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# Prevalence and Risk Factors of Hepatic Steatosis in Kidney Transplant Recipients

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Study Design A
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Statistical Analysis C
Data Interpretation D
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**Background:** Kidney failure and hepatic steatosis (HS) are core elements of cardiovascular-renal-metabolic syndrome. Evidence of HS in kidney transplant (KTx) recipients remains limited. We evaluated the prevalence and determinants of de novo hepatic steatosis (dnHS) after KTx.

**Material/Methods:** We retrospectively analyzed adult KTx recipients from a single outpatient center without HS prior to transplantation. Anthropometric data, laboratory results, comorbidities, and medication use were evaluated. HS was diagnosed based on ultrasonography.

**Results:** In 127 (53 female) KTx recipients with median age of 56.91 (44.91-64.62) years and median estimated glomerular filtration rate of 39.6 (29.76-48.51) mL/min/1.73 m$^2$, 44 patients (30.1%) had dnHS. Patients in the dnHS and nonHS groups were of comparable age, sex, and graft function. Patients in the dnHS group had significantly higher body mass index (BMI) before (25.5±3.29 vs 23.26±3.55 kg/m$^2$; $P$<0.001) and after KTx (27.86±4.06 vs 24.71±3.69 kg/m$^2$; $P$<0.001), and dnHS was associated with higher rates of hyperlipidemia (77.3% vs 54.2%; $P$=0.012), hyperuricemia (52.3% vs 28.9%; $P$=0.009), and ischemic heart disease (34.1% vs 13.1%, $P$=0.006). In multivariable logistic regression, higher post-KTx BMI (OR=1.21; 95% CI, 1.08-1.37; $P$=0.002) and history of ischemic heart disease (OR=3.40; 95% CI, 1.18-9.74; $P$=0.023) were independently associated with the presence of dnHS.

**Conclusions:** Hepatic steatosis is common among KTx recipients and is strongly associated with metabolic comorbidity, particularly higher BMI and ischemic heart disease.

**Keywords:** Hepatic Steatosis • Kidney Transplantation • Metabolic Syndrome

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## Introduction

Hepatic steatosis (HS) refers to the excessive accumulation of triglycerides in hepatocytes. It constitutes a central component of metabolic dysfunction–associated steatotic liver disease (MASLD), whose criteria emphasize metabolic consequences of HS [1]. It is worth noting that, prior to the emergence of MASLD, the literature referred to non-alcoholic fatty liver disease (NAFLD). MASLD diagnosis requires the presence of HS (in the absence of secondary causes) and at least 1 trait of metabolic syndrome [2].

Interestingly, patients with MASLD have a greater risk of developing chronic kidney disease (CKD) [3], particularly with deteriorated kidney function [4]. This relationship appears to be independent of coexisting hyperlipidemia, diabetes mellitus, or hypertension arterialis [5-7]. Both MASLD and CKD increase the risk of cardiovascular complications [2], which happen to be the leading cause of death in the CKD population [8].

Kidney transplantation is regarded as the best form of kidney replacement therapy, alleviating uremia and most complications of kidney failure. Nevertheless, the post-transplantation period can create new metabolic disadvantages [9,10]. Patients return to their daily activities and old dietary habits [11], with the greatest weight gain being observed within the first 12 months after transplantation, most of which is attributable to adipose tissue [12]. Calcineurin inhibitors (CNI), mTOR inhibitors, and glucocorticoids included in the immunosuppressive regimen promote metabolic dysregulation, including dyslipidemia, obesity, and post–kidney transplant (KTx) diabetes mellitus [13,14]. Despite this unfavorable metabolic profile, the relationship between KTx and the development of MASLD remains poorly investigated.

Existing research of MASLD in solid organ transplantation focuses largely on liver transplant recipients [15], including those who developed liver failure through fatty liver disease [16]. Thus, the aim of our study was to determine the prevalence and factors associated with MASLD in KTx recipients.

## Material and Methods

In this retrospective study, we analyzed data from adult White KTx recipients with at least 12 months of post-transplantation follow-up who were treated in the same post-transplant outpatient clinic and had stable kidney graft function (estimated glomerular filtration rate [eGFR] calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation >15 mL/min/1.73 $m^2$ and 3-month serum creatinine level variations <0.3 mg/dL).

