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ORIGINAL ARTICLE

Liver Transplantation and Metabolic Dysfunction Associated Steatotic Liver Disease Is Associated with Markers of Metabolic Risk and Inflammation

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Abstract

Background Liver transplant (LT) recipients are at high risk of cardiometabolic disease and mortality. However, routinely employed clinical risk tools have sub-optimal diagnostic performance due to transplant related biological changes. Metabolic vulnerability index (MVX) is a serum-based composite biomarker comprised of nutritional risk [metabolic malnutrition index or MMX] and chronic inflammation [inflammatory vulnerability index or IVX]. MVX is a predictor of cardiovascular risk and all-cause mortality in the general population, however, the effect of LT on MVX is unknown.

Methods To better quantify MVX after transplantation, LT recipients (n = 181) prospectively enrolled in a natural history study were matched with non transplant controls from the MESA study of healthy individuals. All controls were matched 1:1 regarding age and gender. Additionally, lean controls were identified as those with BMI < 25 kg/m^2 and BMI-matched controls who were propensity matched for BMI.

Results Compared to matched controls, LT recipients had significantly higher MVX (56.9 ± 10.1 vs. 45.8 ± 9.4 vs. 44.8 ± 9.3, p < 0.001), IVX [53.1 ± 12 vs. 39.3 ± 11.2 vs. 40.2 ± 10.9, p < 0.001), and MMX (58.7 ± 8.2 vs. 55.4 ± 6.5 vs. 53.1 ± 6.0, p < 0.001). No significant differences were noted in MVX in LT recipients who developed metabolic dysfunction associated steatotic liver disease (MASLD) after LT. In a multivariate analysis, MVX scores were positively associated with female gender, diabetes, serum AST and BMI, and negatively with dyslipidemia.

Conclusion LT is associated with a significant increase in MVX and its components, suggesting a heightened risk in LT recipients that is above that of the non-LT population. Future well designed prospective studies are required to calibrate MVX to clinical outcomes in LT patients.

Keywords Liver transplantation · Metabolic vulnerability index · Frailty · Inflammation · Metabolic dysfunction associated steatohepatitis

Introduction

Liver transplant (LT) recipients have lower survival when compared to matched controls from the general population [1]. While the exact nature of this discrepancy is not known, it is in part due to a higher burden of cardiometabolic diseases in LT recipients [2–6]. A key emerging concept in metabolic health is the interplay between muscle wasting, malnutrition, and chronic inflammation. Accelerated muscle loss resulting from poor nutritional choices, increased energy expenditure, and muscle catabolism resulting from high systemic inflammation has been associated with increased morbidity and mortality in patients with chronic medical conditions [7–9].

The association between the malnutrition-inflammation complex and increased risk of cardiovascular disease (CVD) and mortality was recently demonstrated in a large cohort of patients with high CVD risk in the Catherization Genetics

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(CATHGEN) cohort [10]. The malnutrition-inflammation complex was quantified via the Metabolic Vulnerability Index (MVX), a blood-based biomarker panel that is a composite of the Inflammation Vulnerability Index (IVX) and the Metabolic Malnutrition Index (MMX) which are simultaneously measured via nuclear magnetic resonance (NMR) analysis. The IVX is calculated from circulating levels of novel inflammatory markers such as small high-density lipoprotein particles (S-HDL-P) and GlycA [10]. The MMX is related to sarcopenia and muscle wasting and is calculated from circulating levels of citrate and the branched chain amino acids (BCAA): valine, leucine, and isoleucine [10].

In LT recipients, chronic inflammation has been associated with increased risk of CVD [9]. Sarcopenia in LT recipients has been associated with increased adiposity and reduced survival [11, 12]. However, there are no data evaluating the malnutrition-inflammation complex in LT recipients. Thus, the aim of the present study was to utilize a prospective cohort of LT recipients and matched non-LT controls from a general population to (1) demonstrate the impact of LT on MVX and its components, (2) evaluate the association between hepatic steatosis, fibrosis, and MVX and (3) identify the clinical profile of LT recipients associated with high-risk MVX.

