findings in patients undergoing SLKT. Analysis of the UNOS database from 2002 to 2011 found that in 2162 SLKT recipients, NASH had similar 5-year patient and liver graft survival to non-NASH groups. However, kidney graft loss was 1.5-fold higher in the NASH group[64]. Some of the findings from registry studies regarding the

favourable post-LT outcomes in NASH may be explained in part by the exclusion of "higher risk" NASH patients from transplantation and the low-risk of recurrent NASH in the graft. Furthermore, the comparator groups to NASH in these studies mostly precede the widespread use of direct-acting antiviral therapy for chronic hepatitis C, thus suggesting that more contemporary outcomes may be different.

It has been previously estimated that approximately 50% of NASH transplant recipients have recurrent NAFLD, of which 75% have NASH[85,86]. However less than 10% have advanced fibrosis[85,87,88]. A recent meta-analysis of 17 studies (2378 patients) examined both recurrent and de novo NASH and NAFLD after LT and found significant heterogeneity in the included studies, suggesting low confidence in the pooled incidence rates[89]. The risk of bias was mostly moderate to high in the included studies, also limiting the applicability of the findings. The authors found that the incidence rates of recurrent NAFLD were 59%, 57% and 82% at 1-, 3- and 5-years or greater post-transplant, while de novo rates were 67%, 40% and 78%, respectively. For recurrent NASH, the 1-, 3- and 5-year or greater rates were 53%, 57% and 48%, while de novo NASH rates were 13%, 16% and 17%, respectively.

Prevention and management of NAFLD after liver transplantation

The prevention and management of post-LT NAFLD is similar to that of the general population. Modifiable risk factors for both de novo and recurrent NAFLD include weight gain, diabetes, hyperlipidaemia, hypertension and possibly female sex[89-92]. The use of high-dose corticosteroids is associated with increased liver steatosis and metabolic syndrome complications post-LT[93], as is the case in the general population. Early steroid minimisation or steroid-free induction immunosuppression protocols may be considered[92,94]. However, the specific effects of other post-transplant immunosuppression such as calcineurin inhibitors on NAFLD and NASH have not been well-studied, unlike metabolic syndrome complications[92,95]. The priorities in management post-LT remains similar to the pre-LT setting and include prevention of excessive weight gain, active weight loss in obese individuals, management of pre-existing metabolic syndrome complications and individualised cardiovascular screening. Additional specific considerations in the post-LT setting are minimisation of immunosuppression to prevent metabolic complications as well

as the influence of potential immunosuppressant drug interactions with therapeutic agents aimed at treating the metabolic syndrome[92]. Further study is required to determine whether any other preventative or management interventions have specific benefit in the post-LT setting.

Liver donor steatosis

Donor steatosis has been associated with adverse graft function from ischaemia-reperfusion injury[96] or primary non-function[97]. This is of significant concern if graft steatosis is severe (>60%) and in such cases the graft should be discarded, whereas moderate steatosis of 30-60% in a donor liver may be possibly considered for use but should be matched carefully with a low-risk transplant recipient[20]. With the rising obesity epidemic, donor steatosis is a foreseeable problem for potential living-related donor and deceased donor liver grafts[98,99]. However, there is a lack of data to suggest that steatotic donor livers should not be allocated to recipients with NAFLD. Ex-situ machine perfusion of donor livers is a promising therapy that may re-condition steatotic livers for transplantation[100] but requires further study.

Conclusions

NAFLD is both a current and future global health concern that has substantial disease burden. It is the leading global cause of liver disease with a prevalence of 25% and is the fastest growing indication for liver transplantation. Liver fibrosis is the only histologic predictor of liver-related outcomes. Metabolic syndrome complications and cardiovascular risk require active assessment and management, particularly in the pre-LT setting. However, post-LT outcomes in well-selected NAFLD patients appear similar to non-NAFLD indications, including in the setting of HCC. The rising prevalence of NAFLD may impact potential liver graft donors, which may in-turn adversely affect post-LT outcomes. Ex-situ machine perfusion may have a potential role in the future to address this issue. In conclusion, NAFLD has emerged as the dominant force in reshaping the current hepatology landscape and poses several therapeutic challenges for the future.

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Table 1: Implications of NAFLD for liver transplantation

	Indication for transplant	Pre- transplant evaluation	Post-transplant care

Considerations	• Leading liver transplant indication for females in US and second only to alcohol in males
	• NAFLD is the fastest rising:
	  ○ indication for LT in US, Europe, Australia and New Zealand
	  ○ cause of HCC on the LT waiting list in the US
	  ○ indication for simultaneous liver and kidney transplantation
		• Associated with metabolic syndrome components – obesity, hypertension, diabetes, dyslipidaemia
		• Regarded as higher cardiovascular risk
		• Renal dysfunction from metabolic comorbidities can impact post liver transplant all-cause and cardiovascular mortality
		• The effect of obesity classified by BMI alone on post-LT mortality is unclear, but increases the risk of metabolic comorbidities
		• Sarcopaenia and sarcopaenic obesity are associated with increased mortality
			• Similar outcomes for NAFLD to non-NAFLD patients after liver transplantation
			• Renal-graft loss is more common after simultaneous liver kidney transplant
			• Both recurrent NAFLD and de novo NAFLD can be common after transplant
			  ○ Recurrent or de novo NASH are less common
			• Metabolic syndrome complications are common in the setting of immunosuppression

Suggested management strategies	• Community awareness and prevention of NAFLD and obesity
	• Primary care NAFLD screening algorithms
	• In established NAFLD cirrhosis, HCC screening is required
	  ○ role of HCC screening in F3 fibrosis is unclear
	• Obesity and metabolic comorbidities require assessment and early management
	• Bariatric surgery can be considered in compensated cirrhosis without significant portal hypertension
		• Screen and manage diabetes, hypertension and dyslipidaemia
		• Assess and manage cardiovascular risk based on established risk factors in general population
		• Encourage weight loss if obese, screen for sarcopaenia and encourage specialist dietitian consultation
		• Consider timing of bariatric surgery in potential candidates
		• In patients with renal dysfunction:
		  ○ Medically optimise renal function
		  ○ Consider renal-sparing immunosuppression regimen
		  ○ Referral for simultaneous liver-kidney transplantation may be required
			• Identify and manage modifiable risk factors for recurrent or de novo NAFLD
			• Aim for early corticosteroid wean or use steroid-free induction protocols
			• Minimise immunosuppression to reduce long-term risk of metabolic syndrome
			• Active weight loss in obese individuals
			• Manage pre-existing or new-onset metabolic syndrome complications
			• Individualised cardiovascular screening
			• Consider bariatric surgery in potential candidates

Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

Table 2: Transplant registry outcomes following liver transplantation for NAFLD

Study	Study Populations (n)	Data Sources	NAFLD Group Outcome	Comparator Group Outcome
Haldar et.al [18]	NASH: 2,741 Non-NASH: 66,209	Retrospective cohort study of primary LT recipients from European Liver Transplant Registry (2002-2016)	**Patient survival** NASH non-HCC 1-year 84%. 5-year 73% 10-year 62% NASH HCC 1-year 89% 5-year 69% 10-year 47%	**Patient Survival** Non-NASH non-HCC 1-year 86% 5-year 75% 10-year 63% Non-NASH HCC 1-year 87% 5-year 68% 10-year 53%
Cholankeril et al. [84]	NASH: 8,266 Non-NASH: 38,861	Retrospective cohort study of primary LT recipients from United Network for Organ Sharing/Organ Procurement and Transplantation database (2003-2014)	**Patient Survival** NASH 1-year 90% 3-year 83% 5-year 77%	**Patient Survival** HCV 1-year 88% 3-year 79% 5-year 80% ARLD 1-year 91% 3-year 84% 5-year 78%
Afzali et al.[30]	NASH: 1,810 CC: 3,843 Non-NASH Non-CC: 48,085	Retrospective cohort study of primary LT recipients from United Network for Organ Sharing database (1997-2010)	**Patient Survival** NASH plus CC 1-year 87% 5-year 81% 10-year 75%	**Patient Survival** Non-NASH non-CC 1-year 88%. 5-year 80% 10-year 73%
Charlton et al. [83]	NASH: 1,959 Non-NASH: 33,822	Retrospective cohort study of primary LT recipients from Scientific Registry of Transplant Recipients (2001-2009)	**Patient Survival** NASH 1-year 84% 3-year 78%	**Patient Survival** Non-NASH 1-year 87% 3-year 78%

Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; CC, cryptogenic cirrhosis; HCV, Hepatitis C Virus; ARLD, alcohol-related liver disease

Figure 1: Implications of NAFLD on liver transplantation

Despite a high community prevalence of NAFLD, only a minority of patients progress to cirrhosis and hepatocellular carcinoma. Liver transplantation for NAFLD appears to have similar outcomes to non-NAFLD indications, however, NAFLD recipients are well-selected. The risk of cardiovascular events, metabolic syndrome complications and extra-hepatic malignancy is pertinent at all disease stages.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma.

Changing trends of liver transplantation and mortality from non-alcoholic fatty liver disease

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Abbreviations
NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH non-alcoholic steatohepatitis; LT, liver transplantation; HCC, hepatocellular carcinoma; MELD, Model for End Stage Liver Disease; CTP, Child-Turcotte-Pugh

Summary

The rising tide of non-alcoholic fatty liver disease (NAFLD) associated with the obesity epidemic is a major international health concern. NAFLD is the leading global cause of liver disease with an estimated prevalence of 25% and is the fastest growing indication for liver transplantation (LT). The presence and severity of liver fibrosis is the only histologic predictor of clinical outcomes in this group. NAFLD poses several challenges in the peri-transplant setting including the management of multiple metabolic co-morbidities, post-transplant obesity and cardiovascular risk. However, post-LT outcomes in well-selected NAFLD patients appear similar to non-NAFLD indications, including in the setting of hepatocellular carcinoma (HCC). The rising prevalence of NAFLD may impact potential liver graft donors, which may in-turn adversely affect post-LT outcomes. This review outlines the current epidemiology, natural history and outcomes of NAFLD with a focus on pre- and post-liver transplant settings.

Introduction

Liver diseases currently affect 844 million persons globally and are responsible for two percent of annual deaths[1,2]. There have been dramatic changes in the landscape of hepatology over the past 3 decades, characterised by the identification of chronic hepatitis viruses and the comparatively recent introduction of potent direct-acting antiviral therapy. Concomitantly, liver transplantation (LT) has emerged as a highly successful therapeutic option in selected individuals with 5-year survival in excess of 85%[3]. As the transition to a “post-hepatitis C era” begins, the rising tide of non-alcoholic fatty liver disease (NAFLD) associated with the obesity epidemic has now become a key focus.

NAFLD is defined as over 5% liver steatosis in the absence of excess alcohol consumption or other concurrent causes of liver steatogenesis such as drugs, genotype 3 hepatitis C infection, Wilson disease, Coeliac disease or disorders of lipoprotein metabolism. It can be sub-classified into simple steatosis without hepatocyte injury (NAFL, non-alcoholic fatty liver) or non-alcoholic steatohepatitis (NASH), which is a histologic diagnosis characterised by hepatocellular injury and inflammation with or without fibrosis[4]. The presence of advanced liver fibrosis is the sole histologic predictor of clinical outcomes in this group[5-7]. Recently, the term Metabolic Associated Fatty Liver Disease (MAFLD) has been proposed as an alternative to NAFLD with the aim of better pathophysiological characterisation of this condition[8,9].

Mortality in NAFLD is predominantly due to cardiovascular disease and extra-hepatic cancers, followed by liver-related complications, namely decompensated cirrhosis and hepatocellular carcinoma (HCC)[10-12]. The presence of NAFLD *per se* might confer additional cardiovascular risk beyond that of traditional risk factors [13,14]. In the United States, NAFLD is the fastest growing indication for LT[15], the leading indication for female LT recipients[16] and the second leading indication overall behind chronic hepatitis C virus[17]. Similar trends are being observed in Europe[18] as well as Australia and New Zealand[19]. Several challenges may be faced when dealing with the patients with NAFLD in the peri-transplant setting including the management of multiple co-morbidities, post-transplant obesity and cardiovascular

risk[20] (Figure 1). This review aims to review the current state of NAFLD in the pre- and post-liver transplant setting.

Epidemiology of NAFLD

NAFLD is the leading cause of liver disease with an estimated global prevalence of 25%[21]. The highest reported prevalence is in the Middle East (32%), followed by South America (31%), Asia (27%), US (24%), Europe (23%) and then Africa (14%). The incidence varies from 28 per 1000 person-years in the West to 52 per 1000 person years in Asia. Both the prevalence and incidence of NAFLD are climbing, with the former increasing from 15% in 2005 to 25% in 2010 and the latter rising from 33% to 59% over the same period [21,22]. As the diagnosis of NASH requires liver biopsy, wider population data are not available, however NASH prevalence is estimated to range between 1.5% and 6.5% in the general population[23]. The true prevalence of NAFLD related advanced fibrosis and cirrhosis in the general population remains elusive.