The current presence of HS symptoms was verified based on available imaging studies: ultrasonography performed routinely once a year in all KTx recipients as part of the post-transplant assessment, or, if available, computed tomography (CT), which were all performed 3 to 6 months before data collection. The inclusion in the analysis required available results of abdominal ultrasonography prior to transplantation, obtained from the application forms for the Polish National Transplantation Waitlist.

Anthropometric data included age, height, and body mass index (BMI) at the time of the analyzed ultrasonography and at the time of transplantation. Comorbid conditions and current medication were obtained from medical records. The causes of end-stage kidney disease (ESKD) and medical history, including hypertension arterialis, diabetes mellitus, and cardiovascular complications, such as ischemic heart disease and peripheral artery disease, were recorded. Hyperlipidemia was considered present if at least 1 of the following was noted: abnormal blood lipid profile (total cholesterol higher than 200.0 mg/dL or triglycerides above 150.0 mL/dL) or hypolipidemic treatment. Hyperuricemia diagnosis was based on medical history and/or medication (treatment with allopurinol).

As all patients were inquired about alcohol consumption during visits, those with known history of alcohol abuse were excluded from the analysis. Occasional alcohol consumption was permitted.

Out of all included individuals, a subpopulation of patients without a history of HS prior to transplantation was chosen. Those who showed HS after KTx formed the de novo (dnHS) group, and those who showed no signs of HS before and after KTx formed the nonHS group. Patients who had shown HS before KTx were excluded from the main analysis.

For patients in the dnHS group, all available imaging studies from transplantation to data collection were assessed; the first study describing signs of HS served as an approximation for the time of HS development.

We analyzed alanine aminotransferase activity, complete blood counts, serum creatinine concentration, eGFR calculated with the CKD-EPI [17] and Cockroft-Gault [18] formulas, proteinuria from spot urine samples, which are considered significant if 0.5g/L or higher, blood lipid concentrations ±3 months from the ultrasonography assessment, together with current and historic serological data regarding hepatitis B, hepatitis C, and cytomegalovirus infection. We analyzed the immunosuppressive regimen, hypolipidemic medications (statins, fibrates, ezetimibe), and type of antidiabetic treatment (sulfonylureas, biguanides, insulin). SGLT2 inhibitors and GLP-1 analogs were not recommended in the KTx population at the time of the





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analysis, and thus no patients received these therapies. All clinical and laboratory parameters were obtained from medical records. We calculated the average concentration/dose ratio of tacrolimus (TAC C/D ratio) from 3 subsequent C/D ratios. To account for differences in drug formulation, we converted total daily doses of extended release and MeltDose TAC to their immediate-release equivalent, as 1.0: 1.0 mg and 0.7: 1.0 mg, respectively [19]. Per Thölking et al, patients were considered fast metabolizers with TAC C/D <1.05 ng/mL ×1/mg [20].

Continuous variables with normal distribution are presented with mean and standard deviation, variables with a non-normal distribution are presented as median with the 25% and 75% quartiles. Accordingly, either unpaired samples *t* tests or Mann-Whitney U tests were applied. Nominal variables were compared with the chi-square test and necessary corrections. To identify variables independently associated with the presence of dnHS after KTx, we used logistic regression. Complete-case analysis was implemented to account for missing data. Given the limited number of dnHS cases, we predefined a parsimonious multivariable enter model based on clinical relevance and the strongest univariate associations. Additionally, as an exploratory analysis, a logistic regression model with stepwise variable selection was performed. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC) and calibration using the Hosmer-Lemeshow test. A significance level of $P$=0.05 was adapted. The analysis was conducted using STATISTICA software (StatSoft, TIBCO, Poland) version 13.3.

## Results

### Study Population

Out of 423 patients in the post-transplant outpatient clinic, 145 (88 male, 57 female) patients with median age of 57.0 (47.0-64.0) years at the time of analysis and mean age of was 46.96±12.37 years at the time of transplantation met the inclusion criteria.

