4-2022

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Review

A Comprehensive Review on the Risk of Metabolic Syndrome and Cardiovascular Disease after Liver Transplantation

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Abstract: Survival rates after liver transplantation have increased dramatically over the past 20 years. Cardiovascular disease is the most common extra-hepatic cause of mortality in the long-term post liver transplant. This is intimately linked with both the higher pre-existing rates of metabolic syndrome in these patients as well as increased propensity to develop de novo metabolic syndrome post-transplant. This unfavorable metabolic profile that contributes to cardiovascular disease is multifactorial and largely preventable. This review explores metabolic syndrome and cardiovascular disease and their contributory factors post liver transplantation to highlight areas for potential intervention and thus reduce the significant morbidity and mortality of patients due to metabolic syndrome and cardiovascular disease.

Keywords: liver transplant; metabolic syndrome; chronic liver disease

Citation: Chauhan, K.; Khan, A.; Chowdhury, S.; Ross, H.M.; Parra, N.S.; Halegoua-DeMarzio, D. A Comprehensive Review on the Risk of Metabolic Syndrome and Cardiovascular Disease after Liver Transplantation. *Livers* **2022**, *2*, 85–96. https://doi.org/10.3390/livers2020006

Academic Editor: Hartmut W. Jaeschke

Received: 6 April 2022
Accepted: 27 April 2022
Published: 29 April 2022

1. Introduction

While a small proportion of liver transplants are performed emergently for acute liver failure, most are for chronic liver disease with decompensation in the form of jaundice, ascites, coagulopathy, encephalopathy, or a combination of these. Indications for liver transplantation (LT) include patients with a MELD score > 15, with features of decompensated cirrhosis significantly impacting patients' quality of life [1]. Specific features that are also associated with significant mortality include hepatocellular carcinoma, variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis, refractory ascites, portopulmonary syndrome, or hepatopulmonary syndrome. In these patients, LT is a lifesaving tool with no current alternative treatment, such as dialysis for kidney disease or ventricular assist devices for heart failure.

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries and is predicted to become the most frequent indication for liver transplantation by 2030 [2]. NAFLD is the liver manifestation of metabolic syndrome, and this manifestation risks progression to non-alcoholic steatohepatitis (NASH), noted by inflammation and potentially fibrosis of the liver [3]. Insulin resistance—and by extension, metabolic syndrome—has long been known to be a reproducible pathogenic factor in the development of NASH [4]. This is most aptly described in the 2017 systematic analysis for the global burden of disease, looking into etiologies of cirrhosis and changes in its incidence over the past 27 years. The study showed a steady mortality rate for NASH cirrhosis despite declines in mortality in all other etiologies of cirrhosis [5–8]. According to data from the Scientific Registry of Transplant recipients, NAFLD is increasing while Hepatitis C is declining as an indication for LT, with an additional rise in the average age of transplant

candidates [9]. Inherent in this change is a trend towards obesity, insulin resistance, hypertension, dyslipidemia, and type 2 diabetes, earning NAFLD the reputation as the manifestation of metabolic syndrome in the liver. A large cross-sectional study found a 5.4% rate of metabolic syndrome diagnosis in patients before transplantation and 59.1% after [10]. Compared to the age-adjusted prevalence of 23.7% reported in the Western population, the rate of LT recipients diagnosed with metabolic syndrome is more than double [10,11]. Further, it is becoming more evident that screening for and treatment of the modifiable risk factors that lead to increased CV mortality are sub-optimal. A 2021 study by Finn et al. of LT patients and their healthcare providers found that there was a large mismatch in the perception of who was responsible for providing patient care with regards to modifiable cardiovascular and metabolic risk factors. Close to 70% of healthcare providers felt that it was the responsibility of the patient's PCP, while most informal caregivers and LT recipients believed they would receive treatments for these conditions from their transplant providers or other specialists (cardiologist, endocrinologist, nephrologist, surgeon) [12]. Further, this study revealed that there was inadequate awareness of the burden of CV causes of morbidity and mortality in LT patients [12]. Half of the patients' providers felt confident discussing CVD risk factors with post-LT patients, approximately one third felt confident managing their patients' CVD risk factors, and only 13% of providers felt like CVD risk factors were well controlled in their patients [12]. This highlights a care gap with significant potential for intervention to reduce rates of CVD mortality in LT recipients.