Methods

Study Design

The current study represents the cross sectional analysis of a prospective cohort of adult participants (≥ 18 years of age) enrolled in a natural history study of LT recipients at the Hume-Lee Transplant Center at Virginia Commonwealth University [6]. All authors had access to full data. The study design was reviewed and approved by the Institutional Review Board (IRB). This study was conducted according to the guidelines of the Declaration of Helsinki and all participants provided written informed consent. The manuscript was reviewed and endorsed by all authors prior to submission.

Patient Population

Adult LT recipients (age ≥ 18 years) were recruited from hepatology clinics between 2/1/2020 and 3/1/2023. Exclusion criteria included medical history of end organ damage (i.e., heart failure, renal failure necessitating hemodialysis, decompensated graft failure), acute cellular rejection, chronic rejection, ongoing therapeutic intervention for Hepatitis C virus (HCV), untreated HCV, and cholestatic hepatitis. Similarly, patients with ongoing history of significant alcohol use were also excluded. All patients were clinically managed at the discretion of the treating transplant hepatologist according to institutional standard of care. Occurrence of metabolic dysfunction associated steatotic liver disease (MASLD) was diagnosed based on a vibration controlled transient elastography (VCTE) exam with a controlled attenuation parameter (CAP) ≥ 270 dB/m based on prior published literature [13].

Metabolic Vulnerability Index

Heparin plasma samples, obtained in the fasting state during the enrollment visit, were analyzed via NMR LipoProfile analysis using the Vantera® Clinical Analyzer at Labcorp (Morrisville, NC, USA) [14]. MVX, IVX, and MMX scores were calculated by Labcorp from concentrations of S-HDL-P, GlycA, leucine, isoleucine, valine, and citrate using proprietary algorithms [10] (Supplemental Fig. 1). The indices were scaled from 1 to 100 and stratified by sex with higher values indicating worse disease. Labcorp did not have access to any clinical meta-data under a research agreement with VCU.

Non-LT Control Population

The LT population was propensity matched 1:1 to the non-LT population. For the non-LT control cohort, the Multi-Ethnic Study of Atherosclerosis (MESA) study was used. This population-based study consists of participants recruited from six field centers throughout the United States as have been described elsewhere [internal.mesa-nhlbi.org/about] [15]. The study included a diverse population representative of the US cohort. The following two control groups were constructed using 1:1 propensity matching:

a. Lean controls: matched for age and gender but BMI < 25 kg/m.^{2}
b. BMI matched: matched for age, gender, and BMI

For our analysis, we focused on participants who had available EDTA plasma for NMR measurements. The MESA study was approved by the National Heart, Lung, and Blood institute (NHLBI) and conducted in accordance with the guidelines of the declaration of Helsinki. All participants gave written informed consent.

Statistical Analysis

All data are presented as means and standard deviation, median with interquartile range, or percentages as appropriate. Statistical comparisons were made using *t*-test, $\chi 2$, analysis of variance (ANOVA), or Wilcoxon-Mann–Whitney as appropriate based on the type and distribution of data. The relationship between MVX and its

components and clinical parameters in LT recipients was initially evaluated via a regression. Variables that were significant on univariate analysis with a p-value less than 0.1 were subsequently entered into backward stepwise regression models. Both univariate and multivariate models were adjusted for age, gender, and presence of coronary artery disease. Chronic exposure to immunosuppression can culminate in higher metabolic burden as time from LT surgery increases [16]. Thus, to evaluate how time from LT can impact MVX, IVX, and MMX, a sensitivity analysis was performed comparing these biomarkers in patients who received a LT within 2 years, between 2 and 5 years, and after 5 years. A nominal p-value of < 0.05 was considered statistically significant. All analysis was performed in SPSS (IBM, Armonk, NY).

