Title page:

Title: Preservation of fat mass at the expense of lean mass in children with end-stage chronic liver disease.

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Abbreviations:

AIH/ASC: autoimmune hepatitis/ autoimmune sclerosing cholangitis,

Alb: albumin,

ALT: alanine transaminase

Bili: bilirubin

BMAD: bone mineral adjusted density

BMI: body mass index

BMT: bone marrow transplant

CFALD: cystic fibrosis associated liver disease

DXA: Dual-Energy X-ray Absorptiometry

ESCLD: end-stage chronic liver disease

FM/ FMI: Fat mass/ Fat mass index

GvHD: Graft versus host disease

HCC: hepatocellular carcinoma

INR: international normalised ration

LM/ LMI: Lean mass/ Lean mass index

LT: liver transplantation

Ne/Ly: Neutrophil to lymphocyte ratio

PFIC: Progressive familial intrahepatic cholestasis

PLT: platelets

WCC: White cell count

Title: Preservation of fat mass at the expense of lean mass in children with end-stage chronic liver disease.

Abstract:

Background: Sarcopenia predicts morbidity and mortality in end-stage chronic liver disease (ESCLD). Here we describe changes in body composition in children with ESCLD before and after liver transplantation (LT).

Methods: Retrospective analysis of whole body DXA scans performed before and after LT over 4 years. Appendicular and whole-body fat mass and lean mass were expressed as fat mass (FMI) and lean mass (LMI) index z-scores. Sarcopenia was defined as leg LMI z-score < -1.96.

Results: 83 DXA scans of children before or after LT were studied. Sarcopenia had a positive correlation with Weight(0.8,$p<0.01$), Height(0.48,$p<0.05$) and BMI z-score(0.77,$p<0.01$), as well as arm, trunk, and total mean mass indices. It correlated negatively with indices of hypersplenism PLTs(-0.57, $p<0.01$), Neu(-0.50, $p<0.05$), WCC(-0.44, $p<0.05$) and days to discharge(-0.46, $p<0.05$).

At baseline: 13/25(52%) children were sarcopenic and stayed in hospital after LT for longer. Eight were stunted with higher WCC and Ne/Ly ratio. All had normal FM indices.

One year after LT, 12/26 children remained sarcopenic. Seven were stunted. Two years after LT, 5/15 were sarcopenic and 5 were stunted. Three years after LT, 1/10 was sarcopenic and 2 were stunted. By 4 years after LT, 1/7 was sarcopenic and the same one was stunted. FM indices remained normal.

Conclusions: Sarcopenic patients stayed longer in hospital after LT. Lean mass indices were mostly within the normal range by 4 years after LT. 32% of children were stunted and markers of inflammation correlated with stunting. Fat mass was preserved at the cost of lean mass.

Keywords:

Sarcopenia, fat mass, children, liver disease, bone density

Main Manuscript:

Introduction

Malnutrition commonly accompanies end stage chronic liver disease in children (ESCLD). In addition to malnutrition, some children with ESCLD have changes in their body composition, in particular, sarcopenia. Sarcopenia is the loss in muscle mass and function, and it does not always correlate with the degree of liver dysfunction[1]. The presence of sarcopenia has a prevalence of about 40% and is associated with increased morbidity (lower quality of life, increased risk of infections and encephalopathy) and mortality, both before and after liver transplantation, in both adult and paediatric patients with ESCLD[2-5]. It is also reasonable to speculate that the children with sarcopenia may be those with more permanent nutritional and neurodevelopmental deficits in their long-term outcomes[6]. Currently there are no effective treatments for sarcopenia as there is limited understanding of the mechanism underlying sarcopenia in cirrhosis and also a lack of robust measures of sarcopenia (particularly in children) including reliable biomarkers[7].

Previous studies have suggested that, even in the sarcopenic patients, fat mass is preserved[8,9]. This phenomenon is consistent with observations in other settings where during periods of stress the body prioritises the maintenance of energy stored in fat[10,11]. We do not know if the increase in metabolic syndrome and obesity observed in patients after solid organ transplantation[12,13] is potentially related to epigenetic changes favouring the preservation of fat mass that occur during this period. In this retrospective audit of our practice, we wanted to explore body composition of patients undergoing liver transplantation, using longitudinal data obtained before and after their liver transplant. Our aim was to assess changes in body composition i.e., lean mass, fat mass, bone mineral density and to evaluate how these changes are associated with clinical parameters, including days in hospital after LT. We also wanted to test if fat mass is preserved at the expense of lean mass, as suggested by other work[8,14], and wanted to assess the evolution of these aberrations in body composition in the four years following LT.

