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ORIGINAL ARTICLE

Liver transplant recipients have worse metabolic body phenotype compared with matched non-transplant controls

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Abstract

Background and Aim: Quantification of body compartments, particularly the interaction between adipose tissue and skeletal muscle, is emerging as novel a biomarker of metabolic health. The present study evaluated the impact of liver transplant (LT) on body compartments.

Methods: Totally 66 adult LT recipients were enrolled in whom body compartments including visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT), muscle fat infiltration (MFI), fat-free muscle volume (FFMV), and liver fat (LF) were quantified via whole body magnetic resonance imaging (MRI). To provide non-LT comparison, each LT recipient was matched to at least 150 non-LT controls for same sex, age, and body mass index (BMI) from the UK Biobank registry.

Results: LT recipients (*vs* matched non-LT controls) had significantly higher subcutaneous (13.82 ± 5.47 *vs* 12.10 ± 5.10 L, $P < 0.001$) and visceral fat (7.59 ± 3.75 *vs* 6.72 ± 3.06 L, $P = 0.003$) and lower LF (5.88 ± 7.14 *vs* $8.75 \pm 6.50\%$, $P < 0.001$) and muscle volume (11.69 ± 2.95 *vs* 12.12 ± 2.90 L, $P = 0.027$). In subgroup analysis, patients transplanted for metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis (*vs* non-MASH cirrhosis) had higher ASAT, VAT, and MFI. A trend toward higher LF content was noted; however, this did not reach statistical significance (6.90 ± 7.35 *vs* $4.04 \pm 6.23\%$, $P = 0.189$). Finally, compared with matched non-LT controls, patients transplanted for MASH cirrhosis had higher ASAT and VAT; however, FFMV and MFI were similar.

Conclusion: Using non-LT controls, the current study established the higher-than-expected adiposity burden among LT recipients, which is even higher among patients transplanted for MASH cirrhosis. These findings provide data needed to design future studies developing radiomics-based risk-stratification strategies in LT recipients.

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Introduction

This risk of metabolic diseases and cardiovascular disease (CVD) is exaggerated in liver transplant (LT) recipients, in whom exposure to chronic immunosuppression and preexisting metabolic diseases (i.e. metabolic dysfunction-associated steatohepatitis or MASH) negatively affects normal metabolic physiological processes such as glucose and lipid metabolism, and biofuel utilization.[1–4] Thus, the net clinical effect of this heightened metabolic burden is significantly lower survival in LT recipients compared with matched cohorts from non-transplant population.[5] Despite this heightened risk, there remains significant gaps in the published literature regarding physiology of this cardiometabolic risk and risk-stratification strategies.

Body compartments, particularly the interaction between skeletal muscle and adipose tissue depots, is emerging as a key predictor of metabolic health.[6] Visceral adipose tissue (VAT) is an established negative predictor of metabolic health and survival. Skewness in visceral and liver fat (LF) distribution patterns can be used to identity phenotypes at elevated risk for incident CVD.[7] Moreover, emerging studies highlight that metabolic conditions and aging can lead to loss of skeletal muscle and increased muscle fat infiltration (MFI), which perturb normal skeletal muscle physiological conditions and lead to deterioration of metabolic health.[8] Therefore, adverse muscle composition (AMC) characterized by loss of muscle volume and increased muscle fat has been associated with increased risk of cardiometabolic burden, hospitalization, and frailty and is an independent predictor of all-cause mortality.[9,10]

The interaction between body compartments and metabolic health has not yet been well defined in LT despite the oversized metabolic burden.[11,12] Specifically, it is currently not known if there are LT specific changes to body compartments and if these body compartment changes may be influenced by the etiology of liver disease (i.e. MASH *vs* non-MASH) among LT recipients. Recent innovations in radiomics-based metabolic risk stratification have also identified distinct phenotypes;[13] however, the prevalence of these high-risk radiomics phenotypes in LT recipients is unknown. Thus, the present study aimed to address these limitations in published literature using a prospectively enrolled cohort of LT recipients who underwent magnetic resonance imaging (MRI)-based body phenotyping.

Methods

This is a single-center prospective study that enrolled adult LT recipients at Virginia Commonwealth University from 2016 to 2021. The study was approved by the Institutional Review Board and conducted in accordance with regulatory guidelines. The manuscript was reviewed and approved by all study investigators prior to submission.

Study cohort. Adult (age ≥18 years) LT recipients at time of study screening were invited to participate in the study. Exclusion criteria included multi-organ transplants, liver graft failure, more than mild alcohol intake (>10 g/day for women and >20 g/day for men), HIV, end organ damage (i.e. heart failure, and dialysis) or non-dermatological malignancy, as these may affect body fat composition independent of LT. Similarly, recent history of liver-associated complications such as acute cellular rejection, chronic rejection, hepatic artery thrombosis, or untreated biliary strictures was also excluded. Patients receiving medications with significant weight loss potential were excluded as this may affect body compartments. All patients were managed via standard clinical care and immunosuppression was managed by the treating transplant hepatologist.

