

Diabetes and Metabolic Disorders: Their Impact on Cardiovascular Events in Liver Transplant Patients

Simone Di Cola,¹Giulia Cusi,¹Lucia Lapenna,¹Jakub Gazda,²Stefano Fonte,¹Marco Mattana,¹Gianluca Mennini,³Patrizio Pasqualetti,⁴and **Manuela Merli**¹

Show more

Academic Editor: Xingshun Qi

Received 03 Dec 2022

Revised 13 Jun 2023

Accepted 15 Jun 2023

Published 23 Jun 2023

Abstract

Cardiovascular diseases are currently one of the most important causes of morbidity and mortality in liver transplant patients over the long term. Therefore, evaluating prognostic factors for cardiovascular events (CVEs) in this population is essential for taking preventive measures. The aim of this study was to identify the impact of diabetes and other metabolic disorders on CVEs in liver transplant patients. Three hundred fifty-six liver transplant recipients who survived at least 6 months after surgery were enrolled. Patients were followed for a median time of 118 months (12–250 months). All cardiovascular events were carefully recorded and detailed in the patients' charts. Demographic data, diabetes, hypertension, dyslipidemia, weight changes, and a diagnosis of metabolic syndrome both before and after transplantation were noted to assess their possible relationship with CVE. The presence of a diagnosis of metabolic-associated fatty liver disease (MAFLD) was also evaluated. Immunosuppressive therapy was included in the analysis. Diabetes mellitus (DM), especially when present before transplantation, was strongly associated with CVEs (hazard risk HR 3.10; 95% confidence interval CI: 1.60–6.03). Metabolic syndrome was found to be associated with CVEs in univariate analysis (HR 3.24; 95% CI: 1.36–7.8), while pretransplantation and de novo MAFLD were not. Immunosuppressive therapy had no influence on predisposing transplanted patients to CVEs during follow-up. Further prospective studies may be useful in investigating the risk factors for CVEs after liver transplantation and improving the long-term survival of transplant patients.

1. Introduction

Liver transplantation (LT) has become a well-established treatment for end-stage liver disease due to advancements in surgical techniques and immunosuppressive therapies. As a result, the survival rate for liver transplant patients has significantly improved over the years. In Europe, survival rates are 84% and 72% at 1 and 5 years after transplantation, respectively [1].

While the short-term survival rates of liver transplant patients continue to improve, various long-term complications have drawn the attention of clinicians. These complications might be related to liver disease recidivism, posttransplant metabolic changes, and chronic immunosuppressive therapy [2, 3].

Furthermore, the progressive increase in age of the surviving population is associated with increased cardiovascular morbidity and mortality, with the cardiovascular risk being even higher in transplant recipients than in the age- and sex-matched control population [4].

This increased risk has been attributed to various factors, including those intrinsic to the patient and those related to transplantation, such as the requirement for long-term immunosuppressive therapy to prevent organ rejection [5, 6]. Metabolic alterations, such as diabetes mellitus, arterial hypertension, dyslipidemia, obesity, and hepatic steatosis may already be present before the transplant; furthermore, the majority of liver transplant recipients develop a metabolic syndrome after transplantation, which can contribute to an increased risk of cardiovascular events in the long term [7–10].

Diabetes is a significant risk factor for cardiovascular events (CVEs) in liver transplant patients [11–14], and some studies have suggested that de novo diabetes may be an even more relevant predictor of CVEs after transplantation [15]. Other metabolic conditions besides diabetes are also relevant. De novo hypertension is a common complication, affecting 50–75% of patients [8, 9, 16], and 20–60% of recipients report hyperlipidemia [17, 18]. The kind of immunosuppressant (such as the calcineurin inhibitor and the mTOR-Mammalian target of rapamycin inhibitors) may also contribute to these alterations [5, 19]. While weight gain after surgery is often desirable to correct malnutrition, continued weight gain can lead to overweight status, affecting approximately 50+% of transplant recipients three years after surgery [20], and the psychological conditions that occur in patients who undergo transplantation can play a fundamental role in this setting [17]. Studies have shown that obesity has a significant impact on long-term morbidity and mortality after liver transplantation in Europe. Additionally, the prevalence of metabolic syndrome after transplantation is estimated to be between 30 and 50% [8], which can increase cardiovascular risk and cause the development of hepatic steatosis in the new graft [21].

Recently, a new definition called MAFLD (metabolism-associated fatty liver disease) has been coined [22]. Indeed, MAFLD is diagnosed when there is documented fatty liver disease associated with overweight/obesity and/or the presence of type 2 diabetes mellitus or evidence of at least two of the seven metabolic dysregulations. MAFLD has been proposed as a contributing predictive factor of cardiovascular risk in the general population, with more capacity to identify people at a higher risk of CVEs and all-cause mortality as compared to the definition of NAFLD [23, 24]. The prevalence and relevance of MAFLD in the liver transplant setting are still unknown.