Results

Description of the Study Cohort

The study cohort consisted of 181 LT recipients that included 66 (36%) females and 140 (77%) non-Hispanic whites (Table 1). The mean age of the study cohort was 60 ± 12 years. The etiology of liver disease requiring LT was MASH (45%), followed by alcohol (25%), and hepatitis C (13%). Prevalence of metabolic diseases was 44% for diabetes, 84% for hypertension, 54% for obesity, and 68% for dyslipidemia. Most patients were managed on tacrolimus (171 or 95%) as the primary immunosuppressant, followed by cyclosporine (10 or 6%). The median time from LT to lab draw was 36 (25th, 75th percentile 13, 95) months.

Impact of LT on MVX and Its Components

Compared to both lean- and BMI-matched controls, LT recipients had higher MVX, IVX, and MMX scores (Fig. 1a). No significant differences in the MVX, IVX, or MMX scores or the concentrations of their components were noted between the control groups (lean vs. BMI-matched controls). The MMX components are presented in Fig. 1b which demonstrates a significant reduction in leucine and valine concentration in LT recipients when compared to non-LT controls. Compared to lean controls, isoleucine levels were significantly higher in LT recipients however, no difference between BMI-matched controls and LT recipients was noted (Fig. 1b). The IVX components are presented in Fig. 1c and show a significant increase in GlycA levels in LT recipients when compared to controls, whereas there were no significant differences in S-HDL-P concentrations noted across groups. Even when LT and matched controls were stratified for co-morbid conditions such as diabetes or hypertension, similar trends were observed (Supplemental Fig. 2). Time from LT surgery did not impact MVX, IVX, MMX or their components (Supplementary Table 1).

Table 1 Clinical characteristics of the liver transplant recipients

	Liver transplant recipients (N = 181)
Demographics	
Age (years)	60 ± 12
Females (%)	66 (36%)
Ethnicity	
White (%)	140 (77%)
Black (%)	29 (16%)
Etiology of liver disease (%)	
MASH	82 (45%)
Alcohol	45 (25%)
Hepatitis C	24 (13%)
Cholestatic liver disease	12 (7%)
Metabolic Co-morbidities	
Body mass index (kg/m^2)	31.2 ± 6.7
Coronary artery disease (%)	23 (13%)
Diabetes (%)	80 (44%)
Hyperlipidemia (%)	123 (68%)
Hypertension (%)	152 (84%)
MASLD Post-LT	103 (57%)
Obesity (%)	98 (54%)
Hyperlipidemia statin treatment (%)	105 (58%)
Diabetes insulin treatment (%)	47 (26%)
Diabetes metformin treatment (%)	26 (14%)
Laboratory	
Alanine transaminase (ALT) (IU/L)	36 ± 27
Aspartate transaminase (AST) (IU/L)	32 ± 20
Alkaline phosphatase (IU/L)	121 ± 78
Bilirubin(mg/dL)	0.73 ± 0.40
Creatinine	1.43 ± 0.65
BUN	22 ± 11
HbA1c (%)	5.83 ± 1.34
HDL-C (mg/dL)	48 ± 15
LDL-C (mg/dL)	81 ± 30
Triglycerides (mg/dL)	152 ± 90
Total cholesterol (mg/dL)	151 ± 36
WBC	6.4 ± 2.3
Hemoglobin	13.2 ± 2.0
Platelets	191 ± 89
Transplant parameters	
Time from transplant	
Tacrolimus (%)	171 (95%)
Cyclosporine (%)	10 (6%)
Sirolimus (%)	5 (3%)