### Presence of HS

HS was diagnosed in 58 KTx recipients and was significantly more common after transplantation than before (n=14; 40.0% vs 9.66%; $P$<0.001). In our cohort, 44 (30.14%) developed dnHS. Moreover, in 4 patients who had HS prior to transplantation, post-KTx ultrasounds showed normal liver echogenicity.

The KTx recipients in the nonHS (n=83) and dnHS groups (excluding pre-KTx patients with HS) were chosen for further analysis, giving a subpopulation of 127 patients (53 female, 74 male), with a median age of 56.91 (44.91-64.62) years and mean age at KTx of 46.53±12.72 years. There was no statistically significant difference in age between patients in the nonHS and dnHS groups (**Table 1**).

The median time between transplantation and first occurrence of HS in available imaging studies was 2.5 years (0.8-5.94), comparable between male and female patients (2.05 vs 3.94 years, $P$=0.373); it did not correlate with age or pre-KTx parameters (**Table 1**).

The mean BMI of the analyzed recipients was 25.82±4.09 kg/m$^2$. Patients who developed HS after KTx had significantly higher BMI than those who did not have HS (27.86±4.06 vs 24.71±3.69 kg/m$^2$, $P$<0.001). Likewise, pre-KTx BMI was higher in the dnHS population (25.5±3.29 vs 23.26±3.55 kg/m$^2$; $P$<0.001).

Thirty-two patients presented lower body mass and BMI at analysis than before KTx, while 87 patients gained weight, with comparable incidence of HS (n=54 nonHS, n=33 dnHS; $P$=0.438). The mean post-KTx weight change in the population was 5.17±8.07 kg and 1.76±2.91 kg/m$^2$ when indexed for height. The relationship between post-KTx weight change and presence of HS after KTx was not statistically significant ($P$>0.05).

### HS and Kidney Graft Function

The median serum creatinine concentration was 1.55 mg/dL (1.23-1.91 mg/dL; reference range 0.55-1.02 mg/dL). The difference in serum creatinine was not statistically significant between the nonHS and dnHS groups (1.57 vs 1.52 mg/dL; $P$=0.577).

Kidney graft function expressed as eGFR remained comparable when calculated using the CKD-EPI formula, with a median eGFR of 49.28 (37.91-60.5) mL/min/1.73 m$^2$ for the nonHS group and 47.25 (37.0-57.58) mL/min/1.73 m$^2$ for the dnHS group ($P$=0.681). Interestingly, when we used the Cockroft-Gault formula, patients in the dnHS group presented higher eGFR; however, the difference narrowly missed statistical significance (58.29 vs 49.94 mL/min, $P$=0.051).

Proteinuria in spot urine samples was identified in 96 recipients; however, it exceeded 0.5 g/L in only 8 patients, with no statistically significant difference between the nonHS and dnHS groups (0.06 g/L; $P$=0.996). Detailed data are presented in **Table 1**.

### HS and Comorbidity

#### *ESKD Etiology*

Almost 20% of our recipients (n=25) had polycystic kidney disease, making it the third most common cause of ESKD, after primary glomerulonephritis (n=32) and undetermined origin of







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**Table 1.** Anthropometric measurements and laboratory parameters in our population of patients with de novo hepatic steatosis (dnHS group) or no hepatic steatosis (nonHS group).