The aim of this study was to evaluate the association of metabolic alterations, including MAFLD, and immunosuppressive treatment with the incidence of CVEs in liver transplant patients over time.

2. Materials and Methods

2.1. Patients

This retrospective study aimed to analyze the demographic and clinical data of patients who underwent elective liver transplantation at the University Hospital Policlinico Umberto 1 between January 2000 and December 2020. The Ethics Committee of the Sapienza University of Rome approved this study (EC Prot. 0560/2022, 06/07/22). Before transplantation, all patients from our center undergo a rigorous cardiovascular assessment, which includes electrocardiography,

echocardiography, and intracardiac pressure measurements if pulmonary hypertension is suspected. In some cases, cardio-CT or coronarography is used to exclude cardiac ischemia.

To be eligible for this study, patients had to have a follow-up of at least 12 months at the center. After excluding 33 patients with less than 12 months of follow-up and 27 patients who continued their follow-up at other regional tertiary centers, a total of 356 patients were enrolled in the study.

2.2. Definitions

A composite variable “cardiovascular event” was created for the purpose of the study, and it included transient ischemic attack (TIA), ischemic and hemorrhagic stroke, cardiac decompensation, cardiac arrest, acute myocardial infarction (MI), symptomatic non-MI ischemic heart disease, and ischemia-based peripheral vasculopathy.

2.3. Data Collection

The data analyzed were extracted anonymously through a thorough review of patients’ charts. The data collected before transplantation included age, sex, reason for transplantation, body mass index (BMI), and presence of metabolic comorbidities such as diabetes (transient posttransplant diabetes lasting less than 6 months during steroid treatment was not considered) [25], arterial hypertension, dyslipidemia, obesity, metabolic syndrome, and liver steatosis. Data were also collected at the last follow-up postliver transplantation, and they included changes in body weight and BMI, occurrence of de novo diabetes, arterial hypertension [26], dyslipidemia [27], overweight or obesity [28], complete metabolic syndrome, or liver steatosis. The definitions of these conditions are provided in the guidelines cited. Details about immunosuppressive therapy were extracted, and the presence of MAFLD [22] was investigated in all patients before and after transplantation if information was available. Additionally, if a patient suffered a major cardiovascular event, their age, time from transplantation, and clinical outcome were recorded. The date and cause of death were also extracted.

2.4. Statistical Analysis

Clinical and demographic characteristics were reported using the mean and standard deviation or median and interquartile range (IQR) based on the distribution’s normality. Categorical variables were expressed as absolute counts and percentages.

We did not perform prior sample size calculations because of the retrospective nature of the study. However, all eligible data available were considered to maximize the power and generalizability of the results.

Univariable and multivariable models were analyzed using complete case analysis. The only potentially relevant predictors with missing values were metabolic syndrome (34 missing values) and MAFLD (100 missing values). Multiple imputation for missing data was performed for the metabolic syndrome by replacing missing values with predicted group membership according to a multivariable logistic model. For MAFLD, no imputation was conducted due to the large number of missing values (28%) compared to the entire sample.

Variables with values <0.10 in the simple model were included in the multivariable model using a change-in-effect criterion. Absolute risks were calculated as the number of events that occurred in a group divided by the number of people in that group.

To compare the risk of CVEs among nondiabetic, pretransplant DM patients and *de novo* DM patients, traditional proportional-hazard Cox regression and Fine-gray competing risk models were utilized, with CVEs as the primary outcome and CVE-unrelated mortality as a competing event. In the multivariable model, we adjusted for demographic characteristics that may be associated with CVEs or death, such as age at LT, sex, etiology of liver disease, hypertension, hyperlipidemia, MAFLD, metabolic syndrome, and treatment.

The significance of differences in continuous variables between groups was tested using Fisher (F) or Mann–Whitney tests with Bonferroni corrections.

3. Results

3.1. General Characteristics of the Entire Cohort

A total of 356 patients were included in the study, and they comprised 277 (77.8%) men and 79 (22.2%) women.

The median age at the time of transplantation was 56 years in the whole population, with no differences between males and females.