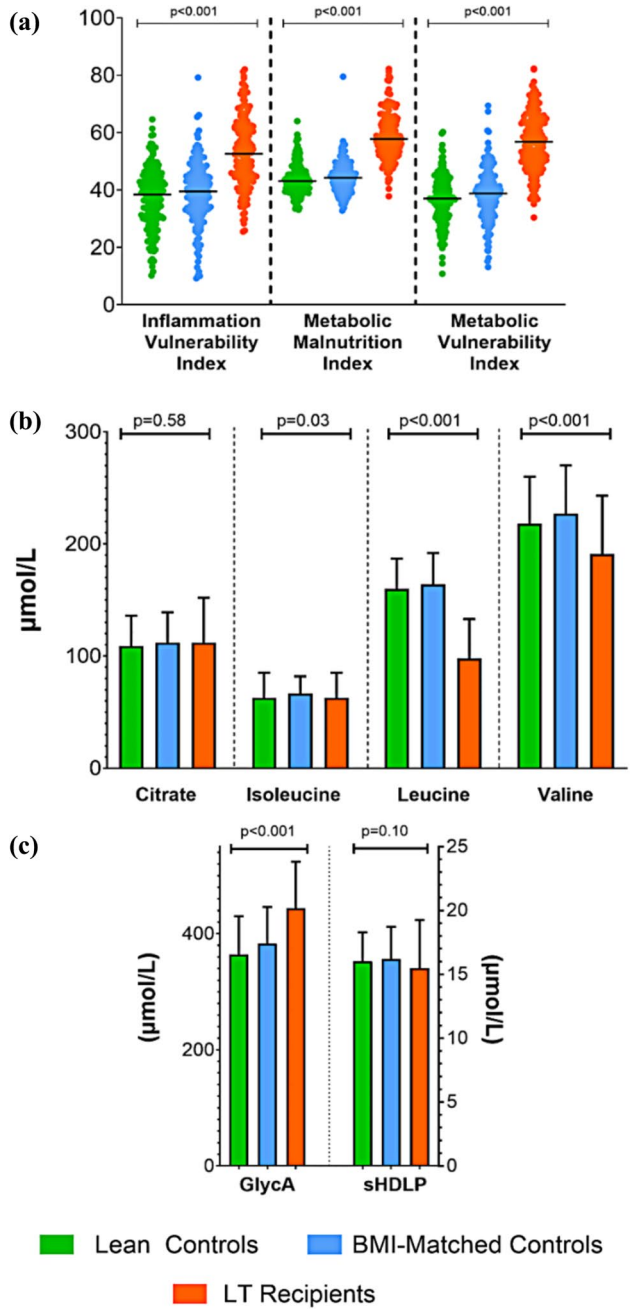

Fig. 1 **a** Liver transplant (LT) recipients have significantly higher metabolic vulnerability index (MVX), inflammation vulnerability index (IVX) and metabolic malnutrition index (MMX) scores when compared to obese controls (matched for age-, gender- and BMI) or lean controls (matched for age- and gender, but BMI < 25 kg/m^2)**. b** Significant differences in components of MMX are noted in LT recipients compared to matched controls that contribute to higher MMX scores**. c** LT recipients have significantly higher serum GlycA levels but no significant differences in S-HDL-P levels

Regression analysis performed to evaluate the relationship between clinical parameters and MVX, IVX, and MMX are presented as univariate and multivariate adjusted (age, gender and presence of CAD) univariate and multivariate analysis (Supplemental Table 2). In the adjusted multivariate analysis, MVX correlated directly with serum creatinine and female gender and inversely with dyslipidemia. A trend between post-LT MASLD and MVX was noted, however, this did not reach the threshold for statistical significance (p = 0.06). IVX was positively associated with BMI and tacrolimus use and inversely with diagnosis of dyslipidemia in adjusted multivariate analysis. MMX correlated positively with female gender and inversely with statin use and post-LT MASLD diagnosis (Supplemental Table 2).

To determine if liver donor characteristics could influence MVX, IVX, or MMX, a multiple backward linear regression was performed with donor variables (diabetes, hypertension, BMI, gender, ethnicity and age). No statistically significant relationship between donor variables and MVX, IVX, or MMX were noted (Supplemental Table 3).

Relationship Between MASH Cirrhosis and MVX in LT Recipients

Among LT recipients, patients transplanted for MASH cirrhosis had lower MMX scores (57 ± 9 umol/L vs. 60 ± 7 umol/L, p = 0.035), which were related to higher concentrations of BCAA (Supplemental Fig. 3A). While IVX scores were similar between patients transplanted for MASH vs. non-MASH cirrhosis, patients transplanted for MASH cirrhosis had significantly higher concentrations of GlycA (456 ± 78 vs. 432 ± 80, p = 0.04). Overall, MVX was similar between the two groups. When the characterization was broadened to compare the three most common indications for LT (MASH, HCV, and alcohol), no significant differences between MVX, IVX, or MMX were noted (Supplemental Fig. 3B).