Methods

This was a retrospective analysis of whole-body Dual-Energy X-ray Absorptiometry (DXA) scans performed before and after LT of children with ESCLD who were assessed for LT during 2014-2019 at the Children's Liver Unit in Leeds, UK. Children with ESCLD over the age of 5 years have a whole body DXA scan as part of their assessment for LT and every year thereafter for the first 5 years after LT. Children coming to LT for acute liver failure, inborn errors of metabolism such as urea cycle disorders and hepatoblastomas were excluded. Weight, height, and body mass index (BMI) were converted to z- scores with reference to UK-WHO data, using the ImsGrowth program. Fat mass and lean mass was recorded for arm, leg, trunk, and whole body. These data were then adjusted for height using the same approach as for body mass index (BMI) and expressed as fat mass index (FMI) and lean mass index (LMI) and then converted to z-scores using UK reference data[15]. The reference data is based on a UK population of a variety of ethnic background, but the children have not been referenced against ethnic specific data. Sarcopenia was defined as leg LMI z-score < -1.96. We also recorded bone mineral adjusted density (BMAD) z-scores for between lumbar vertebrae L1-L4 and severe osteopenia was defined as BMAD z-score below <-1.96.

Correlations of these indices with basic laboratory parameters like full blood count (haemoglobin:Hb, total white cell count: WCC, neutrophils:Ne, lymphocytes: Ly, neutrophil to lymphocyte ration: Ne/Ly and platelets:PLT), and liver function tests (total bilirubin: bili, alanine transaminase: ALT, albumin: alb, international normalised ration: INR and ALT/PLT ratio) as well as with days to discharge after LT, were tested with methods for non-parametric data, e.g., Spearman's rho. The Mann-Whitney U test was used to compare differences between two independent groups when the dependent variable was continuous, but not normally distributed. Normality was tested with the Shapiro- Wilk test. IBM® SPSS® statistics 29 was used for the statistical analysis and statistical significance was set at a $p<0.05$.

DXA was originally designed to measure bone mineral content and bone mineral density but has successfully been applied for body composition assessment[16,17]. The advantages of DXA are that it is easy to perform if the subject can lie still on their back for a few minutes, and it can provide regional body composition measurements. This is particularly relevant for individuals with chronic liver disease who are known to have altered distribution of body fat and lean mass. In terms of disadvantages DXA involves low radiation doses.

Results

During the time period investigated by the study, 83 DXA scans were identified as part of a liver transplant assessment or as part of post liver transplant follow up of children with ESCLD. Of these, 25 were of children with ESCLD that had baseline DXA scans as part of their LT assessment. Twenty-six of them were of children that had scans at 1 year after LT, 19 of which were the same as the ones at baseline. Fifteen scans were of children at 2 years after LT; 10 of which were the same at baseline. Ten scans were of children at 3 years post LT, 7 of which were at baseline and seven scans were of children at 4 years after LT, 5 of which were at baseline.

Baseline:

Out of the 25 children that had DXA scans prior to LT, 13 were male. The median age was 11.7 years (range 6.1 to 15.8 years, SD 2.98). Six had biliary atresia, 5 had cystic fibrosis associated liver disease (CFALD), 4 had autoimmune hepatitis/ autoimmune sclerosing cholangitis (AIH/ASC), 3 had Alagille syndrome, 2 had progressive familial intrahepatic cholestasis (PFIC) and one each had intestinal failure associated liver disease (IFALD), fibrolamellar hepatocellular carcinoma (HCC), congenital hepatic fibrosis, post bone marrow transplant (BMT) graft versus host disease (GVHD) and alpha-1-antritrypsin deficiency.

In terms of anthropometry, as depicted in **Table 1**, weight z-score median was -0.35 (range -4.1 to 1.4, SD 1.41), height z-score median -0.61 (range -4.6 to 2.6, SD 1.62) and BMI z-score median -0.3 (range -1.8 to 1.2, SD 0.87). Median total FMI z-score was 0.3 (range -0.4 to 1.3, SD 0.51) and median total LMI z-score was -1.5 (range -3.5 to 1.3, SD 1.36).

Arm FMI z-score median was 0.8 (range 0.1 to 1.5, SD 0.39), arm LMI z-score median was -2.2 (range -4.9 to 0, SD 1.35), leg FMI z-score median 0.2 (range -1.3 to 1.2, SD 0.65) and leg LMI z-score median -1.9 (range -6.1 to 0.4, SD 1.9). Trunk FMI z-score had a median 0.4 (range -0.3 to 1.3, SD 0.45) and trunk LMI z-score had a median 0.4 (range -2.7 to 3.4, SD 1.49).

Overall leg LMI z-score had a significant correlation with Weight (0.8, $p<0.01$), Height (0.48, $p<0.05$) and BMI z-score (0.77, $p<0.01$) and with the other indices related to LM; arm LMI (0.75, $p<0.05$), trunk LMI (0.53, $p<0.01$) and total LMI z-score (0.86, $p<0.01$). Leg LMI z-score had a significant negative correlation with PLTs (-0.57, $p<0.01$), Neu (-0.50, $p<0.05$), WCC (-0.44, $p<0.05$).