The median duration of follow-up was 118.5 months, with a range of 12 to 250 months. The most common underlying chronic liver diseases were alcohol-related liver disease ($n = 107$, 30.1%) and HCV and/or HBV infection ($n = 196$, 55.1%), followed by autoimmune and/or cholestatic liver disease ($n = 20$, 5.6%) and nonalcoholic hepatitis ($n = 20$, 5.6%), with other diseases accounting for 56 cases (15.7%). Hepatocellular carcinoma (HCC) was concurrently diagnosed in 173 patients (45.8%) (Table 1).

Table 1

Characteristics of the overall cohort and in patients with and without cardiovascular events (CVEs).

Regarding the immunosuppressive maintenance therapy, 192 (53.9%) patients were treated with monotherapy of calcineurin inhibitors, while 47 (13.2%) were prescribed everolimus or sirolimus monotherapy. The remaining 117 patients (32.9%) received various combined therapies. Of these 60 patients (16.8% of the entire cohort) treated with tacrolimus and mycophenolate mofetil, 28 patients (7.8% of the entire cohort) were treated with cyclosporine and mycophenolate mofetil, 1 patient (0.3% of the entire cohort) was treated with sirolimus and mycophenolate mofetil, 4 patients (1.2% of the entire cohort) were treated with azathioprine and tacrolimus, and 24 patients (6.7% of the entire cohort) were treated with tacrolimus and everolimus.

During the follow-up period, a total of 78 (21.9%) patients died. Among them, 21 (26.9%) patients died due to the recurrence of liver disease (such as the recurrence of viral cirrhosis, cholestatic liver disease, and alcohol relapse), 18 (23.1%) died due to the diagnosis of malignancies (of these, 5 patients died for HCC recurrence, the remaining 13 patients from *de novo* malignancies), 11 (14.1%) died due to infections, and 5 (6.4%) died due to cardiovascular disease.

The median BMI value at the time of transplantation was 25 kg/m² (IQR 22.6–28.1), whereas the median value after transplantation was 25.9 kg/m² (IQR 23.2–28.7). In particular, 15.8% of patients were obese (31.9 kg/m²—IQR 30.8–34 kg/m²), and 34.5% were overweight before transplantation (26.8 kg/m²—IQR 25.7–28.1 kg/m²). After transplantation, the percentage of obese patients increased to 18.0% (32.3 kg/m²—IQR 31.2–34.2 kg/m²), while the proportion of overweight patients increased to 40.9% (27.3 kg/m²—IQR 26.0–28.4 kg/m²). Overall, after transplantation, the majority of patients (58.9%) had a BMI >25 kg/m². BMI at the time of transplantation was significantly related with the origin of liver disease ($F(4,276) = 9.584$,) since patients with alcohol-related cirrhosis (27.0; 95% CI: 25.8–28.1) and with nonalcoholic steatohepatitis (NASH) (29.6; 95% CI: 27.3–31.9) had a higher BMI than patients with viral (25.2; 95% CI: 24.6–25.8) or autoimmune hepatitis (22.9; 95% CI: 20.9–25.0). This significant difference persisted even during the posttransplant follow-up period. The modifications of BMI after LT were not significantly different depending on the origin of liver disease ($F(5,307) = 0.46$;).

Prior to transplantation, 93 (26.1%) out of 356 patients had been diagnosed with diabetes. Among them, 8 patients exhibited regression of diabetes following the surgery. Seventy-four (20.8%) patients developed de novo diabetes after transplantation, resulting in a total of 159 (44.7%) patients with diabetes after transplantation. We investigated whether patients who developed de novo diabetes had different demographic and clinical characteristics compared with patients with pretransplant diabetes and nondiabetic patients. However, no significant differences were found (Table 1).

Metabolic syndrome was present in 17 patients (5.3%) prior to liver transplantation. However, its prevalence increased from 5.3% to 10.6%, as 34 patients developed this syndrome following liver transplantation.

Moreover, the percentage of patients developing de novo metabolic alterations after transplantation is noteworthy: 20.8% of patients became diabetic, 40.2% of subjects developed arterial hypertension, and 43% of patients showed dyslipidemia. A smaller percentage of patients also developed either MAFLD or complete metabolic syndrome (as shown in Table 2).

Table 2

Prevalence of metabolic alterations before and after liver transplantation.

3.2. Cardiovascular Events

After transplantation, 63 (17.7%) cases of cardiovascular events (CVEs) were documented. The characteristics of the two cohorts of patients (with CVE and without CVE) are reported in Table 1.

During the follow-up, as reported in Table 3, myocardial infarction, stroke, and a diagnosis of peripheral vasculopathy were the more frequent events.

Table 3

Incidence rates of CVEs among all transplanted patients.

The occurrence of CVEs took place on average 71 months after transplantation, with a range of 12 to 228 months. Of the entire cohort, 5 (7.9%) patients died due to CVE-related complications.