The prevalence of NAFLD and NAFLD related fibrosis increases with age, however, data in the over 70 age group are sparse[21,24]. The peak age group appears to be between 45 and 64 years of age[24,25]. Sex differences also exist and encompass several factors of NAFLD pathobiology including body composition, oxidative stress, fatty acid oxidation, triglyceride synthesis, insulin resistance, bile acids and the intestinal microbiome[26]. In a recent international study of over 450 patients with NAFLD and liver biopsies, male sex and older age were associated with lower survival and greater risk of HCC[27]. The incidence of NAFLD is higher in men than pre-menopausal women, however, the incidence appears similar in men and post-menopausal women[26,28-30]. This may be due to a protective effect of oestrogen, which is supported by the finding that the prevalence of NAFLD is lower in post-menopausal women who take hormone replacement compared to those who do not[31].

The economic burden of NAFLD is substantial, with annual direct medical costs in the United States projected at US $103 billion (US $1613 per patient) according to a Markov model based study[32]. In the same study, the annual direct medical cost per patient estimates for Germany, France, Italy and the United Kingdom were €354,

€784, €1163 and £357, respectively. Total annual cost estimates were approximately 3- to 12-fold higher than direct medical costs due to the addition of societal costs, with the highest costs in the 45-65 age group[32]. However, accurate modelling is challenging in NAFLD due to the less predictable natural history compared to other aetiologies of chronic liver disease, resulting in variability in model outputs.

Natural history of NAFLD

Advanced fibrosis and cirrhosis

Liver fibrogenesis is the process of extra-cellular matrix deposition by activated hepatic stellate cells and portal myofibroblasts in response to repetitive and long-term inflammation. In NAFLD, liver inflammation is the product of several heterogenous insults or "multiple hits" in genetically predisposed individuals[33,34]. Specific genetic polymorphisms in *PNPLA3* (patatin-like phospholipase domain-containing protein) and *TM6SF2* (transmembrane 6 superfamily member 2) have been associated with NAFLD progression[35,36]. Factors that may promote liver inflammation and subsequent fibrosis include the development of obesity with peripheral and hepatocyte fat accumulation, insulin resistance, and changes in the intestinal microbiome, which are also influenced by epigenetics, dietary alterations, and the co-existence of other chronic liver diseases or fibrogenic drugs and toxins[33,34].

Liver fibrosis is graded histologically from F0 (no fibrosis) to F4 (cirrhosis), with advanced (or bridging) fibrosis defined as F3. The presence of F3 or greater fibrosis signifies a higher risk of liver-related and cardiovascular mortality in NAFLD. Of the two NAFLD subtypes, NASH carries the greatest risk of fibrosis progression[37,38]. This was demonstrated in a meta-analysis of 411 patients in 11 paired liver biopsy studies that showed progression of one fibrosis stage occurs over 7 years in NASH and 14 years in NAFL. Furthermore, this study showed that 21% of patients with F0-F1 fibrosis at baseline progressed to F3/F4 fibrosis over a median of 5.9 years, suggesting the existence of a subgroup of "rapid progressors"[38].

A recent analysis of 475 patients with NASH and F3 fibrosis or compensated cirrhosis from two negative placebo-controlled studies of simtuzumab, a humanised anti-lysyl oxidase-like 2 (LOXL2) monoclonal antibody, further described the natural

history of progressive fibrosis in NASH[39]. Progression to cirrhosis occurred in 22% (48/217 F3 patients) and in those whom cirrhosis was already established, 19% (50/258) developed liver-related clinical events over a follow-up of only 96 weeks. The observed liver-related events included ascites (7%), hepatic encephalopathy (5%), variceal bleeding (3%), new onset varices (2%), hepatocellular carcinoma (<2%) and a single death (<1%). In the cirrhosis group, 68% had clinically significant portal hypertension at baseline, defined as hepatic venous pressure gradient (HVPG) measurement ≥10mmHg. The risk of clinical events increased by 15% for every 1 mmHg increase in HVPG. In a prior prospective study of 256 compensated NASH cirrhosis patients, 19% developed decompensation events over a follow-up of 27 months. In patients with HVPG <10mmHg, the event-free survival was 92% as opposed to 75% in those with HVPG of ≥10mmHg[40]. These findings suggest that HVPG has similar prognostic significance in NASH to other liver diseases.

Previous studies have reported variable rates of liver-related events in advanced fibrosis or cirrhosis due to NAFLD. For example, the PRELHIN study reported that 24% (4/17) of compensated cirrhosis and 13% (7/51) of F3 fibrosis patients developed liver-related clinical events over a median follow-up of 12.6 years[5]. Another study of 23 compensated NASH cirrhosis patients found that 39% developed decompensation events over median follow-up of 5 years, which was similar to HCV-related cirrhosis[41]. Furthermore, Hagstrom et al examined 646 biopsy-proven NASH patients with a mean follow-up of 19.9 years and found that the time to decompensation for 10 percent of the cohort was 11.8 years for F3 and 5.6 years for cirrhosis[7]. In a cohort of 437 patients with baseline liver biopsy, 32 patients (7.3%) decompensated or had a liver-related death after a follow-up of 9 years[42]. Predictors of such events were advanced fibrosis, increasing age and higher amount of collagen measured with morphometry (collagen proportionate area) but not NASH. Despite variations in time to decompensation, these studies all concur that fibrosis, rather than NASH, is the main predictor of liver-related outcomes. This is consistent with the paradigm that fibrosis is an impaired tissue response to sustained and repetitive liver inflammation from NASH and is therefore representative of long-standing liver damage on liver biopsy. Conversely, NASH might fluctuate in severity during the disease course and as a result, liver biopsy may

not accurately reflect the degree of disease activity over time[33]. A recent paired biopsy study of 446 patients found that clinical and histological (NAFLD activity score) markers of disease severity were associated with fibrosis progression and to a lesser extent, inversely associated with regression[43].