Body compartment quantification. Body compartments were quantified via a research-dedicated Phillips Ingenia 3.0 T MRI (Philips, Amsterdam, Netherlands) scanner using a 6-min dual-echo Dixon protocol using AMRA® Researcher (AMRA Medical AB, Linköping Sweden), as described previously.[8] Acquired images were analyzed for VAT, abdominal subcutaneous adipose tissue (ASAT), LF by proton density fat-fraction, total thigh fat-tissue free muscle volume (FFMV) and mean anterior thigh MFI.

Virtual control group. The UK Biobank imaging study data were used in this study to better demonstrate the relationship between LT and non-LT (i.e. general population) and to standardize the body composition measurements in the cohorts by calculating body compartment *z*-scores (also known as "standard score" or "standardization") for each LT recipients using virtual cohort groups (VCGs). To create a VCG, the target LT recipient was matched to participants in the UK Biobank with the same sex and within ± 1 kg/m^2 of their BMI (except for FFMV which was within ± 2 kg/m^2) as reported previously (Fig. 1).[8] If less than 150 controls were stratified by these criteria, the BMI interval was incrementally and symmetrically increased by 0.1 kg/m^2 until the VCG contained at least 150 controls. Each LT recipient's body compartment *z*-scores (i.e. *z*-ASAT, *z*-VAT, *z*-LF, *z*-MFI, and *z*-FFMV) were thereafter calculated by subtracting the reference VCG mean from the subject's measurement and then dividing the difference by the reference VCG standard deviation. Thus, the standardized body composition measurements (*z*-scores) are effectively no longer confounded by sex and BMI. Thus, the *z*-score measures how much the LT recipient is deviating for a specific body compartment from what is expected by their sex and BMI. VAT, ASAT, and FFMV values were divided by height^2 before calculation of the *z*-score.[9,14] Due to the skewed distribution of LF, LF values were log transformed before calculation of *z*-LF. MFI was used as is.

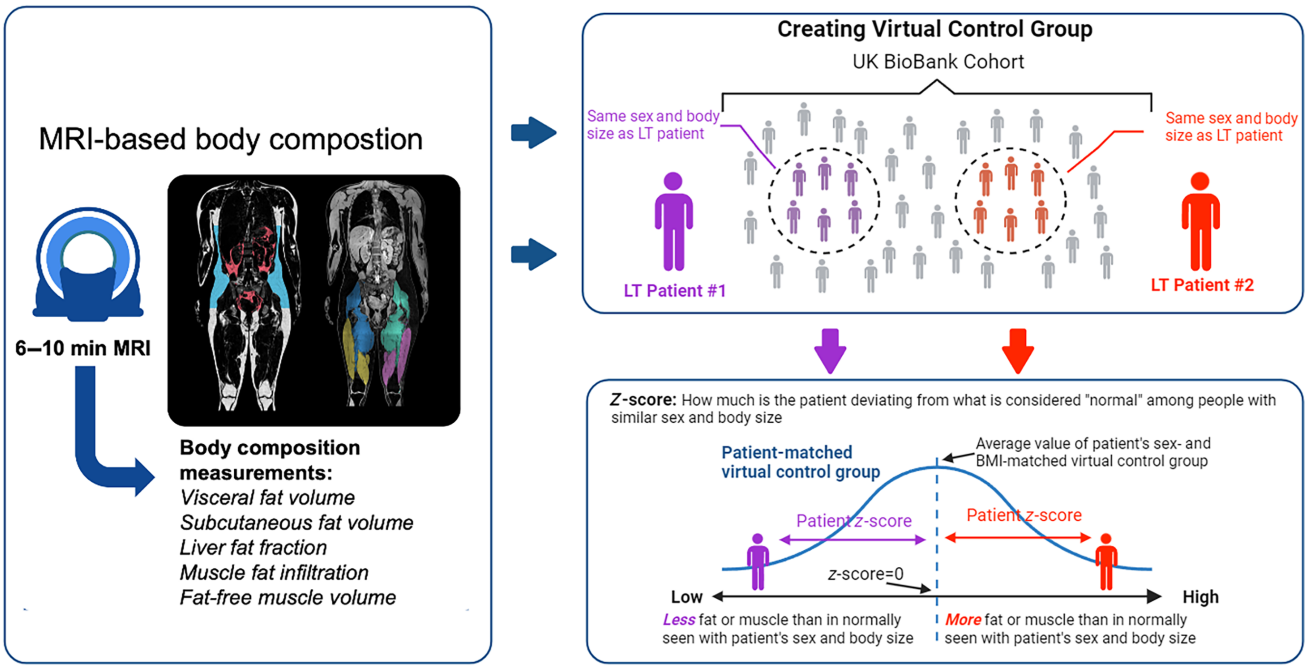

Figure 1 Schematic of methodology to generate standardized controls for liver transplant (LT) recipients. The UK Biobank cohort was utilized to create virtual control group (VCG) that contained 150 sex- and BMI-matched controls for each LT recipients. Using the VCG, a reference standard was created (blue dotted line, third panel) to demonstrate how many standard deviations the LT recipients from what is to be expected (e.g. *z*-score).