Thirteen of the 25 (52%) children at baseline were sarcopenic. Four of the children had CFALD, 3 had biliary atresia, 2 had Alagille syndrome and one each had congenital hepatic fibrosis, HCC, PFIC, and post BMT GvHD. The sarcopenic children had significantly lower weight (mean -1.6 versus 0.4), BMI (-0.8 versus 0.6), arm LMI, trunk LMI, total LMI and leg FMI (-0.2 versus 0.4) z-scores in comparison to the other 12 children.

FM indices for all children were as follows: arm FM (range -0.35 to 1.49, SD 0.48), arm FMI (range 0.13 to 1.49, SD 0.39), leg FM (range -1.65 to 1.07, SD 0.72), leg FMI (range -1.32 to 1.22, SD 0.65), trunk FM (range -0.63 to 1.19, SD0.48), trunk FMI (range -0.32 to 1.25, SD 0.45), total FM (range -0.96 to 1.12, SD 0.58) and total FMI (range -0.42 to 1.25, SD 0.51). All FM indices were within the normal range (Figure 1).

Eight children were stunted with a height z-score <-1.96. They had a significantly lower weight z-score and higher white cell count (WCC) and Ne/Ly ratio in comparison to the other 17 children. Mean total

WCC was 5.7 for the stunted versus 4 for the others. The mean neutrophil to lymphocyte ratio (Ne/Ly) was 5.2 for the stunted children and 3.2 for the others. Their diagnoses were CFALD for 2 of them, Alagille for 2 and one with PFIC, post BMT-GVHD and A1-AT deficiency. Of note, none of the children with biliary atresia were stunted. Six children were both sarcopenic and stunted (two with CFALD, 2 with Alagille syndrome, 1 with post BMT GvHD and 1 with PFIC). This may be more a result of their underlying diagnosis, rather than the effect of ESCLD on their growth.

BMAD z-scores pre-liver transplant had a median of -1.19 (range -4.74 to 2.18, SD 1.38). 5 children had severe osteopenia and the only difference they had in comparison to the other children was a significantly lower FMI z-score (mean of 0.3 versus 0.8). BMAD z-score overall did not correlate with any tested parameter.

We looked at how indirect markers of inflammation like WCC and Ne/Ly correlated with measures of body composition and other blood parameters. WCC had a negative correlation with weight z-score (-0.406, $p<0.05$), leg LMI (-0.442, $p<0.05$) and total LMI (-0.467, $p<0.05$) z-score. WCC also correlated positively with PLTs (0.562, $p<0.01$), Ne (0.836, $p<0.01$), Ly (0.685, $p<0.01$) and Ne/Ly ratio (0.877, $p<0.01$). Ne/Ly ratio had a negative correlation with weight z-score (-0.422, $p<0.05$), trunk LMI (-0.518, $p<0.05$) and total LMI (-0.494, $p<0.01$). Ne/Ly ratio had positive correlations with PLTs (0.758, $p<0.01$), and ALT/PLT ratio (0.485, $p<0.05$).

We also looked at how these parameters at baseline (pre-liver transplant) correlated with days to discharge after liver transplant. Leg LMI z-score, total LMI z-score and BMI z-score had a negative correlation with days to discharge (-0.46, -0.46 and -0.51 respectively, $p<0.05$ for all). Sarcopenic patients stayed in hospital on average for 43 days after liver transplant in comparison to 23 days if they were not sarcopenic ($P<0.05$).

<u>After liver transplantation.</u>

One year after LT, 12/26 (46%) children remained sarcopenic (see **Figure 2**). Seven were stunted and all had normal FM indices. Two years after LT, 5/15 (33%) were sarcopenic, all had normal FM indices and 5 were stunted. Three years after LT, 1 of the 10 children was sarcopenic and 2 were stunted. By 4 years after LT, 1/7 was sarcopenic and the same one was stunted. **Table 1** shows the main body composition measures over the first 4 years after LT. BMAD z-score did show an improvement particularly over the first 3 years, with a tendency for the children that were osteopenic initially to remain osteopenic (see **Figure 3**). **Figure 4** illustrates the Leg LMI z-score for 5 individual patients at baseline and then yearly for four years after LT.

Complications after liver transplant

Five of the 13 sarcopenic patients had complications from the hepatic artery, 3 of which were a hepatic artery thrombosis leading to a second liver transplant. One required hepatic artery angioplasty and stent insertion and also had extensive problems with bowel perforation and intra-abdominal infection, another required hepatic artery reconstruction. Four of the 13 sarcopenic patients experienced biliary complications (one from the group with the hepatic artery complications). Only 2 of the children experienced allograft rejection. These complications, particularly the need for re-transplantation, the insertion and management of biliary drains post percutaneous transhepatic cholangiogram, were the main contributors to the prolonged stay after liver transplantation.