Recently, a multinational study of 458 patients over 5.5 years of median follow-up demonstrated that the clinical sequelae associated with NASH differ for F3 fibrosis and compensated cirrhosis[27]. The predominant clinical events of the 159 F3 fibrosis patients were vascular events and non-hepatic cancers with annual incidence of 0.9 and 1.2, respectively. In patients with Child-Turcotte-Pugh (CTP) score A5 cirrhosis, the major clinical events were decompensation, death or liver transplantation and HCC with annual incidence of 3.3, 2.1 and 1.8, respectively. The annual incidence of the same clinical events increased substantially in CTP A6 cirrhosis patients at 15.6 for decompensation, 11.1 for death or liver transplantation and 4.7 for HCC. These differences were reflected in 10-year transplant free survival rates of 94% for F3 fibrosis, 74% for CTP A5 and 61% for CTP A6. The predictors of the endpoints of death or transplantation, HCC and decompensation in cirrhosis patients were moderate alcohol consumption (up to 70 g/week for women and 140 g/week for men) and <33% steatosis.

There are limited data regarding the outcomes of NASH cirrhosis in comparison to other aetiologies. In a case-control study of 152 NASH cirrhosis patients compared to 150 patients with HCV cirrhosis, the NASH group had a lower mortality in CTP A disease, however, the mortality was equivalent in decompensated cirrhosis (CTP B and C)[44].

Similar to other aetiologies of chronic liver disease[45,46], regression of advanced liver fibrosis has also been observed in NAFLD. Data from the simtuzumab trials reported that 20% of patients with F3 fibrosis and 9% of those with compensated cirrhosis at baseline had fibrosis regression over 96 weeks[39]. Moreover, regression of fibrosis has been shown to occur in up to 40% of NAFLD after bariatric surgery according to a recent meta-analysis of 32 cohort studies[47]. The heterogeneity in fibrosis progression and potential fibrosis regression in NAFLD

suggests that the natural history is not necessarily linear, but may involve periods of stability, progression or regression[22].

Moving forward, since NAFLD is associated with a considerable disease burden but rarely results in advanced fibrosis, non-invasive testing pathways are required for risk stratification, in order to identify those patients at higher risk for liver-related events [48]. When such pathways are implemented in primary care, they can increase the detection of advanced fibrosis 4-fold[49] and the detection of cirrhosis 2-fold[50] compared to standard of care. Moreover, they are cost-effective[51,52] and reduce unnecessary secondary care referrals [53].

NAFLD associated hepatocellular carcinoma

HCC is a major concern in NAFLD related cirrhosis and to a lesser degree, in bridging fibrosis. In data from the Northeast of the UK, by 2010 NAFLD accounted for 35% of HCC cases, while metabolic risk factors were present in 66% of HCC cases irrespective of the underlying aetiology [54]. NAFLD was the third-most common cause of HCC in the US in an analysis from 2005 to 2009, with an increase of approximately 9% annually[55]. In this study, NAFLD related HCC patients were older and also found to be more likely to die from HCC as well as being more likely to have heart disease and have a shorter survival time than non-NAFLD patients with HCC. Furthermore, a recent retrospective analysis of the Veterans Health Administration Corporate Data Warehouse found that the risk of HCC in over 296,000 NAFLD patients was 7-fold higher than matched controls from the general population. The vast majority of the 490 HCCs occurred in those with cirrhosis, resulting in an annual incidence of 10.6 per 1000 person years[56]. However, approximately 13% did not have cirrhosis, which supports the concept that non-cirrhotic NAFLD patients may develop HCC. In a multicentre cohort of 145 patients with HCC on a background of NASH from Italy, only 50% of patients had cirrhosis [57]. Tumours that develop in the absence of cirrhosis have distinct morphological characteristics and are more often well differentiated [58].

An annual HCC incidence of 1.56% in NAFLD was found in an analysis of a Veterans Affairs healthcare system database in a recently published modelling study [59]. In terms of longer-term incidence, a recent meta-analysis of 25 studies calculates the incidence of HCC for cirrhosis as between 6.7% and 15% at 5 to 10

years[60]. These studies support HCC screening in NAFLD related cirrhosis, however the benefit in F3 fibrosis remains unclear[61]. There is no benefit to HCC surveillance in unselected patients with NAFLD.

Trends in liver transplantation

Liver transplantation for NAFLD is performed in selected patients for either decompensated cirrhosis or HCC. In decompensated cirrhosis, the threshold for transplant benefit varies amongst organ sharing jurisdictions but generally is the equivalent of a Model for End-stage Liver Disease (MELD) score or MELD-sodium score of 15 or greater. Similarly, acceptable waitlisting criteria for hepatocellular carcinoma vary internationally, with the original Milan criteria considered the minimum standard[62,63]. The implications for NAFLD in the setting of liver transplantation are summarised in Table 1.

NAFLD is the fastest growing indication for liver transplantation according to data from several transplant registries, including those from the US[17], Europe[18] and Australia and New Zealand[19]. It is also the fastest growing indication for simultaneous liver-kidney transplantation in the US[64]. A recent analysis of the United Network for Organ Sharing/Organ Procurement and Transplant Network (UNOS/OPTN) database from 2004 to 2016 found that NASH is now the leading indication for LT in females, increasing by 91% over the study period. In men, NASH increased by 120% over the same period and was only second to alcohol related liver disease in terms of indication[16].

Transplantation for NAFLD related HCC is also rapidly increasing. In the US, patients undergoing LT for NAFLD associated HCC increased 4-fold from 2002 to 2012, which was higher than any other aetiology of HCC[65]. This trend has continued in a more recent analysis of the US Scientific Registry of Transplant Recipients from 2002 and 2016, which has shown that NASH is the fastest rising cause of HCC on the LT waiting list increasing from 2.1% to 16.2%, or almost 8-fold. Concurrently, the prevalence of HCC in LT candidates with NASH increased almost 12-fold, which was higher than other aetiologies[15]. In Australia and New Zealand, similar trends have occurred with NASH associated HCC increasing from 4% to 14% from 2004 to 2017 in transplant recipients[19]. Analysis of the European Liver

Transplant Registry from 2002 to 2016 revealed that HCC was more common in patients transplanted for NASH compared to other aetiologies at 39% and 29%, respectively[18].