3.3. Factors Associated with Cardiovascular Events

Simple and multiple Cox regression analyses and the fine-gray competing risk regression analysis are reported in Table 4. The following variables were found to be associated with posttransplant CVEs in simple Cox regression analyses: male sex, higher age, alcohol-related liver disease, higher BMI, pretransplant diabetes mellitus, pretransplant arterial hypertension, and de novo arterial hypertension. In the multiple Cox regression analysis, female sex, age, and pretransplant DM remained associated with posttransplant CVEs. In the multiple fine-gray competing risk regression analysis, female sex, age, and pretransplant DM were all found to be associated with posttransplant CVE (the “diabetes” variable was introduced to the multivariable analysis because of significant HR in the univariable analysis).

Table 4

Simple and multiple Cox regression analyses with cardiovascular events as the primary endpoint. Fine-gray competing risk regression analysis with cardiovascular event as the primary endpoint and CVE-unrelated mortality as the competing event.

A diagnosis of MAFLD, neither before nor after liver transplantation, was not associated with CVE, similar to viral hepatitis and the type of immunosuppressive therapy. On the other hand, a diagnosis of metabolic syndrome before liver transplantation was significantly associated with CVEs (Table 4).

3.4. Impact of Pretransplant vs. De Novo DM on CVE

Patients with pretransplant DM had the highest incidence of CVE (31.1%), while those with de novo DM had a lower incidence at 16.1%, and nondiabetic patients had the lowest incidence at 10%. At 5 years postliver transplantation, 20% of subjects with pretransplant DM had experienced a CVE, whereas only 5% of those with de novo DM had experienced one. After 10 years, the respective percentages were 30% in patients with pretransplant diabetes mellitus (DM) and 10% in patients with de novo DM (Figure 1).