In the non-sarcopenic group (12 children) 5 children had rejection, one of which required a second liver transplant. No children had vascular complications and only 1 developed a biliary stricture.

Discussion

Whole body DXA scan is part of the liver transplant assessment for children 5 years old and above at the Children's Liver Unit at the Leeds Teaching Hospitals NHS trust and the children would subsequently have a DXA scan every year after their liver transplant for the first 5 years. This study was to audit the usefulness of this practice and looked at how baseline body composition may

influence outcomes post LT by studying the cohort of patients that was assessed and transplanted between 2014 and 2019. Whole body DXA can give information about whole body and appendicular lean mass (which is fat free mass and would include muscle and bone) and fat mass. Appendicular mass is especially important in children with liver disease because whole body measurements, particularly for lean mass, will include trunk lean mass which would include mass of the liver and spleen, which tend to be enlarged in liver disease, therefore leading to an overestimate of lean mass. In more recent years, another common way to assess for sarcopenia is by using CT scan to quantify total lumbar muscle cross-sectional area (CSA)[18,19] or total psoas[20,21] area with normal values for paediatrics now published for both approaches[22,23]. These approaches have been quite useful in assessing younger children, where DXA scan use is inappropriate due to lack of reference data. For example, the majority of children with biliary atresia would be transplanted under the age of 5 years. Nevertheless, CT involves significant amount of radiation and can only be justified by strong clinical need, so not appropriate for follow-up measurements. In addition to this there have been concerns about the appropriateness of using the psoas muscle in particular as a single sentinel muscle, to diagnose sarcopenia, as it would be difficult to claim that any one muscle is representative[24,25].

Sarcopenia is known to be an independent predictor of survival whilst on the liver transplant list, but also of morbidity and mortality after a liver transplant[26-28]. This study has focused on muscle mass when defining sarcopenia. There are no clear definitions for sarcopenia in children, but we thought reasonable to use Leg LMI z-scores of less than -1.96[3,22]. 52% of the children at baseline were sarcopenic by this definition. This is in line with the published prevalence of sarcopenia in children with end-stage chronic liver disease[3].

As expected, leg LMI z-score correlated positively with other measures of whole-body anthropometry (weight, height, and BMI) and with other measures of lean mass. It also had a significant negative correlation with days to discharge after liver transplantation meaning that the higher the z-score the

shorter the stay. The sarcopenic children stayed on average 20 days more in hospital in comparison to the children that were not sarcopenic. This is in accordance with published data[29-31].

What was less expected was that Leg LMI z-score had a negative correlation with markers of hypersplenism (like neutrophils and platelets). This would indicate that children with portal hypertension and hypersplenism, had a higher leg LMI z-score. There is a plethora of studies showing an improvement in body composition indices, and an increase in muscle mass post TIPSS insertion in cirrhotic patients and therefore alleviation of portal hypertension[32-35]. WCC and Ne/Ly also had a positive correlation with the other full blood count parameters, so perhaps this association had more to do with inflammation or a pro-inflammatory situation and less with portal hypertension.

8 of the children (32%) at baseline had a low height z-score. This correlated with low weight z-score and a higher Ne/Ly ratio. One would expect the children with a lower weight to not be growing in height. The Ne/Ly ratio is an indirect marker of inflammation and inflammation has been linked to growth hormone resistance and poor growth in chronic liver disease[36], but also in other situations[10,11]. None of the biliary atresia patients were stunted, but it is not clear if this is related to the sample of patients or if indeed is related to the diagnosis.

Fat mass indices at baseline were within the normal range for all patients regardless of the presence of sarcopenia. This is a consistent, but under-reported finding[8,37]. Peripheral insulin resistance which would favour preservation of fat mass, has been shown in adults with chronic liver disease[38], and growth hormone resistance has been shown in children[39]. Body composition in these children with ESCLD showed preservation of fat mass at the cost of lean mass, possibly as an attempt to mitigate the energy shortfall between immune related functions of the liver disease and growth[40]. In the paediatric nutrition literature, it has been shown that under stress the body sacrifices lean mass (which is a more expensive tissue to maintain from an energy point of view), in order to maintain a budget of energy for resisting infections[41]. It is also recognised that low fat mass predicts mortality[42].

Indices of lean mass improved after LT and were mostly within the normal range by 4 years after LT. There is little published data on body composition available for the post-LT period and it is helpful to know that one can expect indices to improve in the first 4 years. We know that from a height point of view there is an initial catch up phase in the first 1-2 years, followed by a plateau phase and then a slight decline in height z score[6,43,44].