Pre-transplant evaluation of NAFLD

NAFLD is strongly associated with the metabolic syndrome components of central obesity, hypertension, dyslipidaemia at type II diabetes mellitus (DM) and therefore transplant candidates with NAFLD are considered at increased cardiovascular risk[20]. However, the specific contribution of NAFLD as an independent risk factor for cardiovascular events and whether specialised pre-LT evaluation is required in patients with NAFLD remains unclear. A meta-analysis of 16 observational studies found that NAFLD was associated with a 64% increased risk of fatal or non-fatal cardiovascular events, however, traditional cardiovascular risk factor could not be controlled for in the analysis[66]. Conversely, a European study of four large primary care databases involving over 17 million adults found that there was no association between NAFLD and the risk of myocardial infarction or stroke after adjustment for age, sex and smoking status as well as the metabolic risk factors of hypertension, type II DM, total cholesterol level and statin use[67]. The authors concluded that cardiovascular assessment is important in NAFLD, however, it should be conducted in the same way as in the general population. In terms of post-LT cardiovascular outcomes, a retrospective study of 242 patients found that 26% of NASH patients had adverse cardiovascular events within 1 year of LT, versus 8.2% in the comparator group of alcohol related liver disease ($p<0.001$). Although there was increased risk of cardiovascular events after controlling for established cardiac risk factors in the NASH group, there was no difference in overall mortality[68]. Potential LT recipients with NAFLD therefore should be assessed on the presence of traditional cardiovascular risk factors and undergo formal cardiology assessment based on local protocols. No current gold-standard exists for pre-LT cardiovascular assessment in general or that apply specifically to patients with NAFLD. Generally, this involves electrocardiography, echocardiography, cardiac stress testing and possible invasive angiography[20]. If coronary revascularisation is required, then factors such as the duration of dual antiplatelet or anticoagulation therapy need to be balanced against the potential for clinical deterioration on the waiting list.

The evaluation and management of non-cardiac medical comorbidities pre-LT in NAFLD is challenging. Patients should be routinely screened for hypertension, diabetes and dyslipidaemia and optimised by a multidisciplinary medical team[20]. Renal dysfunction is variably present pre-LT and is often multifactorial from pre-existing comorbidities or due to hepatorenal syndrome. Pre-transplant renal dysfunction has been shown to increase the risk of post-LT mortality and cardiovascular disease. In a retrospective study of 671 LT recipients, each 5-unit reduction in estimated glomerular filtration rate (using MDRD4) was associated with a 2% higher hazard of all-cause mortality and 5% higher hazard ratio of cardiovascular mortality[69]. LT candidates with NAFLD and renal dysfunction should also be medically optimised, use early renal-sparing immunosuppression regimens post-LT and considered for simultaneous liver and kidney transplantation (SLKT) if indicated.

Obesity is a common and complex issue for LT candidates with NAFLD. Between 2002 and 2011, 33% of LT recipients in the US were classified as obese using body mass index (BMI)[70] compared to 20% in the period between 1988 and 1996[71]. However, a BMI-based definition of obesity is less useful in patient with decompensated cirrhosis due to factors including fluid status, altered fat distribution and sarcopenia [72]. Correcting for ascites when calculating BMI reclassified between 11-20% patients to a lower BMI classification of obesity in a study of over 1300 LT recipients[73]. Moreover, corrected BMI did not predict patient or graft survival. These findings are supported by a large analysis of 57,255 LT recipients from the UNOS database where post LT survival did not differ between class 1, 2 or 3 obesity and diabetes, rather than obesity predicted poor post-transplant survival[74]. Similarly, a study of over 80,000 LT recipients from the Scientific Registry of Transplant Recipients (SRTR) database also found that obesity did not impact post-LT mortality, unlike presence of diabetes[75]. The presence of sarcopenia[76,77], sarcopenic obesity[78,79] and subcutaneous adiposity in females[80] all appear to be better predictors of pre- and post-LT mortality but require standardisation of definitions and measurement modalities before being adopted in clinical practice. Therefore, class 1 to 3 obesity is not currently recommended as a contraindication to LT, however, careful selection based on comorbidities is advised[20].

Management of morbid obesity pre-LT in potential bariatric surgery candidates is also challenging. Weight gain is common after LT, with approximately one-third of recipients developing obesity [81]. The timing of bariatric surgery requires careful consideration. In patients with low MELD scores and without portal hypertension, bariatric surgery can potentially be considered pre-transplant. Recently, a single-centre experience of 29 patients with sleeve gastrectomy performed at the time of LT compared to lifestyle intervention in 36 patients found that weight loss was more effective and durable over the 3-year follow-up in the combined sleeve gastrectomy group[82]. In addition, metabolic syndrome complications were lower in this group. This approach may have benefit in patients who are at short-term higher risk of metabolic or cardiovascular problems post-LT. Bariatric surgery may also be performed post-transplant in those who at greater risk of intraoperative complications.

Post- transplant outcomes

The post-LT outcomes of patients with NAFLD are similar to non-NAFLD patients. This is supported by several large registry studies from the US[30,83,84] and the European Liver Transplant Registry (ELTR)[18], which are summarized in Table 2. The ELTR analysis of 68,950 LT recipients from 2002 to 2016 found that survival for LT recipients transplanted for NASH without HCC at 1, 5 and 10 years was 84%, 73% and 62% respectively compared to 86%, 75% and 63%, respectively in non-NASH non-HCC patients. In those transplanted for HCC, NASH 1-, 5- and 10-year survival was 89%, 69% and 47% respectively, compared with 87%, 68% and 53%, respectively in non-NASH recipients. Survival was lower in patients transplanted for HCC compared to those with non-HCC indications for transplantation. Interestingly, cardiovascular mortality was no different in NASH patients and indeed was the second most common cause of death, after infection in both NASH and non-NASH patients. NASH patients were less likely to die from extra-hepatic malignancy or recurrent primary liver disease than non-NASH patients. There are again similar findings in patients undergoing SLKT. Analysis of the UNOS database from 2002 to 2011 found that in 2162 SLKT recipients, NASH had similar 5-year patient and liver graft survival to non-NASH groups. However, kidney graft loss was 1.5-fold higher in the NASH group[64]. Some of the findings from registry studies regarding the

favourable post-LT outcomes in NASH may be explained in part by the exclusion of "higher risk" NASH patients from transplantation and the low-risk of recurrent NASH in the graft. Furthermore, the comparator groups to NASH in these studies mostly precede the widespread use of direct-acting antiviral therapy for chronic hepatitis C, thus suggesting that more contemporary outcomes may be different.