| | All patients (n=127) | nonHS (n=83) | dnHS (n=44) | *P* value |
|---|---|---|---|---|
| Male sex, n (%) | 88 (69.29%) | 45 (54.22%) | 29 (65.91%) | 0.204 |
| Age at analysis [years] | 56.91 (44.91-64.62) | 57.36 (44.04-64.01) | 53.52 (45.88-65.47) | 0.974 |
| Age at KTx [years] | 46.53±12.72 | 45.71±12.9 | 48.07±12.35 | 0.322 |
| BMI at analysis [kg/m$^2$] | 25.82±4.09 | 24.71±3.69 | 27.86± 4.06 | <0.001* |
| BMI at KTx [kg/m$^2$] | 24.04±3.61 | 23.26±3.55 | 25.5±3.29 | <0.001* |
| Time since KTx [years] | 7.02 (3.91-10.9) | 7.58 (3.98-11.47) | 6.1 (3.91-9.19) | 0.167 |
| Weight change [kg, kg/m$^2$] | 5.17± 8.07, 1.76± 2.91 | 4.14±7.8, 1.43±2.63 | 7.05±10.0, 2.36±3.32 | 0.082, 0.098 |
| Serum creatinine [mg/dL, RR 0.55-1.02] | 1.55 (1.23-1.91) | 1.57 (1.23-1.89) | 1.52 (1.27-1.96) | 0.577 |
| eGFRCKD EPI [mL/min/1.73 m$^2$] | 1.55 (1.23-1.91) | 49.28 (37.91-60.5) | 47.25 (37.0-57.58) | 0.680 |
| eGFR Cockroft-Gault [mL/min] | 52.81± 22.74 | 50.49±17.67 | 54.13±17.42 | 0.051 |
| Proteinuria [g/L] | 0.06 (0.02-0.14 | 0.06 (0.02-0.13) | 0.06 (0-0.15) | 0.996 |
| Hemoglobin [g/dL, RR 12.0-16.0] | 13.3± 1.87 | 13.27±1.74 | 13.36±2.13 | 0.797 |
| Mean cell volume [fl, RR 80-100] | 13.47 (87.2-92.98) | 90.37 (87.49-93.55) | 89.72 (40.28-58.51) | 0.494 |
| White blood cells [G/L, RR 4.0-10.0] | 7.75± 1.87 | 7.57±2.01 | 8.09±2.2 | 0.191 |
| Platelets [G/L, RR 150-400] | 214.47± 55.22 | 209.74±53.91 | 233.85±60.44 | 0.178 |
| Alanine aminotransferase activity [U/L, RR 0-35.0] | 21 (16.0-31.5) | 19.1 (15.5-27.5) | 25.04 (16.5-34.08) | 0.073 |
| Total cholesterol [mg/dL, RR<200] | 196 (173.0-214.0) | 194.0 (169.5-211.17) | 209.75 (191.5-226.0) | 0.014* |
| Low-density lipoprotein [mg/dL, RR <100] | 110.63± 33.94 | 105.31±28.82 | 121.01±40.6 | 0.015* |
| High-density lipoprotein [mg/dL, RR >50] | 61.25± 16.0 | 61.57±15.62 | 60.62±17.13 | 0.76 |
| Triglycerides [mg/dL, RR <150] | 130.0 (102.0-175.0) | 120.0 (99.83-158.67) | 144 (122.5-207.0) | 0.004* |

* Indicates *P* values less than 0.05. RR – reference range.

ESKD (n=43). Other etiologies included anti-neutrophil antibody associated vasculitis (n=7), hypertension arterialis (n=7), obstructive uropathy (n=5), lupus nephritis (n=4), diabetic nephropathy (n=2), chronic pyelonephritis (n=1), and mixed connective tissue disease (n=1). There was no statistically significant relationship between the development of HS and ESKD etiology (*P*=0.627).

*Comorbidity*

A total of 114 patients presented with hypertension arterialis, with no statistically significant difference between the nonHS and dnHS groups (90.36% vs 97.73%; *P*=0.241). Likewise, the difference in prevalence of diabetes mellitus, diagnosed in 41 (32%) patients either before or after KTx, was not statistically significant between the groups (31.33% vs 34.1%; *P*=0.751).

Patients with dnHS had a significantly higher rate of hyperlipidemia (77.3% vs 54.2%; *P*=0.012) and hyperuricemia (52.3% vs 28.9%; *P*=0.009). Interestingly, ischemic heart disease was found in only 26 patients (20.5%) but was significantly more prevalent in the dnHS group (34.1% vs 13.1%; *P*=0.006).