Development of post-LT MASLD either as recurrence (i.e. originally transplanted for MASLD cirrhosis who develop graft steatosis) or de novo (non-MASLD indication developing graft steatosis) on MVX was evaluated (Supplemental Fig. 4). No significant differences in MVX, MMX, or IVX were noted in patients who developed post-LT MASLD compared to those who did not (Fig. 2a). However, patients who developed MASLD after LT had higher serum valine (199 ± 56 umol/L vs. 180 ± 45 umol/L, p = 0.014), isoleucine (66 ± 22 umol/L vs. 58 ± 21 umol/L, p = 0.02), and GlycA (458 ± 89 umol/L vs. 425 ± 76 umol/L, p = 0.002) concentrations compared to patients without evidence of MASLD in the transplanted liver (Fig. 2b and 2c).

Interaction Between Metabolic Diseases and MVX in LT Recipients

Presence of diabetes, hypertension, or obstructive sleep apnea following LT did not significantly affect MVX, IVX

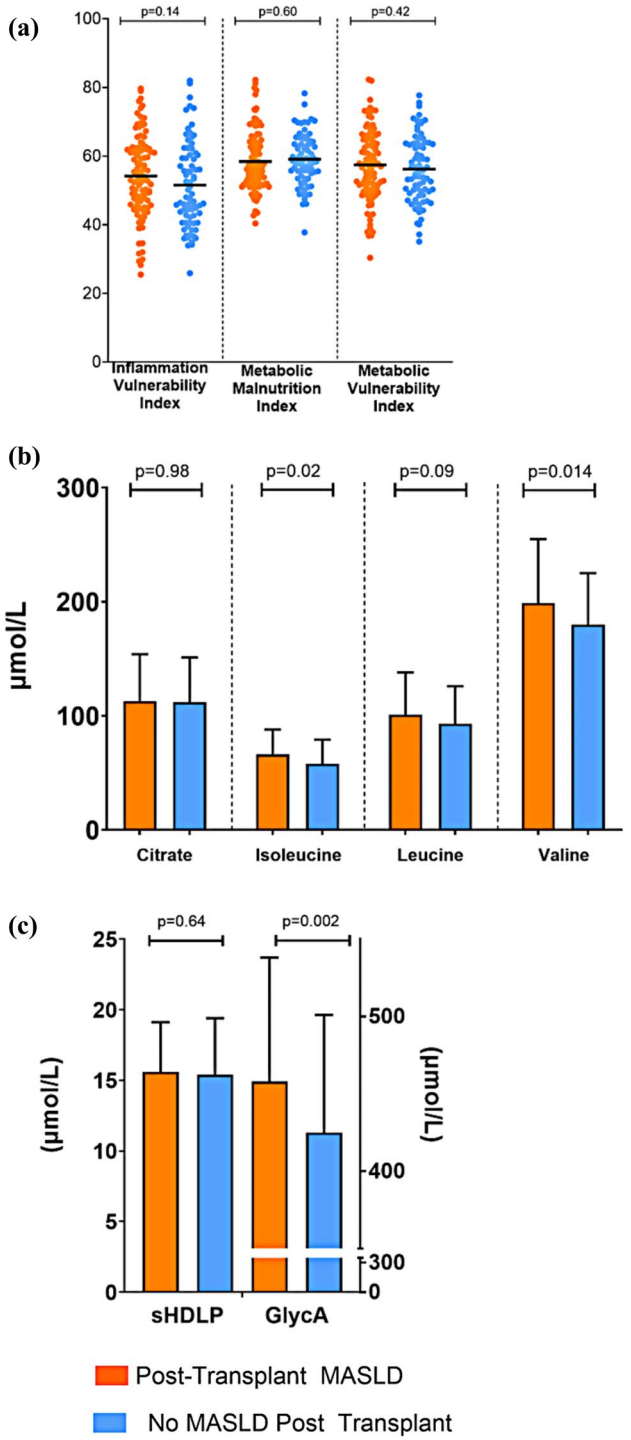

Fig. 2 **a** No significant differences in metabolic vulnerability index (MVX), inflammatory vulnerability index (IVX), and malnutrition vulnerability index (MMX) scores were noted in patients who developed metabolic dysfunction associated steatotic liver disease (MASLD) after liver transplant (LT). **b** The components of metabolic malnutrition index were significantly higher among patients who developed MASLD following LT. **c** Serum GlycA was significantly elevated in patients with post-LT MASLD