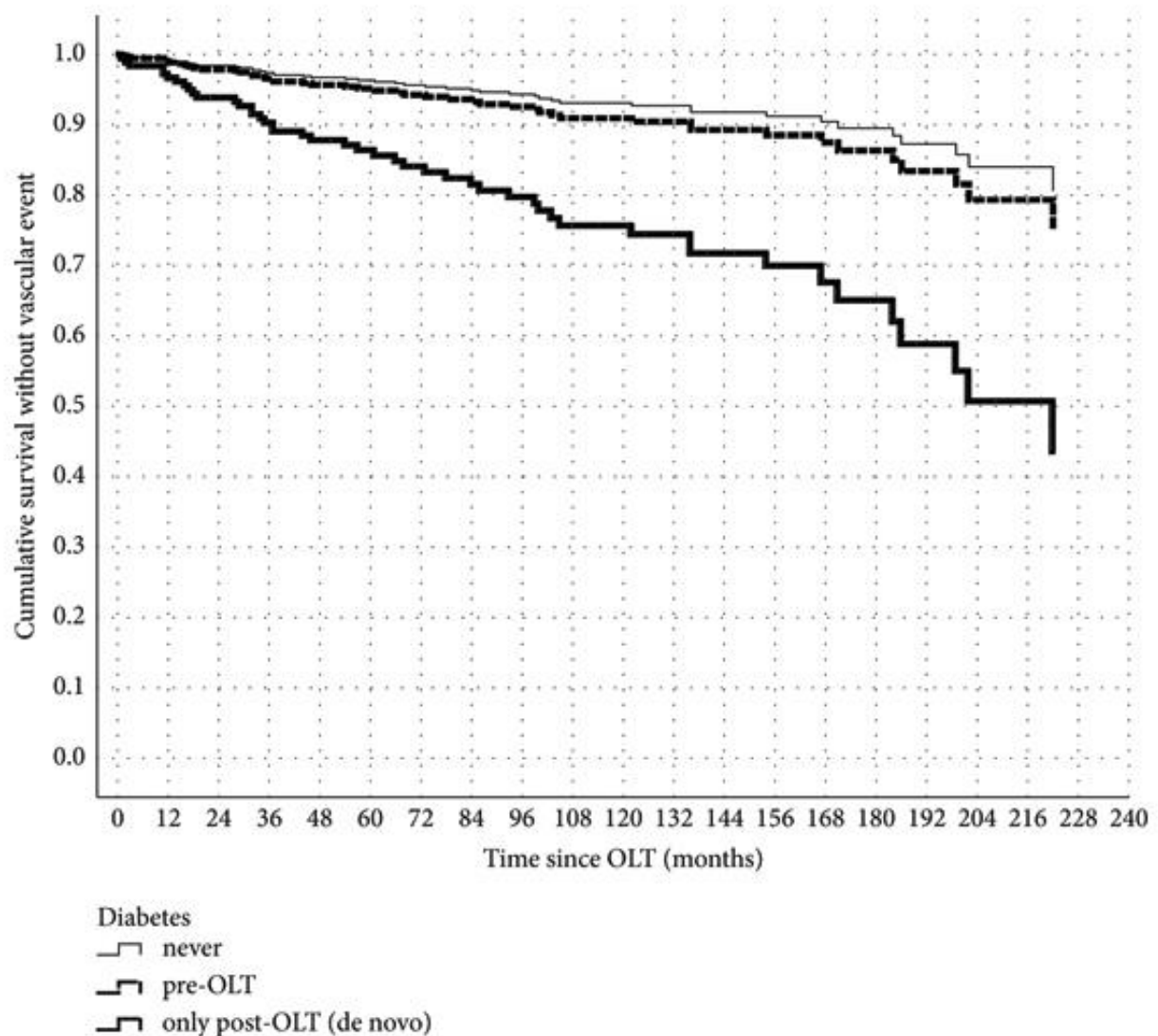


Figure 1
Kaplan–Meier curve of CVE-free survival in nondiabetic patients, pretransplant DM patients, and de novo DM patients.

4. Discussion

Over time, success and survival rates following liver transplantation have risen significantly, resulting in an increasing prevalence of long-term complications. Among these, metabolic complications are common as a consequence of multiple etiologic factors. Cardiovascular events are one of the leading causes of morbidity and mortality in the Western world and are closely linked to metabolic comorbidities.

Our retrospective study aims to explore how metabolic features can be modified in a population of transplant patients and how they may impact on CVEs after transplantation. For this purpose, we analyzed multiple parameters before and after liver transplantation.

In the case of our cohort, viruses and alcohol were the most frequent causes of liver cirrhosis. A moderate percentage of these patients had already been diagnosed with arterial hypertension, diabetes, and dyslipidemia during the pretransplant period (20.5%, 26.1%, and 3.9%, respectively). The recent increase in metabolic cirrhosis as a condition leading to liver transplantation may increase these numbers further in more recent cohorts [29].

During a follow-up period of an average of 10 years after LT, the prevalence of metabolic alterations increased steeply (Table 2), as also previously reported [4].

A consistent number of subjects also presented with issues of overweight and obesity. Weight gain after transplantation may occur due to the modification of dietary habits, increased appetite, and the effect of immunosuppressive drugs (especially as corticosteroids increase hunger and fluid retention) [30]. In addition, in the population transplanted because of alcohol-related liver disease, a transfer of the craving phenomenon from alcohol to food frequently occurs, with increased calorie intake and weight gain [31]. This trend was also present in our cohort.

During the study period, 63 CVEs were observed. The most frequently occurring of these were stroke and myocardial infarction.

CVEs were associated with sex, age, arterial hypertension, dyslipidemia, diabetes, and the presence of the metabolic syndrome. Our multivariate analysis selected the male sex, older age when transplanted, and patients presenting with diabetes and dyslipidemia. The results of other studies are consistent with ours, thus confirming how important it is to focus on these factors during patient follow-up [13, 15, 32]. A review of metabolic complications in liver transplant patients and their management was recently published [33]. The cumulative incidence of cardiovascular disease in the 8 years following transplantation yielded a percentage of 30%. The following factors were identified as risk factors for CVEs: diabetes, dyslipidemia, arterial hypertension, obesity, cigarette smoking, and renal insufficiency. Pretransplant diabetes was identified in 33–66% of patients (26% of the cases included in our cohort) and severely affects the prognosis of the transplanted patient in terms of mortality, CVE, and infection rates. Dyslipidemia was present after liver transplantation in 45–71% of cases (compared with approximately 46% for our cohort) and responded poorly to lifestyle modifications. In our study, approximately 60% of the patients presented with arterial hypertension present after transplantation, a value similar to that of 70% reported in the review.

One of the most frequently acknowledged CVE risk factors in liver transplant patients is diabetes. Two broad-scale studies reported in the literature have, however, provided conflicting results on this particular point [15, 34].

Our single-center study found results similar to those of Kuo et al. [34]. Indeed, we found that a diagnosis of diabetes before transplantation was associated with an increased risk of CVEs (HR 2.90; 95% CI 1.62–5.19), while this association was not significant in patients who experienced de novo DM (HR 1.37; 95% CI 0.69–2.72) (Table 4).

The duration of DM is included in the calculation of CV risk [35], and the risk is reported to be high if the duration is more than 10 years and very high if it is more than 20 years. In our study, the length of the diagnosis of DM before liver transplantation was not available; however, we can assume that the exposure to higher glucose levels lasted for a longer period in these patients in comparison with patients with de novo DM.