There was a substantial difference in vascular complications between the sarcopenic and non-sarcopenic patients, with the sarcopenic patients having significantly more complications in relation to the hepatic artery and particularly hepatic artery thrombosis. The reasons for this can only be speculated. One possibility is the relationship of hypercoagulation with chronic liver inflammation and the formation of neutrophil- platelet complexes[45]. Another possibility may be due to haemodynamic factors related to extensive intrabdominal shunting due to significant portal hypertension[46]. The groups are small for conclusions to be definitive, and data collection on graft type and donor characteristics were not included in this work, but may be something to consider in future larger cohorts.

The strength of this study was the availability of data before and after liver transplantation. The limitations of the study lie in the retrospective nature of the data. In addition, because of a previous change in DXA machine and a shift from paper to electronic notes, follow up scans were not available for all patients, particularly the ones that had transitioned to adult services. With the onset of the covid-19 pandemic, DXA scans were stopped altogether in the hospital, and this triggered this review of practice.

Conclusion

This was a retrospective review of body composition data of children with ESCLD undergoing liver transplantation. About half of them were sarcopenic and the sarcopenic patients stayed in hospital after transplantation for an additional 20 days on average. They also had more vascular complications and a higher rate of re-transplantation. Sarcopenia was associated with a higher white cell, neutrophil,

and platelet count. Fat mass indices were within the normal range regardless of the presence of sarcopenia. By four years after liver transplantation, body composition indices tended to normalise. The relationship, at baseline, between sarcopenia and parameters of portal hypertension as well as the relationship with a proinflammatory state require more study. Sarcopenia is not uniformly present in all patients with chronic liver disease, and the presence of sarcopenia is not necessarily linked to the severity of the liver disease. It may be associated with aspects of the liver disease and understanding these relationships may help professionals anticipate, identify, and potentially treat sarcopenia and its related complications effectively.

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Disclosure: All authors KJ, SR, TM, JW and EK have nothing to disclose.

Ethical Review: The data presented here are from a retrospective review of case notes as part of a registered audit of practice as per procedures of Leeds University Hospitals NHS Trust and therefore did not require separate ethical approval.

Figure Legends:

Figure 1: Fat mass indices were all within the normal range at baseline

13 of the 25 patients at baseline had a leg LMI sds less than -1.96, but all 25 patients had a leg FMI of more than -1.96. Fat mass index; LMI lean mass index; sds standard deviation score

Figure 2: Leg LMI z-score at baseline and yearly after LT.

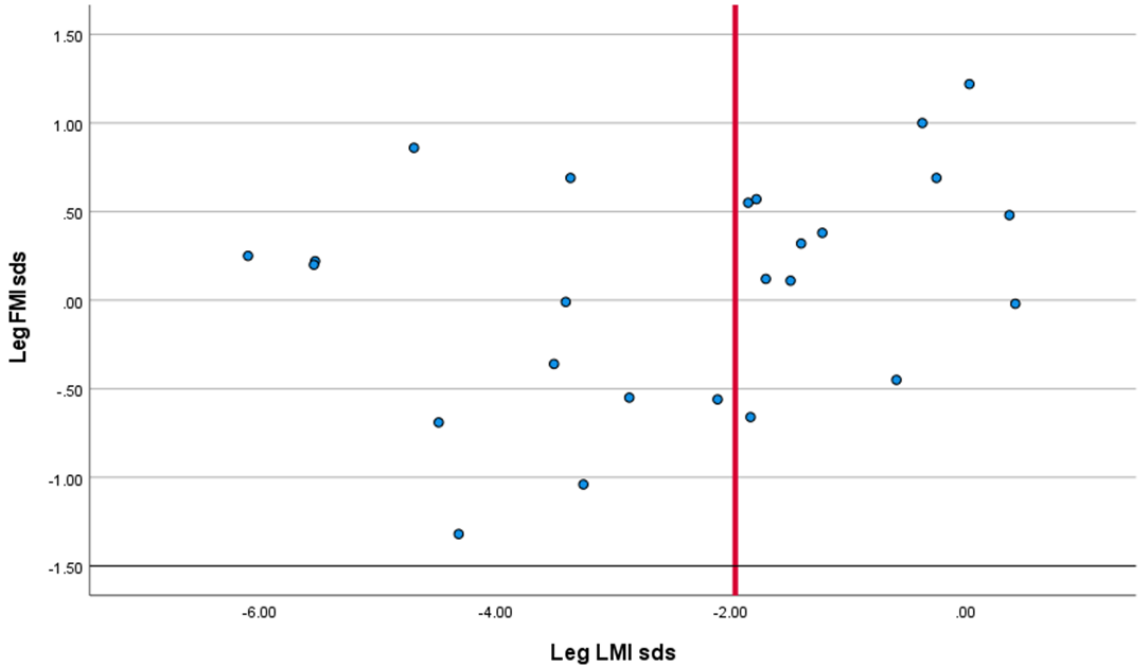
The graph shows Leg LMI z-score at before liver transplantation (baseline) and then for every year after LT for the first four years and demonstrates a steady improvement over time of leg LMI z-score so that by year 3 the measurements are mostly not in the sarcopenic range. LMI lean mass index; LT liver transplant.