or MMX scores. While MVX and IVX were similar in obese and non-obese patients, a trend towards a lower MMX value was noted in obese LT recipients, however, this did not reach statistical significance (57.7 ± 8.5 vs. 59.9 ± 7.8; p = 0.07). Compared to non-obese LT recipients, obese LT recipients had significantly higher concentrations of GlycA (456 ± 80 umol/L vs. 428 ± 77 umol/L, p = 0.017), valine (202 ± 57 umol/L vs. 178 ± 43 umol/L, p = 0.002), leucine (105 ± 39 umol/L, 90 ± 29 umol/L, p = 0.004), and isoleucine (67 ± 23 umol/L, 58 ± 20 umol/L, p = 0.009).

Tacrolimus use when compared to cyclosporine was associated with higher IVX scores (53.5 ± 10.1 vs. 42.1 ± 7.8, p = 0.004) but not MMX scores. The MVX scores approached significance with a value of 57.2 ± 10.1 in patients on tacrolimus compared to 50.9 ± 7.9 in patients on cyclosporine (p = 0.06).

Impact of Gender on MVX and Its Components in LT Recipients

A trend towards higher MMX and MVX scores was noted in female LT recipients compared to males, however, this did not reach statistical significance (Fig. 3a). The components of MVX including serum leucine, isoleucine, and valine levels were significantly lower among females when compared to males (Fig. 3b). In contrast, females had higher concentrations of GlycA and S-HDL-P than males (Fig. 3c).

Discussion

The burden from metabolic disease in LT recipients is high, particularly in patients who develop MASLD post-LT. However, biomarkers or clinical risk assessment tools that are routinely available in clinical practice such as the lipid profile or serum aminotransferases may not fully capture the heightened metabolic risk in LT recipients [6, 9, 17, 18]. The present study is the first to evaluate the relationship between MVX, a novel marker of cardiometabolic risk related mortality, and LT. Using lean and BMI-matched controls from a general (i.e. non-LT) population, our study demonstrated LT is associated with higher MVX and its individual components.

Malnutrition and frailty have previously been associated with increased mortality risk in LT recipients [19]. Frailty in LT recipients can result from cumulative decline across multiple organ systems that include endocrine, neuromuscular, and the immune system [20]. Catabolic muscle loss commonly seen in patients with decompensated cirrhosis may not improve following LT, thereby contributing to the burden of post-LT frailty and sarcopenia [11, 21]. The immediate post-operative course following LT is characterized by the use of high doses of