The aim of this review is to define and investigate the current incidence of metabolic syndrome and cardiovascular disease (CVD) in post-LT patients. We will additionally examine strategies that may be implemented to combat metabolic causes of significant morbidity and mortality in longer-term post-LT patients.

2. Definition of Metabolic Syndrome and Its Prevalence in Liver Transplantation

The National Cholesterol Education Program and the Adult Treatment Panel III defines metabolic syndrome as a constellation of risk factors that promote the development of atherosclerotic CVD (1). The presence of three or more of the following components fulfills the criteria for clinical identification of metabolic syndrome: hypertension ($\geq$130/85 mmHg), abdominal obesity (>102 cm in men, >88 cm in women), dyslipidemia (triglycerides $\geq$ 150 mg/dL or low HDL cholesterol < 40 mg/dL in men, <50 mg/dL in women), and impaired fasting glucose ($\geq$100 mg/dL) [13]. This is summarized in Table 1 below.

Table 1. Table summarizing the most commonly agreed-upon diagnostic criteria of metabolic syndrome according to the NCEP ATP3 2005 guidelines.

Parameters	NCEP ATP3 2005
Number of Abnormalities	**$\geq$3 of:**
Glucose	Fasting glucose $\geq$ 5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol §
Triglycerides	$\geq$1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides §
Obesity	Waist $\geq$ 102 cm (men) or $\geq$88 cm (women) *
Hypertension	$\geq$130/85 mmHg or drug treatment for hypertension

* In Asian patients, waist $\geq$ 90 cm (men) or $\geq$80 cm (women). § Treatment with 1 or more of fibrates or niacin.

3. Complications of Metabolic Syndrome Post-Liver Transplantation

LT recipients experience increased rates of obesity, hypertension, dyslipidemia, and diabetes, which contribute to an abnormal metabolic profile. The development of metabolic syndrome post-transplant has been linked to increased rates of and complications related to CVD, recurrent NASH, and recurrent Hepatitis C. As a result, the development of

metabolic syndrome post-transplant may impact long-term morbidity and mortality, which raises the critical importance of monitoring these patients for signs and symptoms of metabolic syndrome.

NASH has become one of the most common indications for LT. LT recipients for NASH experience a high recurrence of disease post-transplant, estimated to be 25% within three years [14,15]. The pathophysiology of metabolic syndrome and overall metabolic profile of increased rates of obesity, hypertension, and diabetes are associated with the development of recurrent NASH post-transplant [14,16]. Post-transplant diabetes is more strongly associated with NASH recurrence when compared to obesity and hypertension [14]. Long-term complications of NASH recurrence post LT include renal insufficiency, CV complications, and elevated infection-associated morbidity and mortality [17–19]. More than 30% of recipients with NASH post-transplant develop stage 3B chronic kidney disease, and renal insufficiency has recently been recognized as independently predictive of post-LT-related mortality [17,20].

4. Complications of CVD Post-Liver Transplantation

CVD is the most common extrahepatic cause of long-term mortality post-LT, and further examining the contributory risk factors suggests that a sizable proportion of this may be preventable [18,21,22]. Metabolic syndrome increases the risk of developing atherosclerotic CVD as well as CV events such as myocardial infarctions, transient ischemic attacks, strokes, and increases in overall CV-related mortality [23–25]. Specific components of metabolic syndrome such as hyperlipidemia and hypertension have also been independently associated with increased risk of CV deaths and ischemic events post-LT [26]. Metabolic syndrome is also associated with an earlier age of onset for myocardial infarctions and stroke among post-transplant recipients [18,25]. The increased risk of CV events in post-LT patients who develop metabolic syndrome is clinically very significant because post-LT patients who experience a major cardiac event have a lower 5-year survival rate [19].