Figure 3: BMAD z-score at baseline and yearly after LT.

The graph shows BMAD z-score before liver transplantation (baseline) and then for every year after LT for the first four years and demonstrates a steady improvement over time of BMAD z-score particularly in the first 3 years. BMAD bone mineral adjusted density; LT liver transplant.

Figure 4: Leg LMI z-scores of individual patients plotted against time after LT

The graph shows the Leg LMI z-score of 2 patients with and 3 patients without sarcopenia plotted at baseline (before LT) and then yearly for 4 years after LT. LMI lean mass index; LT liver transplant.



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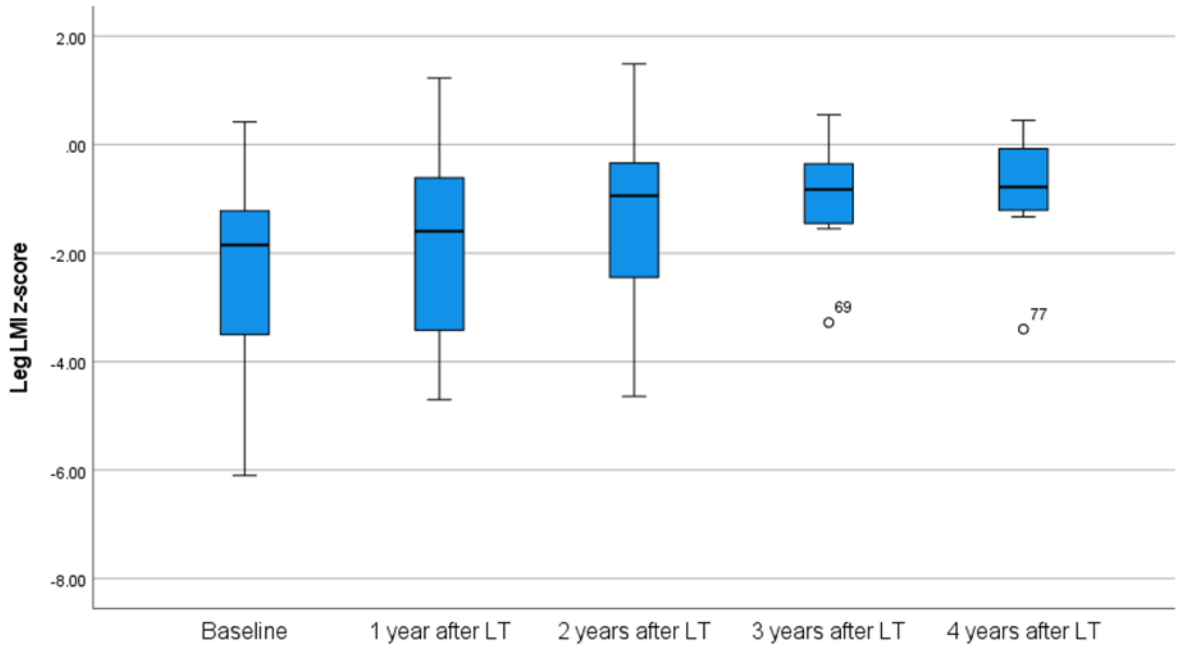