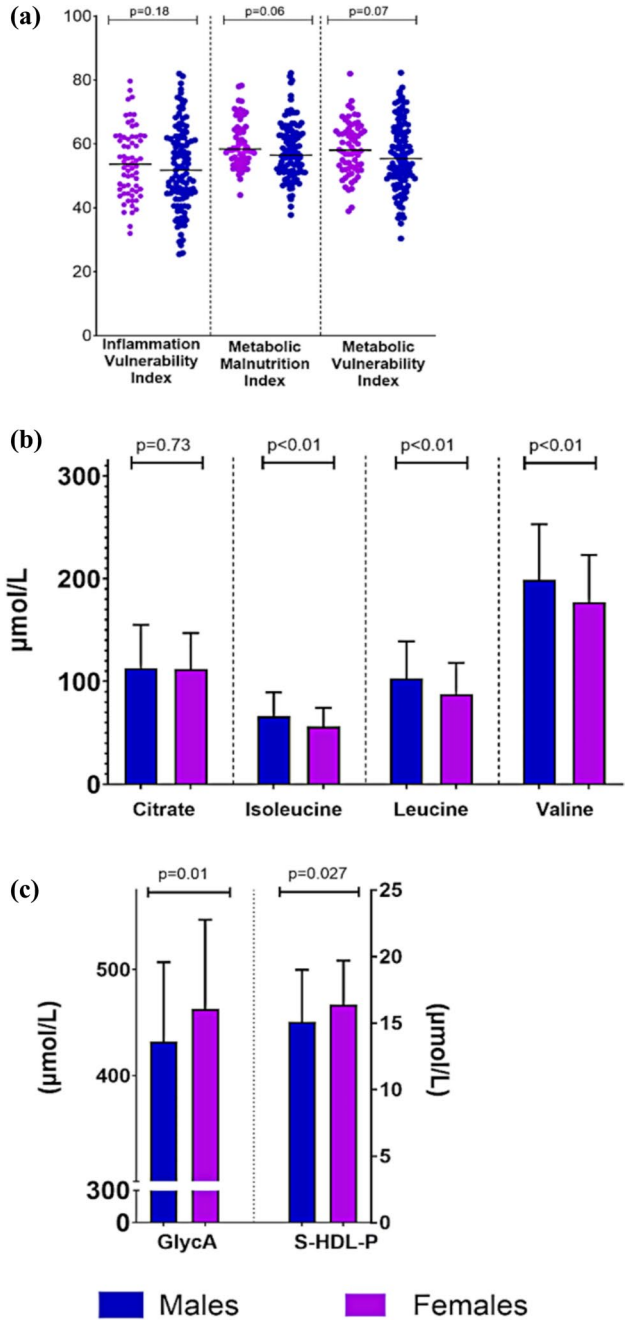

Fig. 3 **a** A trend towards higher metabolic vulnerability index (MVX) and metabolic malnutrition index (MMX) scores was noted in females. **b** Female liver transplant (LT) recipients had lower serum concentrations of branched chain amino acids compared to males. **c** Females LT recipients had higher serum concentrations of small high-density lipoprotein particles (S-HDL-P) and GlycA when compared to males

corticosteroids, calcineurin inhibitors, physical inactivity and decreased food intake, all well-established risk factors for frailty. Interestingly, patients transplanted for MASH cirrhosis had significantly higher MMX scores and higher concentrations of brain chained amino acids (BCAA) compared to non-MASH patients. Moreover, patients who developed MASLD following LT also had higher serum concentrations of BCAA. Similarly, in a Dutch LT cohort study, BCAA elevations have been recently noted to be associated with metabolic syndrome and type 2 diabetes [22]. Studies in the general population (non-LT) have demonstrated a strong relationship between elevated plasma BCAA levels and obesity and adiposity [23, 24]. Similar relationships have been reported in patients with insulin resistance, MASH, and cardiovascular disease [25, 26, 27]. While the exact mechanism linking BCAA elevation to increased cardiometabolic diseases in the human is not known, animal model studies suggest BCAA metabolism may mediate metabolic outcomes via lipotoxicity, metabolic reprogramming, activation of inflammatory cascade, and mitochondrial damage [28–31]. Thus, the significant elevations in MMX and its components in LT recipients (compared to controls) and patients transplanted for MASH likely reflects a patient population with higher metabolic burden [32]. However, the nature of the interaction between components of MMX as a risk factor for future clinical events and mortality require further investigation.

The IVX reflects the inflammatory component of the MVX and is comprised of small HDL particles and GlycA, and has demonstrated robust diagnostic performance for prediction of CVD related and all cause mortality [33–37]. GlycA is a composite biomarker of systemic inflammation and represents *N*-acetyl methyl group protons of mobile glycan residues of glycoproteins [38], thus, allowing for a collective measurement of multiple inflammatory species rather than individual acute phase reactants (i.e. hsCRP). Multiple studies have shown a relationship between GlycA and CVD related mortality [33]. In the present study, serum GlycA concentrations were significantly higher in LT recipients when compared to non-LT controls. Moreover, within LT recipients, patients who developed MASLD following LT had significantly higher GlycA levels. Finally, females had significantly higher concentrations of inflammatory biomarkers than males. These findings are corroborated with prior studies showing a high burden of cardiovascular disease and atherogenic dyslipidemia in LT recipients with MASLD [17, 39, 40].