Radiomics phenotypes. Two radiomics phenotypes were applied to the LT population and included the (i) adverse muscle composition and (ii) adverse fat deposition.[7,10] Adverse muscle composition defined as low muscle volume (<25th percentile of the UK Biobank) and high MFI (>75th percentile for males and females) predicts increase frailty, reduced functional status, and lower survival. Adverse fat deposition incorporates LF and VAT based on *z*-score into the following four phenotypes; (i) "higher *z*-VAT and lower *z*-LF," (ii) "higher *z*-VAT and higher *z*-LF," (iii) "lower *z*-VAT and higher *z*-LF," and (iv) "lower *z*-VAT and lower *z*-LF."[7] Patients with high VAT and low LF are highest risk of incident CVD.[7,10]

For the selection of 1:10 matched controls used in the radiomics phenotype analysis, age (along with sex and BMI) was used as a matching criterion. These matched controls were all unique; that is, no LT recipient could share matched controls as described previously.[9,14]

Statistical analysis. The current analysis was performed in stepwise manner to better define the association between LT and body compartments. First, body compartment measurements were assessed to determine whether LT recipients deviated in body composition compared with sex, age, and BMI-matched non-LT controls using mixed-effects linear models adjusted for sex, BMI, and matching group as random effect. Subgroup analysis for the impact of etiology of cirrhosis (MASH *vs* non-MASH) on body compartments measurements was assessed using linear models adjusted for sex and BMI. Thereafter, body compartment *z*-scores were assessed to determine whether LT recipients had more, less, or similar amounts of VAT, ASAT, MFI, FFMV, and LF as predicted by their sex and BMI; each *z*-score distribution was tested toward 0 using a standard *t*-test. The subgroup analysis for the impact of etiology of cirrhosis (MASH *vs* non-MASH) on body compartments was also carried out on the body compartment *z*-scores using a standard *t*-test between groups and toward 0 within the subgroups *z*-score distribution. Next, we compared the two radiomics-based high-risk phenotypes (see above). The distribution of LT recipients meeting criteria for these phenotypes were evaluated and additional clinical parameters associated with phenotypes were better defined. Phenotype proportions in LT recipients against age, sex, and BMI-matched UK Biobank controls as well as subgroup analysis of etiology of cirrhosis (MASH *vs* non-MASH) was performed using a standard Chi^2-test.

Results

Cohort characteristics. The study cohort consisted of 66 LT recipients that included 41 males and 25 females (Table 1). The mean age of the cohort was 58 ± 12 years with BMI of 35.9 ± 7.5 kg/m^2. The prevalence of metabolic comorbidities including diabetes, hypertension, dyslipidemia, and obesity was 35%, 79%, 58%, and 79%, respectively. The leading etiologies of cirrhosis leading to need for LT included MASH (52%), hepatitis C (13%), and alcohol (12%). Most patients were on tacrolimus-based immunosuppression. The median time from LT to study enrollment was 25 months.

Table 1 Patient characteristics of the study cohort

	Study cohort ($n = 66$)
Demographics	
Age (years)	58 ± 12
Gender (% female)	25 (38%)
Ethnicity (% Caucasian)	55 (83%)
Comorbidities	
Body mass index (kg/m^2)	35.9 ± 7.5
Obesity (%)	52 (79%)
Diabetes (%)	23 (35%)
Hypertension (%)	52 (79%)
Dyslipidemia (%)	38 (58%)
Etiology of liver disease	
Hepatitis C (%)	9 (13%)
Alcohol (%)	8 (12%)
Nonalcoholic steatohepatitis (%)	34 (52%)
Laboratory	
Alanine aminotransferase (U/L)	39 ± 28
Aspartate aminotransferase (U/L)	31 ± 13
Alkaline phosphatase (U/L)	115 ± 48
Bilirubin (mg/dL)	0.75 ± 0.37
Creatinine (mg/dL)	1.30 ± 0.47
Hemoglobin A1c (%)	5.9 ± 1.1
Lipid profile	
HDL-C (mg/dL)	47 ± 14
LDL-C (mg/dL)	89 ± 32
Total cholesterol (mg/dL)	166 ± 37
Triglycerides (mg/dL)	158 ± 134
Transplant parameters	
Time from LT (months; median, IQR)	25 (17, 84)
Tacrolimus (%)	58 (88%)

Impact of transplant and MASH on body compartments. All LT recipients were compared against sex, age, and BMI-matched controls (Fig. 2a). LT recipients had higher levels of subcutaneous fat (ASAT; 13.82 ± 5.47 *vs* 12.10 ± 5.10 L, $P < 0.001$) and visceral fat (VAT; 7.59 ± 3.75 *vs* 6.72 ± 3.06 L, $P = 0.003$), LF (LF; 5.88 ± 7.14 *vs* 8.75 ± 6.50%, $P < 0.001$), and muscle volume (FFMV; 11.69 ± 2.95 *vs* 12.12 ± 2.90 L, $P = 0.027$) was lower for the LT recipients. Muscle fat content was similar (MFI; 8.67 ± 3.04 *vs* 8.58 ± 2.65%, $P = 0.972$).

Compared with patients transplanted for non-MASH cirrhosis, patients transplanted for MASH cirrhosis had higher levels of subcutaneous fat (ASAT; 15.28 ± 3.70 *vs* 11.26 ± 7.03 L, $P = 0.003$), visceral fat (VAT; 9.03 ± 3.56 *vs* 5.07 ± 2.61 L, $P < 0.001$), muscle fat (MFI; 9.53 ± 3.00 *vs* 7.16 ± 2.53%, $P = 0.002$), and muscle volume (FFMV; 12.42 ± 2.94 *vs* 10.41 ± 2.53, $P = 0.006$), but similar LF content (LF; 6.90 ± 7.35 *vs* 4.04 ± 6.23%, $P = 0.153$). After adjusting for sex and BMI in a linear model, visceral (VAT; $P = 0.026$), and muscle fat (MFI; $P = 0.025$) differences remained significant. Thus, MASH cirrhosis LT recipients had higher visceral fat and muscle fat content compared with non-MASH cirrhosis, which was independent of their BMI (Fig. 2b).