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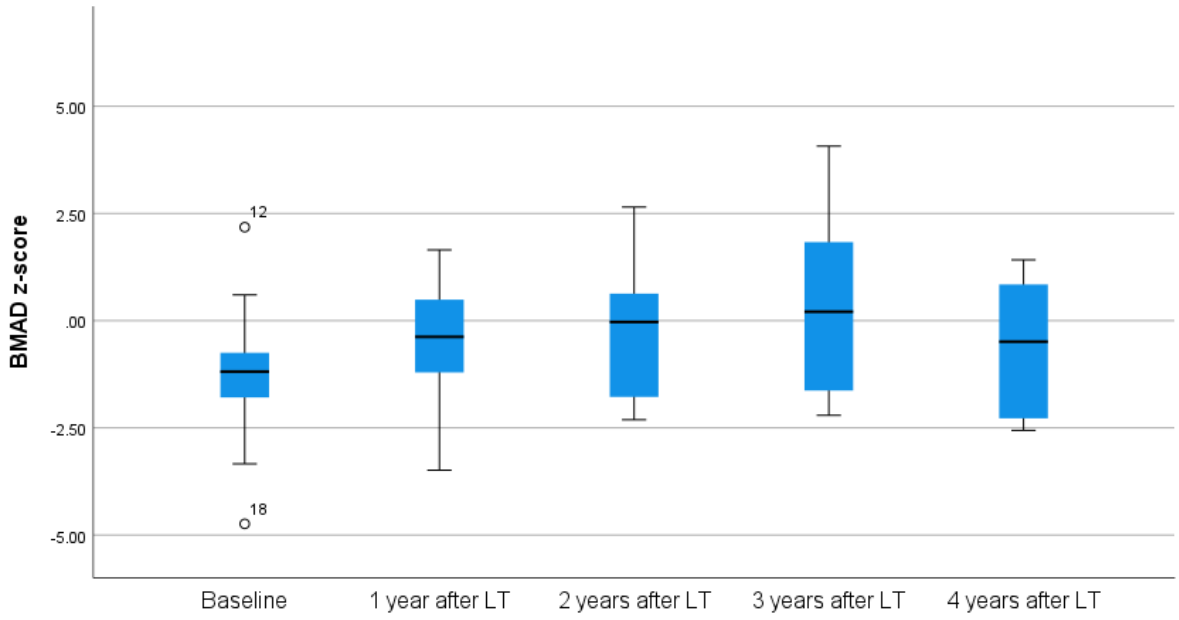

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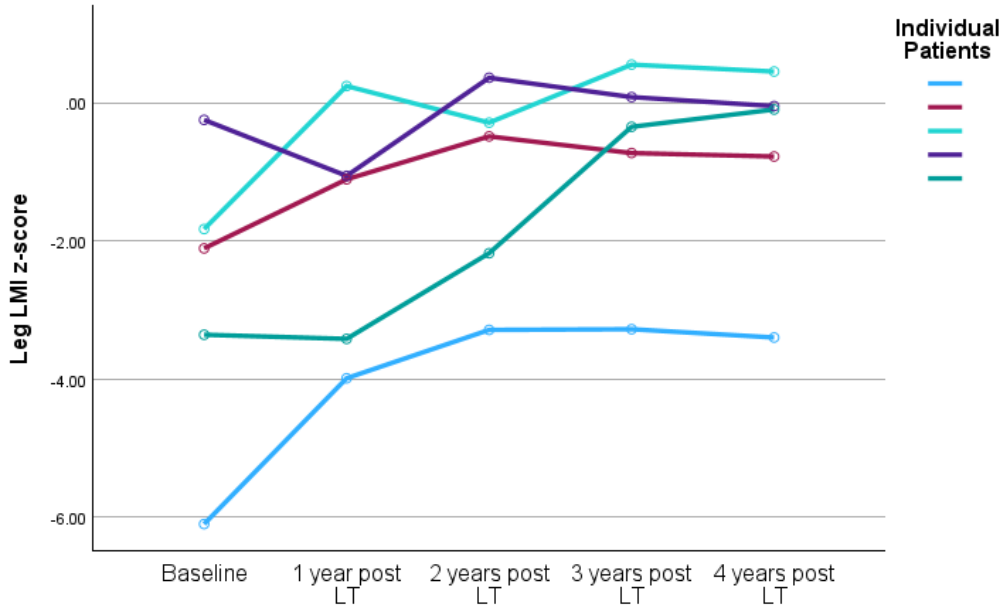

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Table 1: Main body composition indices before and after LT

Post LT	No of pts	Age (yrs)	Sex	Weight z-score	Height z-score	BMI z-score	Total LMI z-score	Total FMI z-score	Leg LMI z-score	Leg FMI z-score
Baseline	25	11.7 (6.1 to 15.8)	13M:12F	-0.3 (-4.1 to 1.4)	-0.7 (-5.1 to 1.9)	-0.3 (-1.8 to 1.2)	-1.5 (-3.5 to 1.3)	0.3 (-0.4 to 1.3)	-1.9 (-6.1 to 0.4)	0.2 (-1.3 to 1.2)
1 year	26	13.3 (7.4-17.2)	15M:11F	-0.3 (-3.2 to 1.6)	-0.7 (-5.1 to 1.9)	0.6 (-2.6 to 1.7)	-1.9 (-3.3 to 0.1)	0.9 (-0.5 to 2.0)	-1.6 (-4.7 to 1.2)	0.6 (-1.2 to 2.2)
2 years	15	13.6 (8.3-17)	10M:5F	-0.1 (-3 to 1.7)	-1.0 (-5.5 to 1.6)	0.3 (-2.1 to 1.7)	-1.3 (-3.5 to 0.3)	1.1 (-0.4 to 2)	-0.9 (-4.6 to 1.5)	1.0 (-0.6 to 2.3)
3 years	10	14.1 (9.3 to 17.3)	7M:3F	-0.3 (-2.3 to 1.2)	-0.7 (-2.8 to 1.6)	0.3 (-2.1 to 0.9)	-1.1 (-3.0 to -0.4)	0.7 (-0.6 to 1.5)	-0.8 (-3.3 to 0.6)	0.6 (-0.8 to 1.8)
4 years	7	14.6 (10.3 to 17.1)	5M:2F	-0.3 (-2.5 to 0.9)	-0.3 (-2.8 to 1.6)	-0.2 (-0.9 to 1.5)	-1.2 (-2.8 to -0.3)	0.1 (0.0 to 0.1)	-0.8 (-3.4 to 0.5)	0.3 (-0.2 to 2.3)