HDL have largely been utilized in clinical practice for quantification of cardiovascular risk as HDL-cholesterol, however, several studies have documented the relationship between sub-species of HDL particles as metabolic risk factors in patients with chronic liver disease or LT [39, 41–43]. This is in part due to the limited ability of smaller HDL sub-particles in cholesterol transport when compared to larger HDL sub-particles [44]. One prior study demonstrated a significant contribution of small HDL particles to multivariable models for mortality that were beyond that of HDL–C [10]. The present study provided

data demonstrating a significant increase in small HDL particles in female LT recipients when compared to male LT recipients and while the exact nature of this association is not known, it may potentially suggest gender- based differences in inflammatory markers and would require further investigation. No significant differences in small HDL particles were noted among LT recipients when they were stratified based on etiology of disease, post-LT MASLD, or weight. Collectively, similar levels of IVX and its components in LT recipients across etiologies of liver disease might suggest a transplant-specific phenomenon, likely dependent on exposure to immunosuppression. This is further supported by the study finding of higher IVX values in patients on tacrolimus, a relatively more potent immunosuppressive.

While chronic inflammation, sarcopenia, and malnutrition are well-established risk factors for reduced survival, the relative ease with which they can be quantified in clinical practice has been a major impediment to incorporating them in clinical practice. In the present study, we provide data using NMR-based quantification of these factors expressed collectively as the MVX. Using matched controls, the study quantified the impact of LT on these parameters, thus providing foundational data on an emerging biomarker in LT recipients. However, the study findings must be evaluated in the context of study limitations. First, the study is cross-sectional in nature and does not provide the association between MVX and its components and clinical outcomes such as mortality and future risk of cardiovascular disease. As this is a relatively novel biomarker, the present study provides the data needed to construct a prospective study according to best practices in biomarker development that would aim to develop transplant specific cutoff values to identify high risk patients. No significant differences were noted across etiologies of liver disease with regards to MVX, however, this might be due to the inherent differences in LT recipients when compared to non-LT controls (i.e. higher burden of metabolic disease and exposure to chronic immunosuppression) and thus, the parameters included in the construction of MVX might require calibration to transplant specific populations. As the majority of patients were on tacrolimus with immunosuppression minimization, the present study is not able to evaluate the true impact of various immunosuppressive regimens on MVX. However, the study population represents current clinical practice in whom tacrolimus-based monotherapy is utilized to minimize immunosuppression.

In summary, the present study demonstrates the negative impact of LT on MVX, a novel NMR based composite biomarker of cardiometabolic health and mortality. Moreover, among LT recipients, components of MVX were further affected by etiology of chronic liver disease (MASH vs. non-MASH), occurrence of post-LT MASLD, and gender. However, well designed prospective studies that align with best practices in biomarker science are needed before MVX can be adopted in clinical practice in LT recipients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-025-09072-1.

Author Contributions A.B., S.G., A.T.B., V.P., V.K., I.Y., and M.S.S contributed to the design of the study. A.B., S.G., G.R., M.N., A.K., R.R., A.A., H.K., S.L.J.B, and R.P.F.D. collected the data for the analysis. M.S.S. and V.P. performed the statistical analysis for the manuscript. M.S.S., A.T.B., and A.B. wrote the main manuscript text. All authors reviewed the manuscript.

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Data Availability All data is provided within the manuscript including supplemental information.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval The study design was reviewed and approved by the Institutional Review Board (IRB) at Virginia Commonwealth University. This study was conducted according to the guidelines of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Disclosures None: AB, SG, MN, RR, AA, TA, HK, VP, DV. MSS: NovoNordisk (institutional grant support); AMRA (Advising). MAC and IS are employees of Labcorp.

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