Finally, MASH cirrhosis LT recipients were compared against sex, age, and BMI-matched controls (Fig. 2c). The MASH cirrhosis LT recipients had higher subcutaneous fat (ASAT; 15.28 ± 3.70 *vs* 13.27 ± 4.47 L, $P < 0.001$) and visceral fat (VAT; 9.03 ± 3.55 *vs* 7.90 ± 2.88 L, $P = 0.004$), LF (LF; 6.90 ± 7.35 *vs* 10.13 ± 6.75%, $P < 0.001$) was lower for the MASH cirrhosis LT recipients. Muscle volume (FFMV; 12.42 ± 2.94 *vs* 12.79 ± 2.76 L, $P = 0.151$) and fat content (MFI; 9.53 ± 3.00 *vs* 8.94 ± 2.57, $P = 0.197$) were similar.

Standardization of body compartments in transplant recipients to non-LT controls. The body compartment z-scores compares each patient with matched non-LT controls (i.e. virtual control groups). The resulting z-score, describing the deviation from expected body compartment values given the patient's sex and BMI, is presented in Figure 2 (Table S1, Supporting information). Thus, a positive z-score indicates higher than expected (i.e. standardized) value for that body compartment, whereas a negative z-score indicates lower than expected value.

First, we established the deviation from expected or standardized results for all LT recipients (Fig. 3a). LT recipients had significantly higher amounts of subcutaneous fat (z-ASAT; 0.86 ± 1.49 SDs, $P < 0.001$) and visceral fat (z-VAT; 0.38 ± 1.51, $P = 0.043$). LF, however, was significantly lower in LT recipients (z-LF; −0.82 ± 1.39, $P < 0.001$). While muscle volume was reduced in LT recipients (z-FFMV; −0.33 ± 1.11, $P = 0.019$), the muscle fat (z-MFI) was as to be expected.

Second, the deviations from expected levels or standardized results for patients receiving LT for MASH and non-MASH indications were established. Patients receiving LT for MASH (Fig. 3b, Table S1) had higher amounts of subcutaneous fat (z-ASAT; 1.01 ± 1.58 SDs, $P < 0.001$), higher visceral fat (z-VAT; 0.51 ± 1.54 SDs, $P = 0.037$), lower LF (z-LF −0.75 ± 1.34 SDs, $P = 0.002$), lower muscle volumes (z-FFMV; −0.35 ± 1.07, $P = 0.039$) than expected for non-LT sex and BMI-matched individuals, but muscle fat content was as expected (z-MFI; 0.19 ± 1.27 SDs, $P = 0.343$).

Patients receiving LT for non-MASH indications (Fig. 3c, Table S1) had higher amounts of subcutaneous fat (z-ASAT; 0.59 ± 1.31 SDs, $P = 0.036$) and lower LF (z-LF; −0.95 ± 1.51 SDs, $P = 0.011$), and muscle fat content (z-MFI; −0.65 ± 1.06 SDs, $P = 0.006$). In patients receiving LT for non-MASH indications, the visceral fat (z-VAT) and muscles volumes (z-FFMV) were as to be expected given sex and BMI.

Application of radiomics-based phenotyping. Radiomics-based phenotyping focused on (i) muscle composition for frailty and (ii) visceral and LF distribution patterns as CVD risk phenotypes is demonstrated in Figure 4. Of the LT recipients, 23 (35%) were found to have adverse muscle composition (low muscle volume by z-FFMV and high muscle fat by MFI), which was more prevalent than in the matched control group (14%, $P < 0.001$). In contrast, normal muscle composition was only present in 24% of LT recipients compared with 44% of the control cohort ($P = 0.002$). LT recipients were more likely to have high muscle fat (68% *vs* 51%, $P = 0.007$) and low muscle volume (42% *vs* 19%, $P < 0.001$) compared with matched non-LT controls (Fig. 4a,b). In subgroup analysis performed only in LT recipients, patients with MASH cirrhosis were more likely to have high muscle fat ($P = 0.001$) and less likely to have normal