In patients with cirrhosis of nonmetabolic origin, the coexistence of low cholesterol levels (following reduced liver synthesis) and reduced mean arterial pressure (as a consequence of vasodilatation) may decrease the rate of cardiovascular complications but the interaction between diabetes and liver disease is likely to be more complex. Some longitudinal studies reported that the low CV complications in cirrhotic patients with diabetes was explained by the higher mortality, mostly related to cirrhosis-related complications, in these patients [36].

A second recognized risk factor for CVE is the presence of metabolic syndrome (MS). The diagnosis of MS should therefore be sought and promptly addressed with multidisciplinary approaches. However, the diagnosis of MS can be complex and fluctuating after liver transplantation, influenced by collateral effects due to immunosuppressive therapies and the trend to increase body weight.

In this regard, the concept of MAFLD has also emerged, as it has broader diagnostic criteria and allows for identifying a segment of the population at risk that is not included in the definition of MS. Unfortunately, only a subgroup of patients in our cohort had complete data for the assessment of MAFLD. Therefore, the number of patients with MAFLD could have been underestimated. Despite this bias, in contrast to the normal population [23], we found no significant association between MAFLD and CVE in our cohort.

Finally, there may be additional factors that have an impact on the onset of metabolic comorbidities and cardiovascular risk. Our study did not reveal any clear association between the type of immunosuppressive therapy and its possible role. Even those patients who were taking everolimus (a non-CNI that may increase the risk of hyperlipidemia) did not exhibit a higher risk of cardiovascular events.

The strengths of the present study are the rather large sample size, the long median follow-up (118.5 months), and the possibility of direct access to patient information.

The limitations of this study are related to its observational and retrospective nature. Some data were missing, as shown in Tables [1](#) and [4](#). We cannot completely exclude the possibility that patients' reporting of some CVEs may have been incomplete.

Additionally, important risk factors (e.g., cigarette smoking or a family history of CVEs) have not been considered, as this information is not always available for each patient.

From a clinical point of view, the present results suggest that special attention should be given to preexisting diabetes, as these patients are at increased risk of cardiovascular morbidity. Patients with preexisting DM could benefit from tighter treatment of diabetes and, at the same time, a strict control of other risk factors for cardiovascular disease, such as hyperlipidemia, arterial hypertension, and overweight. A multidisciplinary approach involving a cardiologist and a diabetic center is recommended.

Patients with de novo metabolic syndrome have an increased risk of CVE; thus, even if de novo DM as a single risk factor is not significantly correlated with CV, it deserves attention in the context of de novo metabolic syndrome.

5. Conclusions

Future prospective studies on large cohorts of liver transplant recipients are needed to better stratify cardiovascular risk after LT and how to act on it: what are the therapeutic interventions and whether they should differ from those applied in the general population. This becomes even more relevant considering the increasing survival of liver transplant patients, the increasing age at transplantation, and the increasing frequency of metabolic etiology of liver disease. For all of these reasons, it is necessary to continue research in this area to identify the best strategy for follow-up and therapy of these patients.

Data Availability

The retrospective data used to support the findings of this study may be released upon application to the corresponding author prof. Manuela Merli, who can be contacted at manuela.merli@uniroma1.it.

Disclosure

The research was performed as part of the employment of Prof. Manuela Merli and her collaborators.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. European Liver Transplant Registry, “ELTR data on liver transplantation in Europe,” 2020, <http://www.eltr.org/Overall-indication-and-results.html>.
View at: [Google Scholar](#)
2. L. S. Yang, L. L. Shan, A. Saxena, and D. L. Morris, “Liver transplantation: A systematic review of long-term quality of life,” *Liver International*, vol. 34, no. 9, pp. 1298–1313, 2014.
View at: [Publisher Site](#) | [Google Scholar](#)
3. S. Henchoz, M. Fraga, A. C. Saouli et al., “Suivi ambulatoire du patient transplanté hépatique: le rôle essentiel du médecin généraliste,” *Revue Medicale Suisse*, vol. 15, no. 660, pp. 1488–1495, 2019.
View at: [Publisher Site](#) | [Google Scholar](#)
4. N. G. Kim, A. Sharma, and S. Saab, “Cardiovascular and metabolic disease in the liver transplant recipient,” *Best Practice and Research Clinical Gastroenterology*, vol. 46, Article ID 101683, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)
5. T. Di Maira, E. C. Little, and M. Berenguer, “Immunosuppression in liver transplant,” *Best Practice and Research Clinical Gastroenterology*, vol. 46, Article ID 101681, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)