Despite this, the prevalence of CV mortality due to coronary artery disease (CAD) is low in the immediate post-LT period and more prevalent in the longer-term post-LT period [27]. With the rigorous pre-LT screening for CAD, most clinically significant CAD is identified and intervened upon prior to LT to reduce immediate post-operative mortality. It has been identified that appropriately revascularized patients are not at increased risk of CV complications compared to the general population in the immediate post-operative period [27]. This suggests that patients are at high risk for the development of de novo and recurrent CAD post-transplant, which in turn contributes to a sizable proportion of CV mortality in the long-term post-LT period.

Differences in CV Outcomes in Liver Transplants Carried out for NASH vs. Any Other Indication

Although CVD is a significant source of mortality in LT for all indications, patients transplanted for NASH have an even greater risk of CV events compared to patients transplanted for non-NASH indications. In one study examining post-transplant outcomes in 588 LT recipients between 1999 and 2006, 172 patients had CV events, with over 20% lower survival at 14 years post-transplant. In this sub-group of patients who had CV events, NASH was the strongest predictor of CV events (HR 2.35, 95% CI 1.41–3.92; $p = 0.001$), higher than even the presence of prior CVD history (HR, 2.31; 95% CI, 1.44–3.70; $p < 0.001$) (12, 86). The only other statistically significant predictor of CV events in this paper was age (per decade: HR, 1.48; 95% CI, 1.20–1.83; $p < 0.001$). Time-dependent higher BMI was statistically significant for association with lower risk of CV events, although with HR of 0.96 (95% CI 0.93–0.99), clinical significance is questionable [20,28]. Further, a review of the NIDDK Liver Transplantation Database of 798 transplant recipients from 1990 to 1994 revealed that the risk of CV death was most common in patients transplanted for cryptogenic cirrhosis, a diagnosis often associated with NASH. (Other risk factors predisposing patients to CV death included alcoholic liver disease pre-LT and age in decades.) This highlights a subgroup of post-LT patients who are at even higher risk of

having CV events in the late post-transplant phase, warranting further study and closer clinical and laboratory-based risk factor monitoring to allow for early intervention [20].

5. Components of Post-Liver Transplantation Metabolic Syndrome

5.1. Hypertension

Although most patients with cirrhosis tend to have very low blood pressure, post-LT HTN is prevalent. A retrospective study in Spain assessed the prevalence of HTN in post-LT patients; 49.1% of those surviving 5 years or more were found to have HTN, while other studies found that up to 70.6% of patients developed HTN within the first year post-LT [29,30].

Steroids are sometimes used after LT to reduce transplant rejection, although their use is falling out of favor for steroid-sparing immunosuppressive regimens. They are sometimes necessary as adjuncts to steroid-sparing agents to prevent rejection, and patients can be on these for long periods of time. With prolonged use, steroids have been shown to cause HTN. Steroid-induced HTN results from the overstimulation of the mineralocorticoid receptor, leading to sodium and water retention in the kidney and increased pressure. Steroid withdrawal after LT decreases the prevalence of HTN, diabetes, and hypercholesterolemia [31].

While steroid use is variable among transplant programs, all patients' post-LT immunosuppressive regimen will include lifelong use of one of three medication classes: Calcineurin inhibitors (CNI), mTOR inhibitors, or inhibitors of purine and pyrimidine synthesis [32]. CNI and mTOR inhibitors increase blood pressure to a larger extent than mycophenolate mofetil (an inhibitor of purine and pyrimidine synthesis) [33]. A European trial comparing CNI and tacrolimus use observed HTN in 25.7% of CNI-treated patients and 17.2% of tacrolimus-treated patients after 6 months and 82% of CNI-treated patients and 64% of tacrolimus-treated patients after 24 months (about 2 years) post-transplant [34]. HTN was associated with more severe renal dysfunction in tacrolimus-treated patients and increased body weight in cyclosporine-treated patients [34].