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**Table 2.** Concomitant diseases and medications used in our population of patients with de novo hepatic steatosis (dnHS group) or no hepatic steatosis (nonHS group).

| Variable | All patients (n=127) | nonHS (n=83) | dnHS (n=44) | *P* value |
|---|---|---|---|---|
| Hypertension arterials | 118 (92.9%) | 75 (90.4%) | 43 (97.7%) | 0.124 |
| Diabetes mellitus | 41 (32.3%) | 26 (31.3%) | 15 (34.1%) | 0.751 |
| Hyperlipidemia | 79 (62.2%) | 45 (54.2%) | 34 (77.3%) | 0.011* |
| Ischemic heart disease | 26 (20.5%) | 11 (13.3%) | 15 (34.1%) | 0.006* |
| Hyperuricemia | 47 (37.0%) | 24 (28.9%) | 26 (59.1%) | 0.009* |
| Renin-angiotensin-aldosterone system inhibitors | 52 (40.9%) | 33 (39.8%) | 19 (43.2%) | 0.671 |
| Beta-blockers | 100 (78.7%) | 64 (77.1%) | 36 (81.8%) | 0.464 |
| Calcium channel blockers | 85 (66.9%) | 54 (65.1%) | 31 (70.5%) | 0.539 |
| Metformin | 9 (7.1%) | 4 (4.8%) | 5 (11.4%) | 0.315 |
| Sulfonylureas | 13 (10.2%) | 8 (9.6%) | 9 (20.5%) | 0.152 |
| Insulin | 25 (19.7%) | 17 (20.5%) | 8 (18.2%) | 0.941 |
| Statin | 73 (57.5%) | 42 (50.6%) | 31 (70.5%) | 0.031* |
| Ezetimibe | 11 (8.7%) | 5 (6.0%) | 6 (13.6%) | 0.263 |

* Indicates *P* values less than 0.05.

*HS and Immunosuppression*

All analyzed patients were treated with mycophenolic acid and prednisone in the maintenance dose of 5 mg/day. Nearly all patients received CNI, most commonly tacrolimus (TAC; n=112), and in rare cases cyclosporin A (CsA, n=11). Two patients received TAC combined with everolimus; 2 were treated only with everolimus and mycophenolate mofetil. The association between the type of CNI (TAC or CsA) used and presence of HS was not statistically significant (*P*>0.05).

The median TAC C/D ratio was 2.46 (1.8-3.04) ng/mL×1/mg. Ten patients were categorized as fast metabolizers. The association between the TAC C/D ratio, expressed as both a continuous and a categorical variable, and the development of HS after KTx was not statistically significant (both *P*>0.05).

*HS and Concomitant Medication*

Of all medications included in the analysis, statins (50.6% vs 70.45%; *P*=0.031) and allopurinol (28.9% vs 52.3%; *P*=0.009) were significantly more common in the dnHS group. There was no statistically significant relationship between the type of statin used and HS. The association between the development of dnHS and use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, ezetimibe, or hypoglycemic drugs was not statistically significant (**Table 2**).

**Laboratory Parameters Analysis**

Patients in the dnHS group presented significantly more lipid disturbances: higher levels of total cholesterol (209.75 vs 194.00 mg/dL; *P*=0.013), low-density lipoprotein cholesterol (121.01 vs 105.31 mg/dL; *P*=0.017), and triglycerides (144.0 vs 120.00 mg/dL; *P*=0.004) than in the nonHS group, while HDL levels remained comparable between the groups (60.62 vs 61.57 mg/dL; *P*=0.734). Alanine aminotransferase activity showed no statistically significant difference between the nonHS and dnHS groups (**Table 1**).

All analyzed recipients were seronegative for hepatitis C virus. Anti-hepatitis B core antibody status was available for 85 patients, 16 (18.8%) of whom were positive, with no statistically significant association with the presence of HS (*P*>0.05). Only 3 patients with positive anti-hepatitis B core status developed HS. There were no statistically significant associations between presence of HS and hemoglobin concentration, white blood cell count, platelet count, or mean erythrocyte volume (**Table 1**).

**Risk of HS Assessment**

To assess risk factors associated with presence of dnHS, we utilized logistic regression model. Due to a relatively small sample size, only 113 patients with complete data were included in this analysis. Univariable logistic regression analyses were







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**Table 3.** Univariable logistic regression analyses of variables potentially associated with the presence of de novo hepatic steatosis in kidney transplant recipients.