6. M. Charlton, J. Levitsky, B. Aqel et al., “International liver transplantation society consensus statement on immunosuppression in liver transplant recipients,” *Transplantation*, vol. 102, no. 5, pp. 727–743, 2018.
View at: [Publisher Site](#) | [Google Scholar](#)
7. B. Lattanzi, D. D'Ambrosio, D. Tavano et al., “Weight gain and *de novo* metabolic disorders after liver transplantation,” *Nutrients*, vol. 11, no. 12, p. 3015, 2019.
View at: [Publisher Site](#) | [Google Scholar](#)
8. M. Iadevaia, M. Giusto, V. Giannelli et al., “Metabolic syndrome and cardiovascular risk after liver transplantation: a single-center experience,” *Transplantation Proceedings*, vol. 44, no. 7, pp. 2005–2006, 2012.
View at: [Publisher Site](#) | [Google Scholar](#)
9. L. R. Anastácio, K. G. Diniz, H. S. Ribeiro et al., “Prospective evaluation of metabolic syndrome and its components among long-term liver recipients,” *Liver International*, vol. 34, no. 7, pp. 1094–1101, 2014.
View at: [Publisher Site](#) | [Google Scholar](#)
10. C. Becchetti, M. Dirchwolf, V. Banz, and J. F. Dufour, “Medical management of metabolic and cardiovascular complications after liver transplantation,” *World Journal of Gastroenterology*, vol. 26, no. 18, pp. 2138–2154, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)
11. S. Desai, J. C. Hong, and S. Saab, “Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management,” *Liver International*, vol. 30, no. 7, pp. 948–957, 2009.
View at: [Publisher Site](#) | [Google Scholar](#)
12. L. Luca, R. Westbrook, and E. A. Tsochatzis, “Metabolic and cardiovascular complications in the liver transplant recipient,” *Annals of Gastroenterology*, vol. 28, no. 2, pp. 183–192, 2015.
View at: [Google Scholar](#)
13. M. Albeldawi, A. Aggarwal, S. Madhwal et al., “Cumulative risk of cardiovascular events after orthotopic liver transplantation,” *Liver Transplantation*, vol. 18, no. 3, pp. 370–375, 2012.
View at: [Publisher Site](#) | [Google Scholar](#)
14. V. N. Munshi, S. Saghafian, C. B. Cook, K. T. Werner, and H. A. Chakkera, “Comparison of post-transplantation diabetes mellitus incidence and risk factors between kidney and liver transplantation patients,” *PLoS One*, vol. 15, no. 1, Article ID e0226873, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)
15. G. A. Roccaro, D. S. Goldberg, W.-T. Hwang et al., “Sustained posttransplantation diabetes is associated with long-term major cardiovascular events following liver transplantation,” *American Journal of Transplantation*, vol. 18, no. 1, pp. 207–215, 2018.
View at: [Publisher Site](#) | [Google Scholar](#)

16. C. Di Stefano, E. Vanni, S. Mirabella et al., “Risk factors for arterial hypertension after liver transplantation,” *Journal of the American Society of Hypertension*, vol. 12, no. 3, pp. 220–229, 2018.
View at: [Publisher Site](#) | [Google Scholar](#)
17. S. C. Ferreira, F. R. de Oliveira Penaforte, A. Cardoso et al., “Association of food cravings with weight gain, overweight, and obesity in patients after liver transplantation,” *Nutrition*, vol. 69, Article ID 110573, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)
18. C. Gisbert, M. Prieto, M. Berenguer et al., “Hyperlipidemia in liver transplant recipients: prevalence and risk factors,” *Liver Transplantation & Surgery*, vol. 3, no. 4, pp. 416–422, 1997.
View at: [Publisher Site](#) | [Google Scholar](#)
19. M. Hecking, A. Sharif, K. Eller, and T. Jenssen, “Management of post-transplant diabetes: immunosuppression, early prevention, and novel antidiabetics,” *Transplant International*, vol. 34, no. 1, pp. 27–48, 2021.
View at: [Publisher Site](#) | [Google Scholar](#)
20. L. Rezende Anastácio, L. Garcia Ferreira, J. Costa Liboredo, H. de Sena Ribeiro, A. Soares Lima, and E. Garcia Vilela, “Overweight, obesity and weight gain up to three years after liver transplantation,” *Nutricion Hospitalaria*, vol. 27, no. 4, pp. 1351–1356, 2012.
View at: [Publisher Site](#) | [Google Scholar](#)
21. M. Laryea, K. D. Watt, M. Molinari et al., “Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events,” *Liver Transplantation*, vol. 13, no. 8, pp. 1109–1114, 2007.
View at: [Publisher Site](#) | [Google Scholar](#)
22. M. Eslam, P. N. Newsome, S. K. Sarin et al., “A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement,” *Journal of Hepatology*, vol. 73, no. 1, pp. 202–209, 2020.
View at: [Publisher Site](#) | [Google Scholar](#)
23. H. Lee, Y. H. Lee, S. U. Kim, and H. C. Kim, “Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study,” *Clinical Gastroenterology and Hepatology*, vol. 19, no. 10, pp. 2138–2147, 2021.
View at: [Publisher Site](#) | [Google Scholar](#)
24. D. Kim, P. Konyn, K. K. Sandhu, B. B. Dennis, A. C. Cheung, and A. Ahmed, “Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States,” *Journal of Hepatology*, vol. 75, no. 6, pp. 1284–1291, 2021.
View at: [Publisher Site](#) | [Google Scholar](#)
25. F. Cosentino, P. J. Grant, V. Aboyans et al., *European Heart Journal*, vol. 41, no. 2, pp. 255–323, 2019.