It has been previously estimated that approximately 50% of NASH transplant recipients have recurrent NAFLD, of which 75% have NASH[85,86]. However less than 10% have advanced fibrosis[85,87,88]. A recent meta-analysis of 17 studies (2378 patients) examined both recurrent and de novo NASH and NAFLD after LT and found significant heterogeneity in the included studies, suggesting low confidence in the pooled incidence rates[89]. The risk of bias was mostly moderate to high in the included studies, also limiting the applicability of the findings. The authors found that the incidence rates of recurrent NAFLD were 59%, 57% and 82% at 1-, 3- and 5-years or greater post-transplant, while de novo rates were 67%, 40% and 78%, respectively. For recurrent NASH, the 1-, 3- and 5-year or greater rates were 53%, 57% and 48%, while de novo NASH rates were 13%, 16% and 17%, respectively.

Prevention and management of NAFLD after liver transplantation

The prevention and management of post-LT NAFLD is similar to that of the general population. Modifiable risk factors for both de novo and recurrent NAFLD include weight gain, diabetes, hyperlipidaemia, hypertension and possibly female sex[89-92]. The use of high-dose corticosteroids is associated with increased liver steatosis and metabolic syndrome complications post-LT[93], as is the case in the general population. Early steroid minimisation or steroid-free induction immunosuppression protocols may be considered[92,94]. However, the specific effects of other post-transplant immunosuppression such as calcineurin inhibitors on NAFLD and NASH have not been well-studied, unlike metabolic syndrome complications[92,95]. The priorities in management post-LT remains similar to the pre-LT setting and include prevention of excessive weight gain, active weight loss in obese individuals, management of pre-existing metabolic syndrome complications and individualised cardiovascular screening. Additional specific considerations in the post-LT setting are minimisation of immunosuppression to prevent metabolic complications as well

as the influence of potential immunosuppressant drug interactions with therapeutic agents aimed at treating the metabolic syndrome[92]. Further study is required to determine whether any other preventative or management interventions have specific benefit in the post-LT setting.

Liver donor steatosis

Donor steatosis has been associated with adverse graft function from ischaemia-reperfusion injury[96] or primary non-function[97]. This is of significant concern if graft steatosis is severe (>60%) and in such cases the graft should be discarded, whereas moderate steatosis of 30-60% in a donor liver may be possibly considered for use but should be matched carefully with a low-risk transplant recipient[20]. With the rising obesity epidemic, donor steatosis is a foreseeable problem for potential living-related donor and deceased donor liver grafts[98,99]. However, there is a lack of data to suggest that steatotic donor livers should not be allocated to recipients with NAFLD. Ex-situ machine perfusion of donor livers is a promising therapy that may re-condition steatotic livers for transplantation[100] but requires further study.

Conclusions

NAFLD is both a current and future global health concern that has substantial disease burden. It is the leading global cause of liver disease with a prevalence of 25% and is the fastest growing indication for liver transplantation. Liver fibrosis is the only histologic predictor of liver-related outcomes. Metabolic syndrome complications and cardiovascular risk require active assessment and management, particularly in the pre-LT setting. However, post-LT outcomes in well-selected NAFLD patients appear similar to non-NAFLD indications, including in the setting of HCC. The rising prevalence of NAFLD may impact potential liver graft donors, which may in-turn adversely affect post-LT outcomes. Ex-situ machine perfusion may have a potential role in the future to address this issue. In conclusion, NAFLD has emerged as the dominant force in reshaping the current hepatology landscape and poses several therapeutic challenges for the future.

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Table 1: Implications of NAFLD for liver transplantation

	Indication for transplant	Pre- transplant evaluation	Post-transplant care

Considerations	• Leading liver transplant indication for females in US and second only to alcohol in males
	• NAFLD is the fastest rising:
	  ○ indication for LT in US, Europe, Australia and New Zealand
	  ○ cause of HCC on the LT waiting list in the US
	  ○ indication for simultaneous liver and kidney transplantation
		• Associated with metabolic syndrome components – obesity, hypertension, diabetes, dyslipidaemia
		• Regarded as higher cardiovascular risk
		• Renal dysfunction from metabolic comorbidities can impact post liver transplant all-cause and cardiovascular mortality
		• The effect of obesity classified by BMI alone on post-LT mortality is unclear, but increases the risk of metabolic comorbidities
		• Sarcopaenia and sarcopaenic obesity are associated with increased mortality
			• Similar outcomes for NAFLD to non-NAFLD patients after liver transplantation
			• Renal-graft loss is more common after simultaneous liver kidney transplant
			• Both recurrent NAFLD and de novo NAFLD can be common after transplant
			  ○ Recurrent or de novo NASH are less common
			• Metabolic syndrome complications are common in the setting of immunosuppression

Suggested management strategies	• Community awareness and prevention of NAFLD and obesity
	• Primary care NAFLD screening algorithms
	• In established NAFLD cirrhosis, HCC screening is required
	  ○ role of HCC screening in F3 fibrosis is unclear
	• Obesity and metabolic comorbidities require assessment and early management
	• Bariatric surgery can be considered in compensated cirrhosis without significant portal hypertension
		• Screen and manage diabetes, hypertension and dyslipidaemia
		• Assess and manage cardiovascular risk based on established risk factors in general population
		• Encourage weight loss if obese, screen for sarcopaenia and encourage specialist dietitian consultation
		• Consider timing of bariatric surgery in potential candidates
		• In patients with renal dysfunction:
		  ○ Medically optimise renal function
		  ○ Consider renal-sparing immunosuppression regimen
		  ○ Referral for simultaneous liver-kidney transplantation may be required
			• Identify and manage modifiable risk factors for recurrent or de novo NAFLD
			• Aim for early corticosteroid wean or use steroid-free induction protocols
			• Minimise immunosuppression to reduce long-term risk of metabolic syndrome
			• Active weight loss in obese individuals
			• Manage pre-existing or new-onset metabolic syndrome complications
			• Individualised cardiovascular screening
			• Consider bariatric surgery in potential candidates

Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

Table 2: Transplant registry outcomes following liver transplantation for NAFLD

Study	Study Populations (n)	Data Sources	NAFLD Group Outcome	Comparator Group Outcome
Haldar et.al [18]	NASH: 2,741 Non-NASH: 66,209	Retrospective cohort study of primary LT recipients from European Liver Transplant Registry (2002-2016)	**Patient survival** NASH non-HCC 1-year 84%. 5-year 73% 10-year 62% NASH HCC 1-year 89% 5-year 69% 10-year 47%	**Patient Survival** Non-NASH non-HCC 1-year 86% 5-year 75% 10-year 63% Non-NASH HCC 1-year 87% 5-year 68% 10-year 53%
Cholankeril et al. [84]	NASH: 8,266 Non-NASH: 38,861	Retrospective cohort study of primary LT recipients from United Network for Organ Sharing/Organ Procurement and Transplantation database (2003-2014)	**Patient Survival** NASH 1-year 90% 3-year 83% 5-year 77%	**Patient Survival** HCV 1-year 88% 3-year 79% 5-year 80% ARLD 1-year 91% 3-year 84% 5-year 78%
Afzali et al.[30]	NASH: 1,810 CC: 3,843 Non-NASH Non-CC: 48,085	Retrospective cohort study of primary LT recipients from United Network for Organ Sharing database (1997-2010)	**Patient Survival** NASH plus CC 1-year 87% 5-year 81% 10-year 75%	**Patient Survival** Non-NASH non-CC 1-year 88%. 5-year 80% 10-year 73%
Charlton et al. [83]	NASH: 1,959 Non-NASH: 33,822	Retrospective cohort study of primary LT recipients from Scientific Registry of Transplant Recipients (2001-2009)	**Patient Survival** NASH 1-year 84% 3-year 78%	**Patient Survival** Non-NASH 1-year 87% 3-year 78%

Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; CC, cryptogenic cirrhosis; HCV, Hepatitis C Virus; ARLD, alcohol-related liver disease

Figure 1: Implications of NAFLD on liver transplantation

Despite a high community prevalence of NAFLD, only a minority of patients progress to cirrhosis and hepatocellular carcinoma. Liver transplantation for NAFLD appears to have similar outcomes to non-NAFLD indications, however, NAFLD recipients are well-selected. The risk of cardiovascular events, metabolic syndrome complications and extra-hepatic malignancy is pertinent at all disease stages.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma.

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Figure
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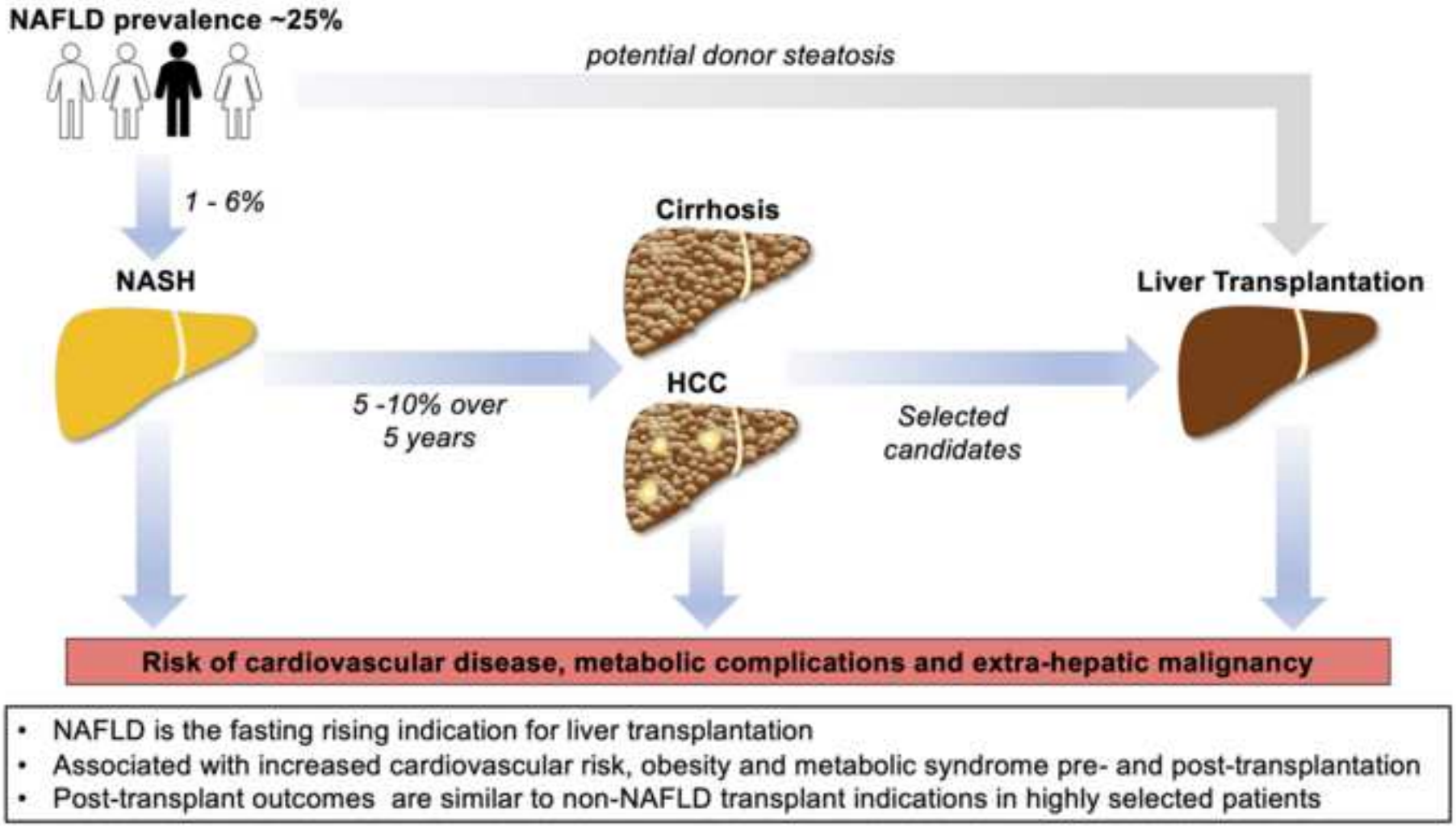

RESPONSE TO REVIERS

We would like to thank the Reviewers for their review and suggestions of our manuscript. We have addressed all comments and suggestions in the attached point-by point reponse.

Reviewers' comments:

Associate Editor:
The authors should be congratulated on their manuscript.
Some minor points of concern:

1. Highlights should be added according to the journal guides.

Our apologies for not meeting this journal requirement previously. Highlights have now been added.

2. The references should be formatted according to the journal guides.

This has now been amended.

3. Conflict of interest and funding declaration should be added.

This has been added.

4. The addition of a figure illustrating the main rates and facts of the field may add to the visibility of the article.

Thank you for the suggestion. Figure 1 has been added to the manuscript.