| | OR (95% CI) | *P* value |
|---|---|---|
| Pre-KTx BMI | 1.18 (1.05-1.32) | 0.005* |
| Post-KTx BMI | 1.22 (1.09-1.36) | <0.001* |
| Age at analysis | 1.00 (0.97-1.04) | 0.925 |
| Total cholesterol | 1.01 (1.00-1.02) | 0.014* |
| Triglycerides | 1.01 (1.00-1.02) | 0.005* |
| High-density lipoprotein | 1.00 (0.97-1.02) | 0.871 |
| Low-density lipoprotein | 1.02 (1.00-1.03) | 0.013* |
| Sex (male) | 1.78 (0.80-3.96) | 0.154 |
| Ischemic heart disease | 3.21 (1.28-8.01) | 0.013* |
| Hyperlipidemia | 2.68 (1.12-6.43) | 0.027* |
| Hyperuricemia | 3.06 (1.37-6.85) | 0.007* |
| Hypertension arterialis | 4.61 (0.55-38.25) | 0.157 |
| Diabetes mellitus | 1.11 (0.48-2.54) | 0.807 |
| ADPKD | 1.01 (0.39-2.57) | 0.976 |
| ACE-I/ARB | 1.02 (0.46-2.25) | 0.960 |
| Serum creatinine | 1.30 (0.57-2.99) | 0.533 |
| eGFR (Cockroft-Gault) | 1.01 (0.99-1.02) | 0.363 |
| BMI change | 1.13 (0.98-1.29) | 0.088 |

Values are presented as odds ratios (OR) with 95% confidence intervals (CI) and *P* values. * Indicates P values less than 0.05.
KTx – kidney transplantation; ADPKD – autosomal polycystic kidney disease; ACE-I – angiotensin-converting enzyme inhibitors; ARB – angiotensin II receptor blockers.

performed (**Table 3**). Differences in baseline characteristics of patients included and excluded from multivariable analysis were not statistically significant (**Table 4**).

The prespecified enter model, including post-transplant BMI, presence of ischemic heart disease and hyperuricemia, and concentrations of triglycerides and total cholesterol was globally significant ($\chi^2(5)=32.23$; $P<0.001$). Higher post-transplant BMI (OR=1.21; 95% CI, 1.08-1.37; $P=0.002$) and presence of ischemic heart disease were independently associated with dnHS (OR=3.40; 95% CI, 1.18-9.74; $P=0.023$).

Total cholesterol concentration, triglyceride levels, and hyperuricemia were not statistically significant. The model demonstrated good discrimination (AUC=0.805; 95% CI, 0.72-0.89) and good calibration (Hosmer-Lemeshow $P=0.767$).

In the exploratory stepwise model, we initially included age at analysis, sex, pre- and post-KTx BMI, presence of hyperuricemia, hyperlipidemia, and ischemic heart disease, concentrations of total cholesterol, low-density lipoprotein, and triglycercides. The final model was globally significant ($\chi^2(3)=27.73$; $P<0.001$), with 3 retained variables. Higher post-transplant BMI (OR=1.24; 95% CI, 1.10-1.39; $P<0.001$), presence of ischemic heart disease (OR=4.07; 95% CI, 1.46-11.32; $P=0.007$), and higher total cholesterol concentration (OR=1.01; 95% CI, 1.00-1.02; $P=0.036$) were associated with presence of dnHS. The stepwise model showed similar discrimination (AUC=0.786; 95% CI, 0.70-0.87) and good calibration (Hosmer-Lemeshow, $P=0.812$).

## Discussion

In our cohort, 40% of KTx recipients showed ultrasonographic signs of hepatic steatosis (HS), with 30% developing it de novo, on average 2.5 years after transplantation. Fewer than 10% of patients presented with HS prior to KTx. The prevalence of HS prior to KTx in our population was comparable to that reported by Adrian et al, who showed a 7.9% prevalence in a CKD cohort [21].