26. B. Williams, G. Mancia, W. Spiering et al., “ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension,” *Journal of Hypertension*, vol. 36, no. 10, pp. 1953–2041, 2018.
View at: [Google Scholar](#)
27. A. L. Catapano, I. Graham, G. De Backer et al., “ESC/EAS guidelines for the management of dyslipidaemias,” *European Heart Journal*, vol. 37, no. 39, pp. 2999–3058, 2016.
View at: [Publisher Site](#) | [Google Scholar](#)
28. C. M. Apovian, “Obesity: definition, comorbidities, causes, and burden,” *American Journal of Managed Care*, vol. 22, no. 7, pp. 176–185, 2016.
View at: [Google Scholar](#)
29. B. Li, C. Zhang, and Y. T. Zhan, “Nonalcoholic fatty liver disease cirrhosis: A review of its epidemiology, risk factors, clinical presentation, diagnosis, management, and prognosis,” *Canadian Journal of Gastroenterology and Hepatology*, vol. 2018, Article ID 2784537, 8 pages, 2018.
View at: [Publisher Site](#) | [Google Scholar](#)
30. M. Giusto, B. Lattanzi, V. Di Gregorio, V. Giannelli, C. Lucidi, and M. Merli, “Changes in nutritional status after liver transplantation,” *World Journal of Gastroenterology*, vol. 20, no. 31, pp. 10682–10690, 2014.
View at: [Publisher Site](#) | [Google Scholar](#)
31. R. Alarcon, M. Tiberghien, R. Trouillet et al., “Sugar intake and craving during alcohol withdrawal in alcohol use disorder inpatients,” *Addiction Biology*, vol. 26, no. 2, Article ID e12907, 2021.
View at: [Publisher Site](#) | [Google Scholar](#)
32. L. De Luca, M. Kalafateli, S. Bianchi et al., “Cardiovascular morbidity and mortality is increased post-liver transplantation even in recipients with no pre-existing risk factors,” *Liver International*, vol. 39, no. 8, pp. 1557–1565, 2019.
View at: [Publisher Site](#) | [Google Scholar](#)
33. S. Battistella, F. Arcangelo, M. Grasso et al., “Liver transplantation for non-alcoholic fatty liver disease: indications and post-transplant management,” *Clinical and Molecular Hepatology*, vol. 29, pp. 286–301, 2023.
View at: [Publisher Site](#) | [Google Scholar](#)
34. H. T. Kuo, E. Lum, P. Martin, and S. Bunnapradist, “Effect of diabetes and acute rejection on liver transplant outcomes: An analysis of the organ procurement and transplantation network/united network for organ sharing database,” *Liver Transplantation*, vol. 22, no. 6, pp. 796–804, 2016.
View at: [Publisher Site](#) | [Google Scholar](#)

35. D. Atar, J. W. Jukema, B. Molemans et al., “New cardiovascular prevention guidelines: how to optimally manage dyslipidemia and cardiovascular risk in 2021 in patients needing secondary prevention?” *Atherosclerosis*, vol. 319, pp. 51–61, 2021.

View at: [Publisher Site](#) | [Google Scholar](#)

36. L. Elkrief, P. E. Rautou, S. Sarin, D. Valla, V. Paradis, and R. Moreau, “Diabetes mellitus in patients with cirrhosis: clinical implications and management,” *Liver International*, vol. 36, no. 7, pp. 936–948, 2016.

View at: [Publisher Site](#) | [Google Scholar](#)

Copyright

Copyright © 2023 Simone Di Cola et al. This is an open access article distributed under the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited