Prevalence and predictors of metabolic-associated fatty liver disease in liver transplant recipients: A cross-sectional prospective study

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Abstract

Background and Aim: Metabolic-associated fatty liver disease (MAFLD) has emerged as a significant global health concern. However, the prevalence and predictors of MAFLD in post-liver transplantation (LT) patients remain uncertain. This study aimed to determine the prevalence and predictors of MAFLD in LT recipients and to assess the effectiveness of controlled attenuation parameter (CAP) values in diagnosing post-transplant MAFLD.

Materials and Methods: A cross-sectional prospective study was conducted involving 128 adult patients who had undergone LT, and had received liver imaging, and vibration-controlled transient elastography (VCTE). MAFLD was diagnosed on the basis of the presence of liver steatosis detected through imaging and specific metabolic risk abnormalities.

Results: The prevalence of MAFLD after LT was 34.4%, with 22.1% categorized as de novo MAFLD, and 12.3% as recurrent MAFLD. Posttransplant diabetes (OR: 4.88; 95% CI 1.30–18.34; p<0.019) and higher CAP values (OR: 1.04; 95% CI 1.02–1.06; p=0.000) were identified as independent predictors of post-LT MAFLD. A CAP cutoff value of 270 dB/m exhibited an area under the receiver operating curve of 0.84 in detecting MAFLD.

Conclusion: These findings underscore the notable prevalence of MAFLD in liver transplant recipients and suggest the potential utility of VCTE as a non-invasive tool for its detection.

Keywords: Controlled attenuation parameter score; fatty liver disease; liver transplantation; metabolic-associated fatty liver disease; non-alcoholic fatty liver disease; steatosis.

Introduction

Metabolic-associated fatty liver disease (MAFLD) has been suggested as a replacement for non-alcoholic fatty liver disease (NAFLD) to emphasize the connection between liver disease and metabolic dysfunction.[1] In a recent meta-analysis, the global prevalence of NAFLD was 30%,[2] and the overall prevalence of MAFLD was 38.77%.[3] NAFLD is a growing global health burden as it has been independently associated with all-cause, cardiac, and cancer mortality.[4] NAFLD is becoming one of the most common causes of chronic liver disease and is now among the top reasons for liver transplantation (LT) due to cirrhosis and hepatocellular carcinoma.[5]

Following LT, immunosuppressive drugs lead to metabolic dysfunction through the development of insulin resistance (IR), diabetes, hypertension, obesity, and hyperlipidemia. Given all the metabolic complications that could affect patients after LT, the risk of developing NAFLD after transplantation can be considered high, although studies published on post-transplant NAFLD are based on small sample sizes and have different definitions of disease recurrence.[6,7] The most comprehensive meta-analysis to date found that the incidence of recurrent and de novo NAFLD was more than 50% in transplant recipients within 1 year of LT.[6] The true effects of de novo NAFLD and NASH in transplant recipients remain uncertain. The suggested criteria for a positive diagnosis of MAFLD could be useful for identifying metabolic dysfunction and treating metabolic diseases in pre-, peri-, and post-liver transplant settings.

Vibration-controlled transient elastography (VCTE) is a noninvasive imaging technique that is widely used to assess the degree of liver fibrosis with liver stiffness measurement (LSM) and steatosis with a controlled attenuation parameter (CAP). Recent studies evaluating VCTE in LT patients have used different cutoff values to detect steatosis.[8–14] Only Siddiqui et al.[12] evaluated the diagnostic performance of VCTE in the detection of hepatic steatosis and fibrosis in LT patients using liver biopsy as the reference standard and provided clinically relevant cutoff values.


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Materials and Methods

Study Design and Patients

This cross-sectional prospective study enrolled all adult post-LT patients (n=128) who underwent liver imaging (ultrasound, magnetic resonance imaging, or computed tomography) within 3 months between May 2022 and January 2023. Patients were invited to undergo transient
elastography (TE), and demographic parameters, clinical data, and laboratory values were collected on the same day. Patients after 6 months who underwent LT surgery (cadaveric or living donor), and age ≥18 years were included in this study. Patients with ascites, right-sided heart failure, pregnancy, cholestasis, and elevated aminotransferase levels >5 times the upper limit of normal, implantable cardiac devices, dialysis, or failed TE measurements were excluded. The study procedures were in accordance with the Helsinki Declaration and were approved by the Local Ethics Committee (174, 174-May 26, 2022). All the participants provided written informed consent.

Diagnostic Criteria
MAFLD was diagnosed based on liver steatosis detected by liver imaging and at least one of the following three criteria to be met: (1) a body mass index (BMI) ≥25 kg/m²; (2) type 2 diabetes; (3) at least two of the following metabolic risk abnormalities were identified: waist circumference ≥102/88 cm in men and women; blood pressure ≥130/85 mmHg or specific drug treatment; plasma triglyceride (TG) levels ≥150 mg/dL or specific drug treatment; plasma high-density lipoprotein (HDL) cholesterol levels <40 mg/dL for men or <1.3 mmol/L for women or specific drug treatment; prediabetes (characterized by fasting blood glucose levels of 100–125 mg/dL or 2 h post-load glucose levels 140–199 mg/dL or HbA1c levels of 5.7–6.4%); homeostasis model assessment of IR score ≥2.5, or plasma high sensitivity C-reactive protein levels >2 mg/L.[13]

VCTE
VCTE assessment was performed using the FibroScan® Compact 530 (Echosens SA, Paris, France) by a single operator (GA). Patients were instructed to fast for a minimum of 3 h, and all patients were examined in the supine position with the right arm in maximal abduction according to the manufacturer’s instructions. All examinations started with the M probe, and if prompted by the automatic probe selection tool, the XL probe was used. Only cases with at least 10 valid measurements and an interquartile range/median <30% were considered reliable TE examinations. LSM was expressed as kPa, and LSM and CAP values were obtained simultaneously. All CAP values were acquired using second-generation CAP (CAPc) and expressed as dB/m. The examination was maintained until 100% CAP measurement was obtained. The CAP cutoff used for the presence of hepatic steatosis was 270 dB/m, and to identify advanced fibrosis, an LSM cut-off of 10.5 kPa was used.[12]

Statistical Analysis
Continuous variables are presented as mean±SD or median with minimum and maximum values. Categorical variables were expressed as numbers and percentages. Differences between continuous variables were compared using the t-test or Mann–Whitney U test. Categorical variables were compared using the χ² test. Correlations between CAP values and clinical variables were examined using Spearman’s correlation coefficient. The diagnostic performance of CAP values for diagnosing MAFLD was evaluated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating curve, and 95% confidence intervals (CIs). Binary logistic regression analysis was used to identify the independent variables associated with MAFLD after LT. Statistical significance was set at p<0.05. All statistical analyses were performed using the SPSS software (version 29.0; IBM Corporation, Armonk, NY, USA).

Results
Study Population and Transient Elastography
The study population consisted of 122 patients with a median age of 57 years (19–78) and 63.9% were male. Hepatitis B virus-related cirrhosis (n=66, 54.1%) was the major etiology for LT. The median age at transplantation was 51 years (10–71). The mean follow-up time after transplantation was 65.7±42.2 months. Most patients underwent living-donor LT (n=98, 80.3%). Of the study patients, 56 (45.9%) were overweight and 26 (21.3%) were obese. Only 104 patients had BMI values before LT: 38 (35.1%) were overweight and 25 (23.1%) were obese. Twenty-nine patients (23.8%) had diabetes before LT.

All patients received a standard 6-month triple immunosuppressive regimen (corticosteroids, mycophenolate mofetil, and calcineurin inhibitors [CNI]) after LT. At the time of the study, 110 patients (90.2%) received only CNI, seven patients (5.7%) received a combination of CNI and corticosteroids, and four patients (3.3%) received a combination of everolimus and tacrolimus. The general characteristics of the liver transplant recipients are shown in Table 1.

A total of 128 patients underwent VCTE and 122 (95.3%) reliable measurements were obtained. In 19 of 122 patients, the probe was switched to the XL probe. The prevalences of liver steatosis (CAP >270 dB/m) and advanced fibrosis (LSM >10.5 kPa) were 27% (n=33) and 16.4% (n=20), respectively.
Prevalence and Predictors of MAFLD in LT Recipients

Only one patient (0.8%) had a normal BMI and steatosis on imaging, without metabolic risk abnormalities, and did not fulfill the MAFLD criteria. Seventeen patients (13.9%) had MAFLD before LT. Forty-two (34.4%) patients had MAFLD after LT, 27 (22.1%) had de novo MAFLD, and 15 (12.3%) had recurrent MAFLD (Fig. 1). Of the 17 patients with MAFLD before transplantation, 15 (88.2%) had recurrent MAFLD. A comparison of patients with and without post-liver transplant MAFLD is presented in Table 2. In the univariate analysis, patients with MAFLD were older and had a higher BMI and waist circumference; NAFLD etiology, diabetes, and obesity were more common; glucose, TG, and ALT levels were higher; and HDL cholesterol levels were lower than in those without MAFLD. Patients with MAFLD had higher CAP and LSM scores than those without MAFLD. As shown in Figure 2, the median CAP scores of patients with and without MAFLD are presented as boxplots. In the logistic regression analysis, the independent predictors of post-LT MAFLD were diabetes (OR: 4.88; 95% CI 1.30–18.34; p=0.019) and CAP scores (OR: 1.04; 95% CI 1.02–1.06; p=0.000). A CAP value of >270 dB/m demonstrated a sensitivity, specificity, PPV, NPV, and AUROC of 71.4%, 96.3%, 90.9%, 86.5%, and 0.838 (95% CI 0.751–0.925), respectively, for the detection of MAFLD in LT patients (Fig. 3).

Table 2: Comparison of patients with and without post-liver transplant MAFLD

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Non-MAFLD (n=80)</th>
<th>MAFLD (n=42)</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (19–77)</td>
<td>61.5 (34–78)</td>
<td>0.001</td>
<td>1.04</td>
<td>0.92–1.17</td>
<td>0.532</td>
</tr>
<tr>
<td>Male gender</td>
<td>50 (62.5)</td>
<td>28 (66.7)</td>
<td>0.649</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (14.8–37)</td>
<td>28.4 (23.4–42.6)</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>95 (69–116)</td>
<td>105 (90–149)</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology of liver disease</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis B</td>
<td>41 (53.8)</td>
<td>23 (54.8)</td>
<td>0.915</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td>1 (1.3)</td>
<td>9 (21.4)</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>11 (13.8)</td>
<td>2 (4.8)</td>
<td>0.215</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2 (2.5)</td>
<td>2 (4.8)</td>
<td>0.607</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol related</td>
<td>3 (3.8)</td>
<td>1 (2.4)</td>
<td>0.687</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (25)</td>
<td>5 (11.9)</td>
<td>0.089</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (28.8)</td>
<td>27 (64.3)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (36.3)</td>
<td>22 (52.4)</td>
<td>0.086</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>8 (10)</td>
<td>18 (42.9)</td>
<td>0.000</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VCTE</th>
<th>Non-MAFLD (n=80)</th>
<th>MAFLD (n=42)</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP score (dB/m)</td>
<td>200 (100–301)</td>
<td>282 (154–370)</td>
<td>0.000</td>
<td>1.04</td>
<td>1.02–1.06</td>
<td>0.000</td>
</tr>
<tr>
<td>LSM (kPa)</td>
<td>5.9 (2.8–35.6)</td>
<td>7.2 (4.4–40.5)</td>
<td>0.010</td>
<td>1.09</td>
<td>0.95–1.24</td>
<td>0.215</td>
</tr>
</tbody>
</table>

Data presented as n (%) or median (minimum–maximum). MAFLD: Metabolic dysfunction-associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FIB-4: Fibrosis-4 index; VCTE: Vibration-controlled transient elastography; CAP: Controlled attenuation parameter; LSM: Liver stiffness measurement; OR: Odd ratios; CI: Confidence interval.

Discussion

MAFLD has a worldwide prevalence of 33%, and its global burden is growing. This applies to liver transplant recipients exposed to long-term immunosuppressive therapies, which are drivers of metabolic al-

Figure 1. Flowchart of the study population.
terations. However, the prevalence of MAFLD among LT recipients remains unclear. This study was the first to evaluate the prevalence and predictors of MAFLD in LT recipients and revealed that approximately one-third of LT recipients had MAFLD, and post-LT DM and higher CAP values were independent predictors of MAFLD.

This study found that 34.4% of the patients developed MAFLD after transplantation, 22.1% had de novo MAFLD, and 12.3% had recurrent MAFLD. Although the majority of LT etiology was Hepatitis B-related cirrhosis one in three patients developed MAFLD in the post-transplant period, which is likely attributable to the metabolic complications associated with immunosuppression. A recent study conducted in our country involving 909 consecutive patients with dyspepsia revealed a prevalence of 45.5% for MAFLD when using US for steatosis detection. Several factors may have contributed to the lower prevalence of MAFLD observed in our study. First, the relatively short follow-up time after transplantation, which was approximately 5 years, might have limited the detection and manifestation of MAFLD in our patient population. In addition, the small sample size could have influenced the prevalence, as it may not fully represent the diverse demographics and characteristics of the broader population. Other potential reasons for the lower prevalence could include variations in the imaging tools employed to detect steatosis in the patient population. Another recent cross-sectional study examined kidney transplant recipients and found that 42.3% had MAFLD. The lower prevalence of MAFLD in our study compared to kidney transplant recipients may be attributed to various contributing factors. First, the follow-up time after LT was relatively short for the development of MAFLD. However, with an extended follow-up period, the prevalence of MAFLD may increase over time. Second, our patient population had a lower incidence of diabetes (41%) than the kidney transplant population (58%). In addition, kidney transplant recipients are exposed to corticosteroids for longer durations and at higher doses than liver transplant recipients, which could affect MAFLD development. Although the etiology of renal disease was not specified by the authors, it is highly probable that the majority of patients had pre-existing diabetes, leading to a higher likelihood of MAFLD before transplantation. There is a lack of information regarding MAFLD prevalence following LT. Relevant studies have mainly focused on NAFLD and NASH and varying time intervals between LT and biopsy or imaging techniques. The rate of recurrence or de novo occurrence varies significantly, depending on whether the diagnosis is based on histology or imaging techniques. A meta-analysis of 12 studies involving 2166 patients who had undergone post-liver transplant biopsy revealed that the pooled weighted prevalence of de novo NAFLD was 26%. In a recent meta-analysis of 17 studies representing 2378 post-LT patients, which included 15 studies with post-LT liver biopsies and 2 studies with imaging techniques, the ≥5-year incidence rates were 82% for recurrent NAFLD and 78% for de novo NAFLD and a summarized prevalence of either recurrent or de novo NAFLD was 44.4%. Similarly, our study showed that 88.2% of patients with MAFLD before LT had % recurrent MAFLD.

Several factors have been identified as predictors of post-liver transplant NAFLD and NASH, such as post-LT BMI, pre- and post-LT alcohol use, post-LT hyperlipidemia, post-LT DM, pre-LT BMI, graft steatosis, and immunosuppressive drugs. Subsequent meta-analyses of these risk factors only noted a significant impact for post-LT BMI with a summarized OR of 1.27. Although most studies analyzing the risk factors for post-LT NAFLD were single-center, nonrandomized retrospective analyses, these factors are consistent with the known risk factors for MAFLD. In our study, the presence of diabetes after transplantation was a strong independent predictor of post-transplant MAFLD, indicating the importance of glycemic control in this population. In addition, higher CAP scores obtained through VCTE were associated with an increased risk of MAFLD in multivariate analysis. Our study population had a median of 26.6 kg/m² BMI; however, post-LT BMI was not an independent predictor of MAFLD, possibly because of the small sample size. In the univariate analysis, older age, higher BMI, NAFLD etiology for LT, DM, higher TG and ALT levels, lower HDL-cholesterol levels, and higher CAP and LSM scores were significant predictors for MAFLD. These findings suggest that metabolic syndrome risk factors contribute to the development of MAFLD in liver transplant recipients. Despite concerns regarding the effects of immunosuppressive agents, our analysis did not reveal any consistent effects of immunosuppressive regimens on the risk of post-transplant MAFLD similar to the findings of the recent meta-analysis of Saeed et al.
The findings of this study revealed that the prevalence of liver steatosis in post-liver transplant recipients was 27%, as determined by the CAP value obtained through VCTE. This non-invasive imaging technique provides reliable measurements in the majority of patients, highlighting its feasibility in this population. A previously determined CAP cutoff value of 270 dB/m in LT recipients by Siddiqui et al. demonstrated good diagnostic performance for the detection of MAFLD in our study patients, with a specificity of 96.3%, a PPV of 90.9%, and a NPV of 86.5%. These results indicate that VCTE can be a valuable tool for the noninvasive assessment of steatosis in this specific population. Our study also showed that LSM values were higher in MAFLD patients with a median of 7.2 kPa and 16.4% had advanced fibrosis according to a previously determined cutoff of 10.5 kPa. This could be attributed to possible steatohepatitis; however, some patients had biliary anastomotic strictures and recurrent cholangitis, which could also be the reason for the high LSM values. However, LSM values can be used to identify LT recipients who require confirmatory liver biopsy or more intensive surveillance.

The results of this study have several important clinical implications. The use of VCTE with CAP measurements can provide a non-invasive and reliable method for assessing steatosis in post-liver transplant patients with MAFLD. The early detection of steatosis is crucial for implementing appropriate interventions, such as lifestyle modifications and pharmacological treatments, to prevent disease progression and improve long-term outcomes. Furthermore, identifying the predictors of post-transplant MAFLD can help identify high-risk patients who may benefit from closer monitoring and targeted interventions.

This study has some limitations. First, the study had a cross-sectional design, which limited the ability to establish causal relationships. Longitudinal studies are needed to further investigate the natural history and progression of MAFLD in post-LT recipients. Second, the sample size was relatively small, which may have affected the generalizability of our findings. Future studies with larger cohorts are required to validate our results. Third, liver biopsy, the gold standard for diagnosing steatosis and fibrosis, was not performed in this study. Although VCTE has shown good diagnostic performance, the use of liver biopsy as a reference standard would have provided a more robust validation of noninvasive measurements. Finally, it is crucial to acknowledge the limitations associated with imaging methods used to detect steatosis in LT recipients. These imaging methods may not be optimal for detecting steatosis, primarily because of the absence of magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) or MR spectroscopy, as these advanced imaging techniques have demonstrated superior accuracy in steatosis assessment. Furthermore, a range of imaging modalities, including ultrasound, MRI, and CT, were utilized instead of relying solely on a single method as each technique has different sensitivities for detecting steatosis.

Conclusion

This study demonstrated the high prevalence of MAFLD in LT recipients and the utility of VCTE with CAP measurements in evaluating steatosis in this population. These findings emphasize the importance of the early detection and management of MAFLD in LT recipients. Identifying the predictors of post-transplant MAFLD contributes to risk stratification and personalized interventions. Further research is needed to validate these findings and explore the long-term impact of MAFLD on graft and patient outcomes in liver transplant recipients.

Ethics Committee Approval: The Umniyane Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 26.05.2022; number: 174).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – GA; Design – GA; Supervision – GA; Data Collection and/or Processing – NMB, AEK; Analysis and/or Interpretation – GA; Literature Search – GA; Writing – GA; Critical Reviews – OO, KO.

Conflict of Interest: The authors have no conflict of interest to declare.

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