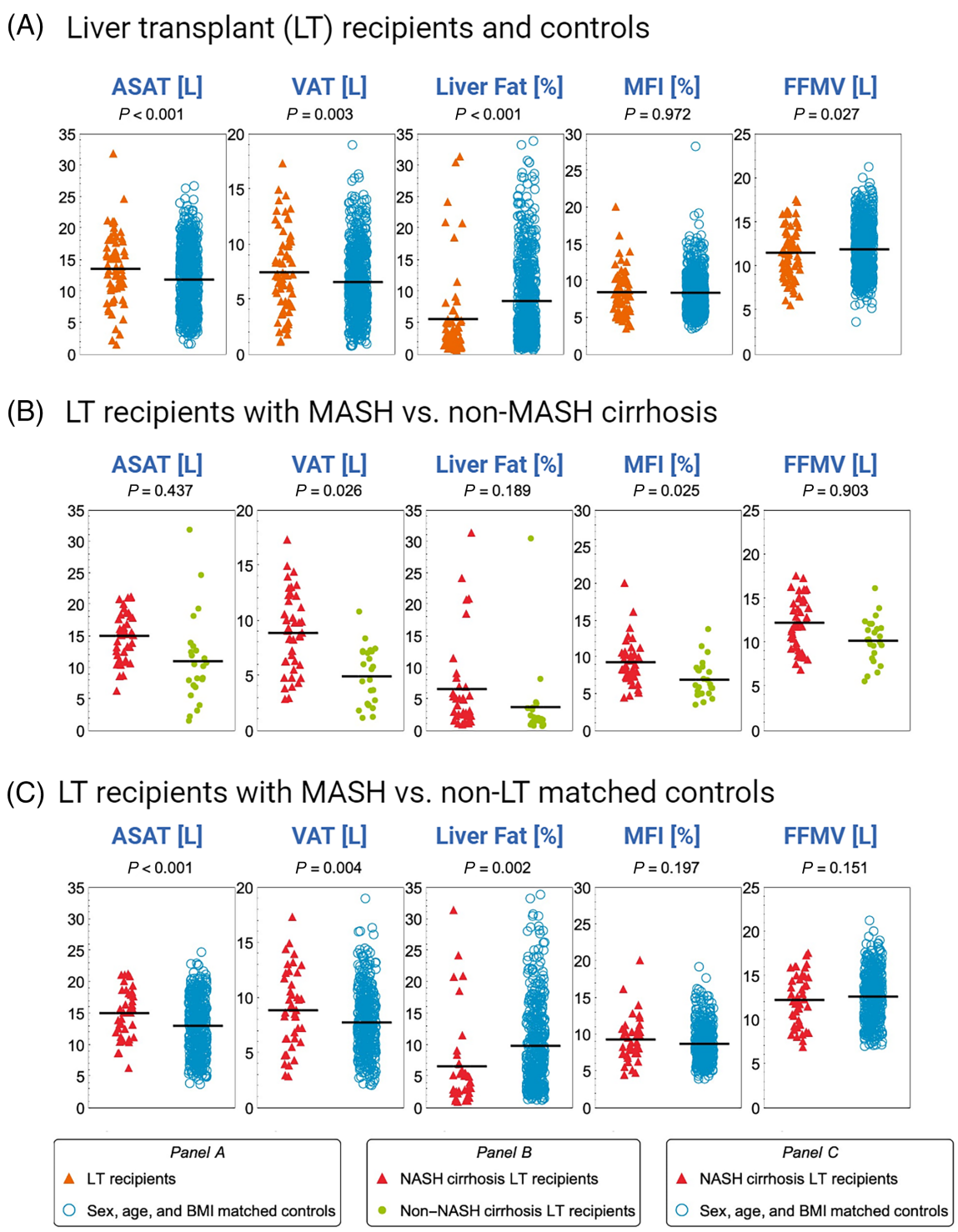

Figure 2 Impact of liver transplant (LT) on body compartments compared with sex, age, and BMI-matched non-transplant controls. The *P*-values are based on mixed-effects linear models adjusted for sex, BMI and matching group as random effect (a, c) and linear models adjusting for sex and BMI (b). The black solid lines represent mean values (ASAT, abdominal subcutaneous adipose tissue; FFMV, fat-free muscle volume; LF, liver fat; MFI, muscle fat infiltration; VAT, visceral adipose tissue).

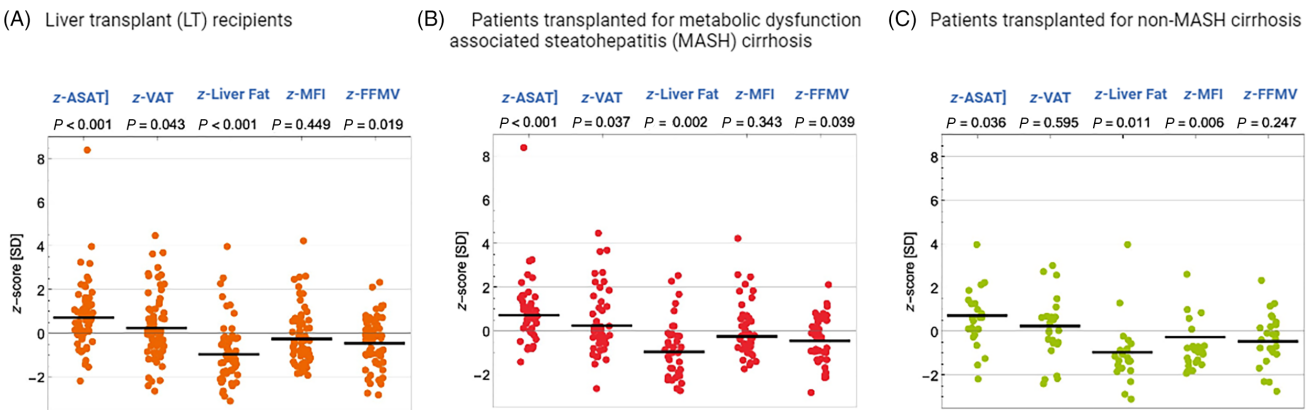

Figure 3 Impact on liver transplant (LT) on body compartments using standardized measurements (*z*-scores), for all LT recipients (a) and subgroup analysis for metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis (b) and non-MASH cirrhosis (c). The *P*-values are based on t-tests to assess deviation from expected value (*z*-score = 0) within each group, a positive *z*-score indicates more than expected of that body compartment. The black lines represent the mean (*z*-ASAT, abdominal subcutaneous adipose tissue *z*-score; *z*-FFMV, fat-free muscle volume *z*-score; *z*-LF, liver fat *z*-score; *z*-MFI, muscle fat infiltration *z*-score; *z*-VAT, visceral adipose tissue *z*-score).

muscle composition ($P = 0.017$) compared with patients transplanted for non-MASH cirrhosis (Fig. 4c).

Radiomics-based CVD risk stratification that quantified visceral and LF quantification demonstrated that LT recipients were more likely to have the higher CVD risk profile (*z*-VAT >0 and *z*-LF < 0) than matched controls (Fig. 3d). Conversely, the phenotype characterized by both lower visceral and LF content (*z*-VAT <0 and *z*-LF < 0) was present in only 41% of LT compared with 33% in matched controls; however, this did not reach statistical significance.

Discussion

In the present study, the relationship between body compartments and LT was investigated using prospective cohort of patients who had received a LT and matched cohorts from non-transplant (i.e. general population). Transplant specific changes in skeletal muscle and adipose tissue were noted that not only provides a deeper understanding of how these compartments may potentially be interacting to impact metabolic burden in these patients.

Study findings in the context of published literature. LT recipients had higher adipose tissue and lower muscle volumes compared with matched controls, which were worse in patients transplanted for MASH cirrhosis. Conceptually, initial weight gain leads to expansion of adipose tissue and normally the fat is stored in more inert adipose tissue such as gluteofemoral fat.[15] However, excessive and rapid weight gain leads to fat accumulation in less favorable storage depots such as visceral or subcutaneous fat.[16] Moreover, comorbid conditions such as insulin resistance may further promote expansion of less favorable depots such as VAT and ASAT. While subcutaneous adipose tissue has a more favorable metabolic profile than visceral fat, the metabolic profile and impact of subcutaneous fat is intermediate between visceral fat and non-abdominal subcutaneous tissue.[15,17]

Skeletal muscle is responsible for over half of total body energy expenditure and reduction in skeletal muscle volume and health have been associated with obesity, CVD, and increased metabolic burden.[18,19] Prior studies in LT recipients have demonstrated muscle quality was associated with decreased metabolic flexibility and obesity.[4] In the present study, LT had significantly lower skeletal muscle volume compared with matched controls, which was even lower among patients transplanted for MASH (*vs* non-MASH) cirrhosis. This coupled with higher fat compartments (VAT and ASAT) underscores the significantly higher prevalence of sarcopenic obesity among patients transplanted for MASH cirrhosis. Sarcopenic obesity is clinically important as it has been associated with increased risk of CHD and lower survival.[6] Collectively, these findings provide insight into higher metabolic risk profile among patients transplanted for MASH cirrhosis that potentially is due to perturbed fat deposition and reduced skeletal muscle.

Future implications of study findings. Liver fat was lower among LT recipients compared with matched non-LT controls. While the exact nature of is not known, it is possible that preexisting metabolic comorbidities and exposure to chronic immunosuppression leads to preferential deposition of fat in high-risk body compartments. A recent study of 40 174 subjects demonstrated that patients with low LF and high VAT, were at significantly higher risk of CVD with adjusted HR 7.3 (6.5, 8.0).[13] Expansion of visceral and subcutaneous fat is associated with increased adipose tissue inflammation, insulin resistance, and metabolic burden that results in clinically higher incidence of CVD and reduced survival.[20] Thus, underscoring the inverse relationship between visceral and LF as driver of CHD risk and future studies to mechanistically better understand this relationship.

Application of novel radiomics-based risk stratification including adverse muscle composition and CHD risk profile demonstrates the potential to use rapidly evolving technology to potentially direct clinical care. For example, radiomics-based CHD risk profile with low LF and high VAT was nearly twice as prevalent among LT recipients compared with matched controls. Moreover, patients transplanted for MASH cirrhosis (*vs* non-MASH cirrhosis) had considerably higher visceral and muscle fat content. These findings partly explain the disproportionately

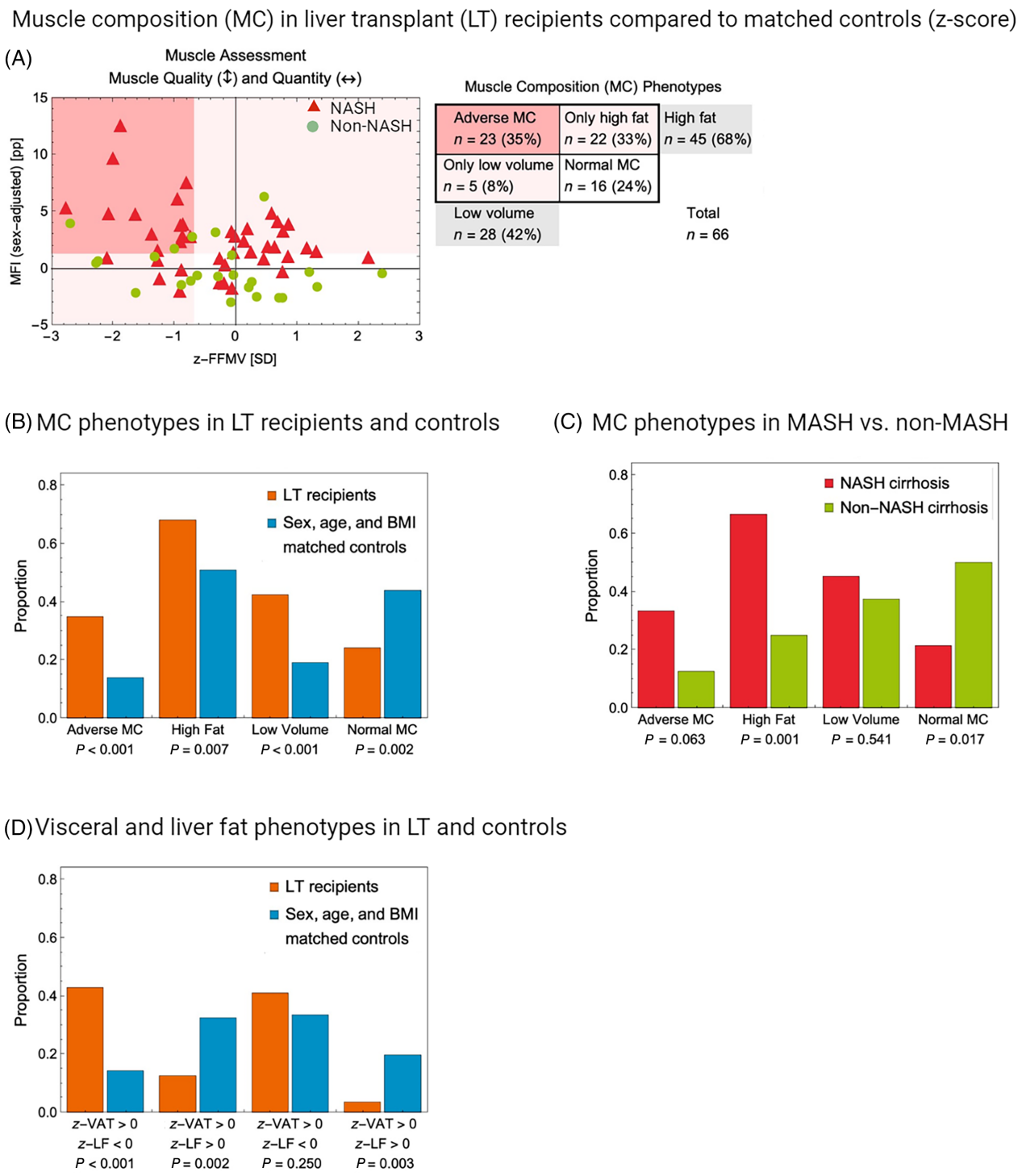

Figure 4 Radiomics-based phenotype analysis with metabolic dysfunction-associated steatohepatitis (MASH) and non-MASH cirrhosis. (a) Muscle quality and quantity assessment with muscle composition (MC) phenotypes. The *y*-axis shows the muscle fat, indicating quality of muscle, and on the *x*-axis the muscle quantity. The four MC-based phenotypes are shown in red/pink/white background as shown in the legend on the right. (b) Impact of LT on proportions of MC phenotypes compared with matched controls. (c) Subgroup analysis of proportions of MC phenotypes for MASH and non-MASH cirrhosis. (d) Proportions of visceral fat (VAT) and liver fat (LF) phenotypes, defined as *z*-scores higher (>0) and lower (<0) then expected given their sex and BMI.

higher CHD risk in LT recipients and increased risk of CHD in LT recipients with adverse adipose tissue profile characterized by low levels of serum adiponectin, a protective adipokine.[21] However, these radiomics-based risk stratification approaches require validation in well-designed studies including cost-effectiveness analysis given the higher cost of MRI before they can be incorporated into clinical practice.

Study strengths and limitations. The present study provides novel insights into body compartments in LT recipients using standardized controls from matched non-LT subjects. Body compartments associated with higher metabolic burden, CHD, and mortality were significantly larger among LT recipients, thus, providing foundational data for the development of radiomics-based approaches for risk stratification. Furthermore, the adverse muscle composition and discordant visceral fat and LF phenotypes are two examples of how such radiomics-based scores can be adopted to risk stratify patients. Early identification of at-risk patients with associated metabolic perturbation (high LF *vs* visceral fat *vs* muscle fat, etc.) is the first step in developing precision medicine among LT recipients to combat the rapidly growing metabolic burden and associated increase in mortality.

The study findings are novel and bridge our understanding of the impact of LT and MASH on body compartments; however, these findings must be interpreted within the context of study limitations. Due to the cross-sectional nature of the study design, it is difficult to provide the natural history of how LT surgery might longitudinally affect body compartments as patients transition from decompensated cirrhosis to post-LT state. As tacrolimus was the most commonly used immunosuppression, it is difficult to ascertain the impact of other immunosuppression, such as cyclosporine or sirolimus, on body compartments. However, as tacrolimus forms the backbone of immunosuppression in clinical practice, the study cohort reflects the population that is likely to be encountered in clinical practice. Finally, data linking body compartments to clinical outcomes are needed to establish LT specific cutoff values and the present study provides data necessary to construct prospective biomarker development studies.

In summary, LT recipients have higher abdominal fat compartments (visceral and subcutaneous) but significantly lower LF content. The abdominal fat compartments are even higher among patients transplanted for MASH cirrhosis and accompanied by reduced skeletal muscle volume, thus, linking sarcopenic obesity to MASH following LT.

References

1 Rinella ME, Satapathy SK, Brandman D *et al*. Factors impacting survival in those transplanted for NASH cirrhosis: data from the NailNASH consortium. *Clin. Gastroenterol. Hepatol.* 2023; **21**: 445–55.e2.
2 Chhatrala R, Siddiqui MBS, Stravitz RT *et al*. Evolution of serum atherogenic risk in liver transplant recipients: role of lipoproteins and metabolic and inflammatory markers. *Liver Transpl.* 2015; **21**: 623–30.
3 Idowu MO, Chhatrala R, Siddiqui MB *et al*. De novo hepatic steatosis drives atherogenic risk in liver transplant recipients. *Liver Transpl.* 2015; **21**: 1395–402.
4 Siddiqui MS, Patel S, Forsgren M *et al*. Differential fuel utilization in liver transplant recipients and its relationship with non-alcoholic fatty liver disease. *Liver Int.* 2022; **42**: 1401–9.
5 Aberg F, Gissler M, Karlsen TH *et al*. Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study. *Hepatology*. 2015; **61**: 668–77.
6 Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. *J. Am. Geriatr. Soc.* 2014; **62**: 253–60.
7 Tejani S, McCoy C, Ayers CR *et al*. Cardiometabolic health outcomes associated with discordant visceral and liver fat phenotypes: insights from the Dallas Heart Study and UK Biobank. *Mayo Clin. Proc.* 2022; **97**: 225–37.
8 Linge J, Borga M, West J *et al*. Body composition profiling in the UK Biobank imaging study. *Obesity.* 2018; **22**: 1785–95.
9 Linge J, Ekstedt M, Dahlqvist LO. Adverse muscle composition is linked to poor functional performance and metabolic comorbidities in NAFLD. *JHEP Rep Innov Hepatol.* 2020; **3**: 100197.
10 Linge J, Petersson M, Forsgren MF, Sanyal AJ, Dahlqvist LO. Adverse muscle composition predicts all-cause mortality in the UK Biobank imaging study. *J. Cachexia. Sarcopenia Muscle*. 2021; **12**: 1513–26.
11 Bhati C, Idowu MO, Sanyal AJ *et al*. Long-term outcomes in patients undergoing liver transplantation for nonalcoholic steatohepatitis-related cirrhosis. *Transplantation*. 2017; **101**: 1867–74.
12 Siddiqui MS, Charlton M. Liver transplantation for alcoholic and nonalcoholic fatty liver disease: pre-transplant selection and post-transplant management. *Gastroenterology*. 2016; **150**: 1849–62.
13 Linge J, Cariou B, Neeland IJ, Petersson M, Rodriguez A, Dahlqvist LO. Skewness in body fat distribution pattern links to specific cardiometabolic disease risk profiles. *J. Clin. Endocrinol. Metab.* 2024; **109**: 783–91.
14 Linge J, Heymsfield SB, Dahlqvist LO. On the definition of sarcopenia in the presence of aging and obesity-initial results from UK Biobank. *J. Gerontol. A Biol. Sci. Med. Sci.* 2020; **75**: 1309–16.
15 Borges MC, Oliveira IO, Freitas DF *et al*. Obesity-induced hypoadiponectinaemia: the opposite influences of central and peripheral fat compartments. *Int. J. Epidemiol.* 2017; **46**: 2044–55.
16 Pasarica M, Sereda OR, Redman LM *et al*. Reduced adipose tissue oxygenation in human obesity evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes*. 2009; **58**: 718–25.
17 Lee JJ, Pedley A, Hoffmann U, Massaro JM, Fox CS. Association of changes in abdominal fat and cardiovascular risk factors. *J. Am. Coll. Cardiol.* 2016; **68**: 1509–21.
18 Daniele G, Xiong J, Solis-Herrera C *et al*. Dapagliflozin enhances fat oxidation and ketone production in patients with type 2 diabetes. *Diabetes Care*. 2016; **39**: 2036–41.
19 Sugai T, Watanabe T, Otaki Y *et al*. Decreased psoas muscle computed tomography value predicts poor outcome in peripheral artery disease. *Circ. J.* 2018; **82**: 3069–75.
20 Scherer PE. The many secret lives of adipocytes: implications for diabetes. *Diabetologia*. 2019; **62**: 223–32.
21 Siddiqui MBS, Patel S, Arshad T *et al*. The relationship between hypoadiponectinemia and cardiovascular events in liver transplant recipients. *Transplantation*. 2019; **103**: 2323–8.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Patient body composition measurements. ASAT, abdominal subcutaneous adipose tissue volume; FFMV, fat-free muscle volume; LF, liver fat fraction; MFI, muscle fat infiltration; VAT, visceral adipose tissue volume.