Reviewer #2:

Dear Editor,

Thank you for the opportunity to review this elegant paper by Majumdar and Tsochatzis on the issue of liver transplantation and NAFLD. The subject of NAFLD as an increasingly important cause of chronic advanced liver disease and cirrhosis with its inherent complications is timely. The review tackles several key aspects of this problem and highlights the main questions related to it. The different aspects are approached in a way that relevant clinical questions are asked, with an attempt to answer as far as current knowledge allows. The paper is comprehensive and very well written. There are only a few issues that I would like the authors to consider.

Pages refer to pages of the pdf file.
P5, line 20: Not only alcohol should be excluded but also other causes e.g. use of steatogenic
medication, Wilson's disease … to compile with the definition of NAFLD.

We thank Reviewer #2 for the suggestion. This has been amended. We have also added a line to include the proposed change in nomenclature to MAFLD.

P6, line 20: Check spaces after mortality.

This has been amended.

P7, line 31: This interpretation of the data is correct, but this sentence (and it is often formulated this way) suggests that, or could be misinterpreted as suggesting that fibrosis drive these outcomes, which is probably not true. NASH is fluctuating and its activity varies over time. Fibrosis is the result or read-out of prolonged liver damage vs. insufficient repair, resulting in lesions of which the amount is progressive over time. There is a fundamental difference between NASH that fluctuates between several degrees of severity, and fibrosis, that is more or less progressive over time. As such, biopsy is only a snapshot showing the actual degree of steatohepatitis at the time of biopsy, without any information about the severity of NASH in the period preceding the biopsy, whereas fibrosis at the time of biopsy to some extent reflects the degree of damage the liver was suffering from over a longer time period. So hence, not surprisingly, fibrosis is the strongest
predictor of outcome, as it better reflects a mean degree of disease activity on a longer period than a snapshot picture of something as fluctuating as NASH.
Please add some sentences to put the statement better into perspective.
A recent paper by the NASH CRN Kleiner et al, PMID 31584681 illustrates that changes in disease activity associate with changes in fibrosis scores over a mean period of almost 5 years, further supporting the concept of NASH being the driver of disease progression.

Thank you for this pertinent comment. We have added additional sentences and referenced the NASH CRN study as suggested.

P5, line 33: It is worth mentioning here (although it is also briefly touched upon in a later section) that the risk of CVD in NAFLD seems to exceed the risk dictated by the background cardiometabolic risk factors and points towards an independent contribution of NAFLD in the overall CVD risk (Anstee etal PMID 23507799, Francque et al PMID 27091791).

A sentence has added to address this point and we have referenced the two review articles as requested.

P9, line 53 and 55: Check spaces after punctuation.

Thank you for this suggestion. The spacing has been altered by the text being aligned as "justified". The manuscript has been altered to "left-alignment" to avoid this issue.

P10, line 13: fasting rising : fastes

This has been amended.

P10, line 29 and beyond: I think I get the point, but it reads a little awkward. The issue of NAFLD as an independent contribution raises the question whether patients with NAFLD need a different approach to pre-LT cardiac assessment than other indications for liver LT. This question is not so explicitly formulated. This could help for the structure and the reading of this paragraph. As this pre-LT cardiovascular evaluation is largely driven by cardiovascular risk assessment, the presence of NAFLD as aetiology of the liver disease is currently indeed not dictating as such the protocol of cardiac evaluation to be followed. On the other hand, this is more experience than evidence-based medicine, the pre-test probability of cardiac lesions in NASH patients is high, and cardiac procedures performed during pre-CT evaluation, by the use of drug-eluting stents and such for anticoagulation as anti-aggregant therapy, may delay liver transplantation, putting the patient … risk of further deterioration without transplant.

Thank you for these suggestions, we have restructured the paragraph for clarity.

P13, line 16 and 27: These are redundant sentences.

The first version of this repeated sentence has been removed.

P13, line 31: A recent… that examined… found…
Otherwise there seems to be something wrong grammatically with this sentence.

The sentences has been revised.

Reviewer #3: This is a well written,detailed review focusing on NAFLD, NASH, cirrhosis, HCC and liver transplantation.

A few comments:

In the summary, please handle abbreviations as you did in-text:
Line 8 change to: liver transplantation (LT).
Line 17 change to: hepatocellular carcinoma (HCC).

This has been addressed

Please consider adding epidemiologic information on gender and age disparities as well as the economic burden of disease.

Thank you for this comment. Two additional paragraphs have been added to the section address this point.

In the natural history of the disease, the authors have meticulously described the complications of NASH and fibrosis. It is the reviewer's opinion that in the beginning of this section, factors that promote fibrogenesis should be mentioned .

Thank you for this suggestion. An new introductory paragraph to the natural history section has been included to address this.

Reference # 22 does not seem relevant to the simtuzumab trials. Please review this citation and its in-text position.

This reference has been corrected. Thank you.

In the "Natural History of advanced fibrosis and cirrhosis" section:
"Furthermore, Hagstrom et al described 646 patients with liver biopsies for a mean follow-up of 19.9 years and found that the time for 10 percent of the patients developed decompensation was 11.8 years for F3 and 5.6 years for cirrhosis".
Please consider formulating this differently.

This sentence has been revised.

It is the reviewers opinion that the section "NAFLD associated hepatocellular carcinoma" could be incorporated in the "Natural History of advanced fibrosis and cirrhosis".
This section has some broad information on HCC but relevant and important data on HCC are also found in the next sections (trends in liver transplantation, post-transplant outcomes) making it seem incomplete.

We thank the reviewer for this comment. We have altered the structure of these sections. We felt that the entire section should be titled "Natural history of NAFLD" with sub-headings of "Advanced fibrosis and cirrhosis" and "NAFLD associated hepatocellular carcinoma".

The tables are very well-constructed and concise.

Metabolism has implemented a new set of guidelines for authors. Please refer to these guidelines at https://eur01.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.metabolismjournal.com%2Fauthorinfo&data=02%7C01%7C%7C1ab35b7c40c64905a4e108d7ef75108d%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C637241158378307711&sdata=%2BMKZdJGm6W4iQSpbXKSQioN3VbTsfZfgAbuBDQDa5A4%3D&reserved=0 and format your manuscript accordingly. Only manuscripts that are in the proper format are considered. Please make sure acknowledgements, funding info, conflicts of interest, contributions of authors are added at the end of manuscript.

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***Reporting Guidelines Checklist**

Not applicable

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Author credit statement: Dr Majumdar and Dr Tsochatzis were equally involved in the conception and design of the review article, drafting the article and revising it critically for important intellectual content and approved the final version to be submitted.

***Conflict of Interest Statement**