As a result of the known side effects of the above immunosuppressive agents, the international LT society's consensus statement suggests minimizing the use of corticosteroids and CNIs post LT when possible. This, in addition to lifestyle changes and medical therapy for HTN if necessary, is a "strong recommendation" with a "moderate quality/certainty of evidence" [35]. Specific management of HTN post-LT is discussed later.

5.2. Diabetes Mellitus

The prevalence of post-transplant diabetes mellitus (PTDM) among LT recipients is greater than that of the general population at 20–40% [36]. Both NASH and Hepatitis C are associated with predisposition to develop PTDM, and combined these indications for LT are almost greater than patients undergoing transplantation for any other reason put together [37].

Corticosteroids used post-LT increase the hepatic output of glucose and decrease insulin production and insulin sensitivity. Reduction in steroid therapy has had efficacious results, but avoiding steroids entirely is not recommended [38]. CNIs induce insulin secretory dysfunction, with a greater degree of glucose impairment noted with tacrolimus over cyclosporine [37]. Studies have also shown that tacrolimus use lessens the need for concomitant steroid therapy and lessens graft loss and rejection [9]. The use of sirolimus remains conflicting in the literature. While some studies associated mTORs with a higher risk of developing PTDM than other immunosuppressants, others found them to have a less pronounced impact on glucose regulation than CNIs [39,40].

Ultimately, regardless of the chosen immunosuppression regimen, screening regularly for diabetes and ensuring strict control remain important. Both pre-LT diabetes as well as PTDM are associated with increased liver-related mortality in the long-term post-LT phase, independent of other factors [36]. In the study reviewing post-LT causes of mortality of 798 transplant recipients from the NIDDK Liver Transplantation Database, when pre-LT

diabetics are excluded, new onset diabetes is associated with increased long-term mortality (HR 1.61, CI 1.05–2.48, $p = 0.039$) [20]. When pre-LT diabetics are included, sustained diabetes without adequate control is also independently associated with death in a time-dependent fashion (HR 1.87, CI 1.41–2.48, $p < 0.001$) [20].

Management of PTDM remains similar to that of non-transplant patients and involves lifestyle modifications, pharmacotherapy, and the monitoring of immunosuppressive agents. These patients, however, are more complicated because they are more frequently exposed to steroids and other immunosuppressants with frequently changing doses, making their diabetes more difficult to control. While steroid and CNI withdrawal would be beneficial to manage PTDM, this decision should be made with priority given to maintaining allograft viability [41].

5.3. Obesity

One component of metabolic syndrome is elevated waist circumference, measured as greater than 102 cm in males (40 inches) or greater than 88 cm in females (35 inches). Weight gain is a common manifestation after LT; nearly two thirds of patients become obese after transplantation [41,42]. The weight gain associated with LT is multifactorial in nature. Cirrhosis presents as a hypermetabolic and malabsorptive state. Thus, prior to LT, patients may be malnourished; this is especially common with alcoholic liver disease. With the reversal of cirrhosis and chronic disease, there is also a reversal of patients' appetites [43].

Another challenge of managing post-transplant obesity is related to the role that immunosuppressives play in inducing obesity. LT has an 83% and 75% 1- and 5-year survival rate, respectively, with developments in immunosuppression playing a significant role in this improvement [44,45]. The mainstay of immunosuppression post-LT includes corticosteroids, which are used initially at high intravenous doses and tapered to maintenance doses within the first 6 months of transplant [44]. The other mainstays of immunosuppression include CNIs such as tacrolimusa and cyclosporine, and mTOR inhibitors such as Sirolimus and Everolimus. Glucocorticoids activate gluconeogenesis in the liver promote insulin resistance in adipose tissue, and modulate insulin and glucagon secretion to increase blood glucose levels [46]. In acute situations, these changes help to increase glucose levels in response to stress; however, chronically they can cause long-term effects in the hypothalamus-pituitary axis and influence eating behavior that may promote the consumption of higher calories and sweeter food [47].

Further, the challenges of post-transplant obesity are complicated by the overall obesity epidemic in the United States (US). Obesity, defined by the World Health Organization as a BMI above 25, is seen in up to 42% of the US population according to the CDC (Centers for Disease Control). NAFLD is a spectrum of disease that includes progression to NASH and eventually cirrhosis. In 2013, NASH became the second leading indication of LT and is projected to become the leading indication for LT in the future [48]. These trends have also been reflected in the increased prevalence of obesity in LT candidates. Data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients 2017 report revealed that 38.5% of LT candidates were obese [49]. This trend has had implications in LT; one medium-sized retrospective study at a European center showed increased mortality in obese patients compared to non-obese patients [50]. Another study based at a university hospital in the United States showed more postoperative complications in obese patients undergoing LT [51]. While in the previously mentioned study, the long-term patient survival was comparable, a larger database study conducted using the United Network for Organ Sharing database concluded that obesity is associated with increased mortality in patients undergoing LT [52].

Management of obesity after LT has become an important consideration. Bariatric surgery has been proposed as a management option and is indicated for patients with a BMI > 35 and comorbidities or BMI > 40. Lasailly et al. demonstrated that bariatric surgery caused histologic improvements in NAFLD, including the resolution of NASH in 84% of patients and the regression of fibrosis in 70% of patients, which was maintained through

5 years of follow-up [53]. Unfortunately, bariatric surgery in the LT patient is vastly more complicated than it is for other patients. Changes in anatomy post-LT must be considered, as must several risks unique to this population, including: causing variceal bleeding when accessing the gastric fundus, risk of injury to the allograft, or causing issues related to impaired gastrointestinal absorption that affect immunosuppression [54]. In their large review of bariatric surgery and LT, Diwan et al. recommended Sleeve Gastrectomy as their procedure of choice due to minimal operative risk, lack of prosthetic device insertion, and minimal changes to immunosuppression absorption, although they did note that the body of evidence was small [54]. Timing of the surgery has not been directly compared, including pre-LT, simultaneous with LT, and post-LT. Further prospective studies may elucidate more on this topic.

5.4. Dyslipidemia

The liver is known to play a crucial role in lipid and lipoprotein metabolism. Dyslipidemia, specifically an increased ratio of low-density lipoprotein compared to high-density lipoprotein, predisposes patients to atherosclerosis, which is in turn linked to the increased morbidity and mortality of CVD seen in post-LT patients [55]. Hyperlipidemia has been reported in up to 66% of patients, with dyslipidemia reported in 46% of patients in one smaller study [25,56]. Contributions to the dyslipidemia seen in post-transplant liver patients include the rising prevalence of NAFLD as an indication for LT obesity and the metabolic effects of immunosuppressives. Glucocorticoids and CNIs are known to induce insulin resistance, leading to dyslipidemia, which favors the production of atherogenic lipoproteins [46,55,57]. Studies investigating different CNIs, specifically tacrolimus compared to cyclosporine, have shown that tacrolimus-based immunosuppression reduces the incidence of dyslipidemia compared to cyclosporine [57,58]. While the exact mechanisms by which cyclosporine affects lipoprotein metabolism are unclear, one proposed mechanism of dyslipidemia is through altering bile-acid synthesis, a way in which the body lowers serum cholesterol [55]. Cyclosporine inhibits 7-alpha hydroxylase, the rate-limiting enzyme of bile-acid synthesis [59]. Studies that evaluated switching from cyclosporine to tacrolimus in renal and LT patients showed significant reductions in lipid levels [60,61]. Sirolimus, an mTOR inhibitor, is also associated with significant dyslipidemia, including hypertriglyceridemia and hypercholesterolemia; interestingly, sirolimus has been shown in some studies to not increase CVD due to a postulated protective affect against atherosclerosis [62]. In a large, randomized clinical trial of LT patients, immunosuppressive regimens with conversion to sirolimus had higher incidence of hyperlipidemia compared to patients who continued tacrolimus therapy [63].

In terms of the management of dyslipidemia associated with LT, lifestyle and dietary interventions should be employed early. Patients should be followed with a fasting lipid panel annually [64]. For patients with persistent dyslipidemia, HMG CoA reductase inhibitors should be considered, especially in patients with an LDL > 100 mg/dL [43]. Consideration should be given to the fact that many statins and immunosuppressives including calcineurin and mTOR inhibitors are metabolized by cytochrome P450-3A4. It has been noted that interactions occur more frequently with cyclosporine compared to tacrolimus. LeMahieu et al. demonstrated that tacrolimus does not interact with atorvastatin in the same way that cyclosporine does, and hence does not require dose reduction [65]. Pravastatin is not metabolized by the P450 system, and Rosuvastatin is metabolized through the 2C9 pathway, both of which may be reasonable options [66]. Fluvastatin has been shown to be safe and well tolerated in renal transplant patients on cyclosporine [67]. Hypertriglyceridemia can be treated effectively with fish oils, with previous studies showing no significant effects on cyclosporine metabolism [68]. PSK-9 inhibitors have shown promise in treating dyslipidemia; however, further prospective studies are necessary to assess their efficacy and safety in LT patients.

6. Strategies to Reduce Metabolic Syndrome and CVD Morbidity and Mortality Post-Liver Transplantation

The development of metabolic syndrome and CV risk factors in post-LT patients lead to long-term post-LT mortality. The components of metabolic syndrome have robust literature surrounding their management in non-LT patients; however, LT recipients are more susceptible to these conditions. Additional obstacles include poor awareness amongst patients and providers surrounding their risk of developing these conditions and low provider comfort and success in managing these conditions.

Uncontrolled HTN is associated with increased mortality post-LT (HR 1.46, CI 1.08–1.97, $p = 0.011$) [20]. HTN is ideally managed with calcium channel blockers followed by beta blockers and ACE inhibitors or angiotensin receptor blockers (ARBs) thereafter. Amlodipine and felodipine are preferred over diltiazem, nifedipine, or verapamil due to minimal cytochrome p450 activity and minimal interference with immunosuppressive drug levels [40,69]. Beta blockers are less effective and are used as a second line therapy [70]. ACE inhibitors and ARBs have more use during the later stages post-transplant when renin activity is more pronounced [40,69]. Patients with comorbid conditions may benefit from combination therapy of the above in addition to diuretic use. Despite consensus on the initiation of antihypertensive therapy, recent data from a study of 602 LT recipients indicated only 29% of patients had blood pressure controlled to <140/<90 mmHg (prior to the revisal of guidelines determining ideal BP control is <135/<85 mmHg) (90). Further, only one third of these patients who did not meet recommended BP targets were referred to HTN specialists for further management [71].

There are similar trends in the management of dyslipidemia and the use of statins for secondary prevention of CV events. A recent study of 495 LT patients at the Virginia Commonwealth University demonstrated that statin therapy for the management of dyslipidemia and secondary prevention were underused. In patients with known CAD pre-LT, only approximately half the patients were on statin therapy. Further, statin therapy was not initiated for nearly 30% of patients with new-onset dyslipidemia post-LT, with a mean time to initiation of statin therapy of 2.5 years in the other patients [72]. This study also confirmed previous studies showing that pre-LT CAD was not predictive of post-LT survival, suggesting that there is an accelerated rate of development of dyslipidemia and atherosclerosis post-LT that should be managed aggressively with statins where appropriate. In patients appropriately started on statin therapy, there was a significant survival benefit noted (HR 0.25; 95% CI 0.12–0.49) [72].

The suboptimal management of both HTN and dyslipidemia in post-LT patients, especially considering both are independently predictive of mortality, argues for regular preventative cardiology follow up for all post-LT patients, with a goal to improve BP control, increase statin use in appropriate patients for secondary prevention, and reduce mean time to statin initiation for patients with new onset dyslipidemia post-LT.

With regards to diabetes in the post-LT period, there is an increased risk of sustained PTDM as well as increased risk of mortality in post-LT patients with new-onset diabetes, as previously mentioned [20]. It is thought that the primary reason for increased mortality in patients who develop PTDM is their propensity to progress rapidly from NAFLD to NASH [20]. The treatment remains the same, with lifestyle and dietary modifications, as well as weight loss to prevent the onset or reverse the incidence of diabetes. Pharmacotherapy should be initiated if necessary to maintain insulin sensitivity. Further, vast variations exist in metabolic patterns between individuals, lifestyle parameters, dietary habits, and the quality of literature and misinformation surrounding diet; thus, involvement of a nutritionist is warranted pre-LT with continued follow up post-LT to identify nutrition goals and plan to achieve these goals.

Pre-LT obesity is associated with increased morbidity in the immediate post-operative period. A retrospective review performed in England demonstrated that people who were overweight and obese had increased infective complications post-LT, increased hospital length of stay, and longer ICU length of stay in the immediate post-operative period [73].

Obesity continues to be associated with increased morbidity post-LT. A recent meta-analysis of nine studies investigating risks factors of post-LT NASH demonstrated that post-LT BMI was statistically significant for predicting the development of NASH. No other factors were significant in the meta-analysis; however, multivariable analysis of the nine studies showed that hyperlipidemia and history of alcohol use were also consistent predictors of post-LT NASH [74]. Various options have been proposed to manage patients with obesity requiring LT. Sleeve gastrectomy (SG) is the most common option; however, data around the timing of SG remain scant. Several case reports as well as case series have demonstrated that SG after LT is feasible, but notable obstacles include altered anatomy and adhesions post LT, insurance barriers to the coverage of SG, and potential delays related to post LT complications such as rejection or infection [75–77]. More recently, however, large case series, such as that by Zamora-Valdes et al., have demonstrated that patients who undergo simultaneous LT and SG have more significant and durable weight loss when compared to patients who achieved weight loss prior to LT [78]. Further, this case series demonstrated a more favorable change in modifiable cardiovascular risk factors compared to patients who underwent weight loss pre-LT, demonstrating that simultaneous SG and LT is a potentially profound intervention to improve post-LT metabolic and cardiovascular risk profiles of patients with obesity [78,79].

7. Summary

NAFLD- and NASH-related morbidity and mortality are sure to increase rapidly over the coming years with the ongoing obesity epidemic, increasing rates of diabetes, and an aging population. One study by Sanyal et al. projected a 63% increase in the number of NASH cases, a 168% increase in incidents of decompensated cirrhosis, and a 178% increase in liver related death by 2030 [2]. With this increase in age and incident, NASH will follow the increase in incident of major adverse cardiac outcomes in the long-term post-LT phase because both factors are independently associated with reduced long-term survival [20,28]. This is compounded by a lack of standardized post-LT immunosuppressive regimens, which would otherwise be amenable to standardized side effect screening and management. Common regimens post LT include the use of CNIs such as tacrolimus, despite its side effect of increasing post-LT HTN and diabetes, as well as the continued use of mTOR inhibitors, despite the side effect of dyslipidemia [34,37,62]. Additionally, post-LT providers' previously highlighted discomfort, being aware of, screening for, and managing incident modifiable cardiovascular and metabolic risk factors, contributes significantly to the development of occult metabolic syndrome and worsened cardiovascular risk profile [12]. This ultimately is the mechanism by which cardiovascular mortality remains the most common extra hepatic reason for mortality in the long-term post-LT period, and much of this mortality is preventable [22].

In summary, careful monitoring for HTN, diabetes, and hyperlipidemia in the pre- and post-LT population is important to decrease CV complications and progression to metabolic syndrome. Transplant surgeons should highlight the importance of modifiable risk factor reduction as well as the need to maintain multidisciplinary continuity, as illustrated in Figure 1. In addition to medical screening and management of modifiable risk factors, there must be increased levels of provider, patient, and caregiver education regarding these risk factors to reduce the long-term, extra-hepatic causes of post-LT mortality. A system for multidisciplinary collaboration is vital to prevent important evidence and practices from falling through the cracks.

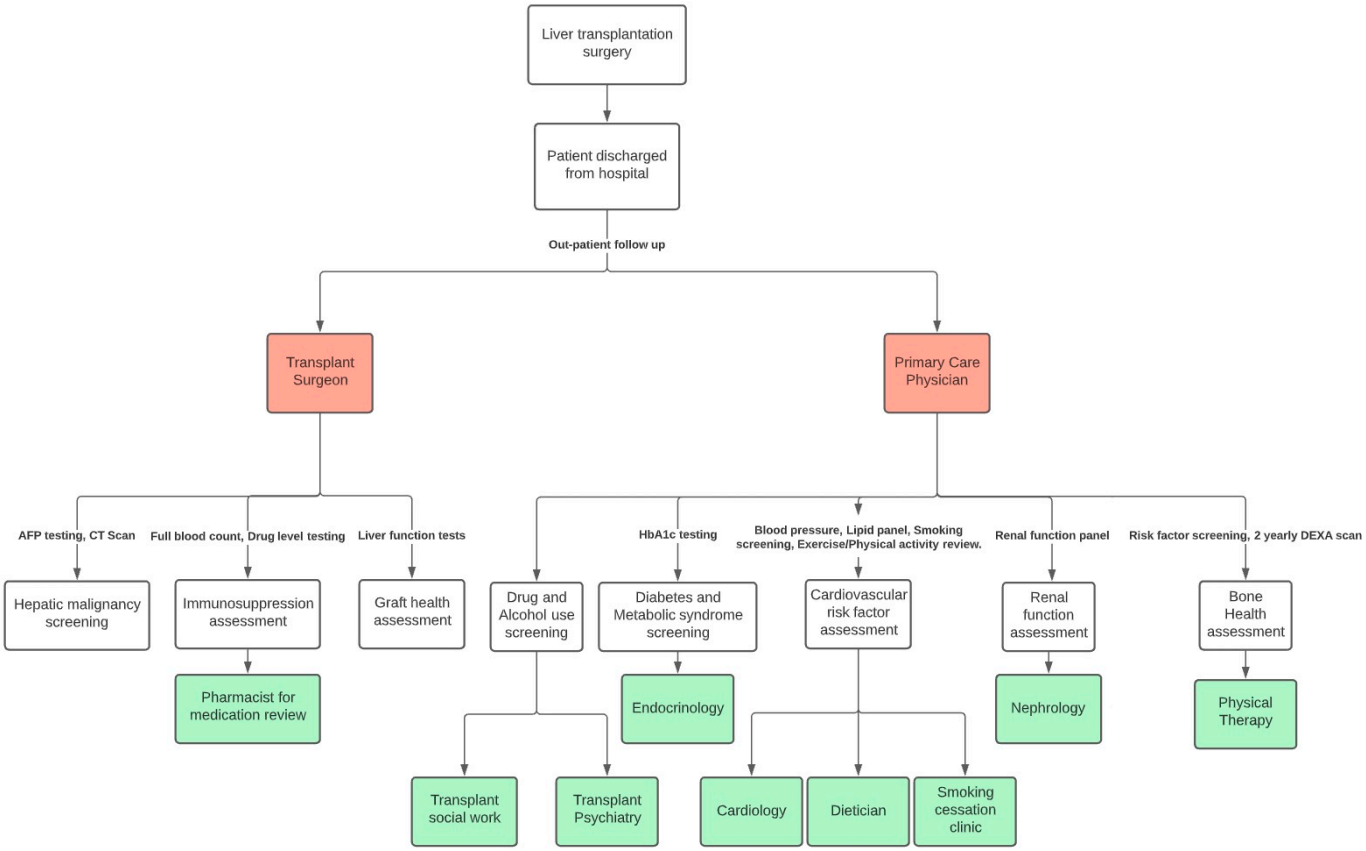

Figure 1. Flow chart demonstrating the summary of the multidisciplinary team approach to whom referral should be considered based on indication and assessment.

Author Contributions: Writing—original draft preparation, A.K., K.C., S.C., H.M.R. and N.S.P.; writing—review and editing, A.K. and D.H.-D.; visualization, K.C.; supervision, D.H.-D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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