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**Table 4.** Comparison of baseline characteristics between patients included in the multivariable regression model (complete-case analysis) and those excluded due to missing data.

| | Included (n=113) | Excluded (n=14) | *P* value |
|---|---|---|---|
| HS presence, n (%) | 39 (35.5) | 5 (35.7) | 0.835 |
| Male sex, n (%) | 62 (54.87) | 12 (85.71) | 0.055 |
| Age at analysis [years] | 56.07 (44.84-64.01) | 57.12±11.12 | 0.467 |
| BMI post-KTx [kg/m$^2$] | 26.05±4.17 | 25.45±2.50 | 0.886 |
| BMI pre-KTx [kg/m$^2$] | 23.98±3.70 | 24.53±2.86 | 0.589 |
| Serum creatinine [mg/dL, RR 0.55-1.02] | 1.55 (1.23-1.91) | 1.52 (1.30-1.66) | 0.635 |
| eGFR Cockroft-Gault [mL/min] | 48.3 (37.67-62.84) | 52.26±15.84 | 0.230 |
| Total cholesterol [mg/dL, RR <200] | 197.83 (173.0-214.0) | 195.98±44.93 | 0.847 |
| Low-density lipoprotein [mg/dL, RR <100] | 110.87±34.73 | 107.17±20.77 | 0.806 |
| High-density lipoprotein [mg/dL, RR >50] | 58.0 (49.0-73.5) | 60.21±18.70 | 0.896 |
| Triglycerides [mg/dL, RR <150] | 130.0 (103.0-173.0) | 150.52±82.40 | 0.790 |
| Ischemic heart disease N (%) | 25 (22.12) | 1 (7.14) | 0.337 |
| HIperuricemia N (%) | 44 (38.94) | 4 (28.57) | 0.644 |

Values are presented as mean±SD, median (IQR), or n (%), as appropriate. HS – hepatic steatosis; KTx – kidney transplantation; RR – reference range.

General population studies indicate obesity, diabetes, change in weight, and elevated serum uric acid levels as possible risk factors of MASLD [22]. Overall, our dnHS had a significantly higher BMI before and after KTx. Surprisingly, the association between post-transplant weight change and development of HS was not statistically significant, although the relationship between weight gain and development of NAFLD has been reported in other cohorts [15,23,24]. Gender showed no statistical significance in our sample; a similar observation was made by Zein et al, who analyzed HS in liver transplant recipients [16].

In our cohort hyperlipidemia occurred in 62% of KTx, with a significantly higher percentage among dnHS. In our model total cholesterol was retained in the exploratory stepwise selection; however, its association was attenuated and not statistically significant in the prespecified enter model. This discrepancy likely reflects collinearity among metabolic variables (eg, BMI and lipid parameters) and the limited number of events. A recent meta-analysis by Silva et al of almost 7000 liver transplant recipients, with a comparable prevalence of HS with 39.76%, reported an association of HS and post-Tx dyslipidemia, but no association of HS with pre-transplantation [15].

Another factor associated with presence of dnHS in our patients was hyperuricemia. Our observation could be consistent with other studiesKliknij lub naciśnij tutaj, aby wprowadzić tekst. that show high levels of uric acid constitute an independent risk factor of non-alcoholic steatohepatitis [25,26]. Nevertheless, the etiology of hyperuricemia in KTx recipients reaches beyond metabolic syndrome, as it may result as well from impaired kidney graft function, seeing as most KTx recipients fall within the third and fourth stage of CKD per KDIGO. Moreover CNIs, particularly CsA, are known risk factors of hyperuricemia [27].

The seemingly protective effect of ACE-inhibitor treatment on NAFLD has been reported in specific subpopulations [28]; however, in our study, no statistically significant relationship was found between renin-angiotensin-aldosterone system inhibition and HS development. Likewise, other hypotensive medication and the presence of hypertension arterialis itself were not significantly associated with HS. The presence of diabetes mellitus in our patients, both before and after KTx, was also not significantly associated with development of HS, even though it is widely considered as an HS risk factor, previously described by other authors [2,15,16].

ESKD and HS are acknowledged as risk factors for cardiovascular complications [2]. In our KTx recipients, 20.5% presented with ischemic heart disease at time of the analysis, and it was significantly more common in patients with dnHS. Furthermore, in multivariable analysis, ischemic heart disease was independently associated with the presence of dnHS, although it is necessary to stress that given the cross-sectional design of the study, this association reflects coexistence rather







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than a temporal or causal relationship. Considering the cumulative cardiovascular risk of patients with a MASLD (+)/CKD (+) phenotype and the high prevalence of MASLD in KTx recipients, assessment for HS in this population should be routinely implemented to facilitate early interventions and lifestyle modifications.

Such a great increase in HS incidence following kidney transplantation would suggest an impact of the immunosuppressive regimen, especially considering a similar rise in incidence of HS following liver transplantation and the negative effects of CNIs and glucocorticoids on insulin resistance, cholesterol levels [14], and TAC hepatotoxicity [29]. A retrospective study in liver transplant recipients found an inverse correlation of TAC blood levels and liver graft function [30], while Binbin et al reported an 8.9% incidence of drug-induced liver injury due to TAC in kidney transplantation [31]. A direct link between CNI use and HS development is yet to be shown; likewise, we did not find any statistically significant association between either type of CNI used or TAC C/D ratio and HS development. However, given the relatively small sample size and limited variability of C/D ratios, this study may have been underpowered to detect modest effects. Therefore, the possibility of a type II error could not be excluded. Another study conducted in liver transplant recipients also found that the type of CNI was unrelated to HS development [16]. It is worth noting that, regardless of HS presence, our patients presented comparable alanine aminotransferase activity.

To the best of our knowledge, this is the first study to examine prevalence of HS in KTx recipients, as existing works focus on liver transplant recipients. A recent study by Mak et al reported a 27.4% prevalence of post-transplant HS in liver transplant recipients, diagnosed by magnetic resonance imaging. The prevalence increased with BMI, consistent with our findings [32]. Their model selected 2 independent risk factors – central obesity (defined through waist circumference) and hypertension – highlighting the key role of metabolic factors over immunosuppressive exposure in HS pathogenesis. From a different standpoint, another recent study showed that markedly steatotic liver allografts (up to 50%) provided good clinical outcomes, which gives a different perspective on HS itself in the context of transplantation [33]. Moreover, SGLT2 inhibitors and GLP-1 receptor agonists recommended as nephroprotective treatment in chronic kidney disease [34,35] may be beneficial in fatty liver disease [36,37]; however, no patients in our cohort were treated with tirzepatide or GLP-1 receptor agonists during the assessed period.

Our study faced several limitations, the most important being its retrospective nature and the relatively small cohort. Only alanine aminotransferase activity was available, as other liver enzymes were not routinely assessed in an outpatient setting. Likewise, the serological status for hepatitis B and C virus and cytomegalovirus was frequently unavailable. We were unable to objectively assess dietary habits and concomitant medications aside from immunosuppression, antihypertensive, and hypolipidemic drugs; therefore, we could not rule out the confounding effects of lifestyle and dietary variability. Furthermore, we were unable to assess the cumulative lifelong dose of glucocorticoids, due to incomplete data.

Diagnosis of HS was determined solely by abdominal ultrasonography studies, which constituted a primary methodological limitation. Thus, the HS prevalence was probably underestimated. Moreover, our findings relate to imaging-defined steatosis and did not delve into the full spectrum of MASLD. Although, as MASLD diagnosis requires coexistence of at least 1 component of the metabolic syndrome [2], all of our patients with dnHS would have met the diagnostic criteria; however, all but 1 patient had hypertension arterialis, with the remaining patient presenting with diabetes mellitus. The study was powered to detect moderate-to-large associations; smaller effect sizes may not have been identified due to limited event numbers. Complete-case analysis may introduce bias if the missing data mechanism is not completely at random. Although the proportion of missing data was relatively small (approximately 11%), residual selection bias could not be excluded. Although the main associations were consistent across modeling approaches, the variability observed for total cholesterol illustrates the potential sensitivity of results to model specification. The relatively wide confidence interval for ischemic heart disease reflects the limited number of affected patients and event counts, underscoring the need for cautious interpretation and external validation. Due to the retrospective design and the lack of standardized longitudinal imaging assessments, a longitudinal analysis was not feasible in our study. Multiple statistical comparisons were performed when analyzing laboratory and clinical parameters without formal adjustment for multiplicity. Thus, secondary findings should be interpreted cautiously and considered hypothesis-generating.

## Conclusions

KTx recipients are at a high risk of HS development. HS is associated with higher BMI, hyperuricemia, dyslipidemia, and ischemic heart disease but is unrelated to kidney graft function and immunosuppression regimen. Screening for HS in KTx should be recommended, as its presence indicates the need for strict metabolic control and lifestyle interventions to avoid future complications.





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