Table representing the main body composition indices with median and range at baseline and then yearly for the first 4 years after liver transplantation. LT liver transplantation; BMI body mass index; LMI lean mass index; FMI fat mass index.

References:

1. Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle.* 2017;8(1):113-121.
2. Lurz E, Quammie C, Englesbe M, et al. Frailty in Children with Liver Disease: A Prospective Multicenter Study. *J Pediatr.* 2018;194:109-115 e104.
3. Woolfson JP, Perez M, Chavhan GB, et al. Sarcopenia in Children With End-Stage Liver Disease on the Transplant Waiting List. *Liver Transpl.* 2021.
4. Boster JM, Browne LP, Pan Z, Zhou W, Ehrlich PF, Sundaram SS. Higher Mortality in Pediatric Liver Transplant Candidates with Sarcopenia. *Liver Transpl.* 2021.
5. Mager DR, Hager A, Ooi PH, Siminoski K, Gilmour SM, Yap JYK. Persistence of Sarcopenia After Pediatric Liver Transplantation Is Associated With Poorer Growth and Recurrent Hospital Admissions. *JPEN J Parenter Enteral Nutr.* 2019;43(2):271-280.
6. van Mourik ID, Beath SV, Brook GA, et al. Long-term nutritional and neurodevelopmental outcome of liver transplantation in infants aged less than 12 months. *J Pediatr Gastroenterol Nutr.* 2000;30(3):269-275.
7. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol.* 2016;65(6):1232-1244.
8. Mangus RS, Bush WJ, Miller C, Kubal CA. Severe Sarcopenia and Increased Fat Stores in Pediatric Patients With Liver, Kidney, or Intestine Failure. *J Pediatr Gastroenterol Nutr.* 2017;65(5):579-583.
9. Kyrana E. Significance of sarcopenia in children with end-stage liver disease undergoing liver transplantation. *Pediatr Transplant.* 2021;25(5):e14038.
10. Urlacher SS, Ellison PT, Sugiyama LS, et al. Tradeoffs between immune function and childhood growth among Amazonian forager-horticulturalists. *Proc Natl Acad Sci U S A.* 2018;115(17):E3914-E3921.
11. McDade TW, Reyes-Garcia V, Tanner S, Huanca T, Leonard WR. Maintenance versus growth: investigating the costs of immune activation among children in lowland Bolivia. *Am J Phys Anthropol.* 2008;136(4):478-484.
12. Bondi BC, Banh TM, Vasilevska-Ristovska J, et al. Incidence and Risk Factors of Obesity in Childhood Solid-Organ Transplant Recipients. *Transplantation.* 2020;104(8):1644-1653.
13. Rothbaum Perito E, Lau A, Rhee S, Roberts JP, Rosenthal P. Posttransplant metabolic syndrome in children and adolescents after liver transplantation: a systematic review. *Liver Transpl.* 2012;18(9):1009-1028.
14. Kyrana E, Williams JE, Wells JC, Dhawan A. Sarcopenia and Fat Mass in Children With Chronic Liver Disease and Its Impact on Liver Transplantation. *JPGN Rep.* 2022;3(2):e200.
15. Wells JC, Williams JE, Chomtho S, et al. Body-composition reference data for simple and reference techniques and a 4-component model: a new UK reference child. *Am J Clin Nutr.* 2012;96(6):1316-1326.
16. Laskey MA. Dual-energy X-ray absorptiometry and body composition. *Nutrition.* 1996;12(1):45-51.
17. Toombs RJ, Ducher G, Shepherd JA, De Souza MJ. The impact of recent technological advances on the trueness and precision of DXA to assess body composition. *Obesity (Silver Spring).* 2012;20(1):30-39.
18. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab.* 2008;33(5):997-1006.
19. Deyell RJ, Desai S, Gallivan A, et al. Prediction of whole body composition utilizing cross-sectional abdominal imaging in pediatrics. *Eur J Clin Nutr.* 2023;77(6):684-691.

20. Rodge GA, Goenka U, Jajodia S, et al. Psoas Muscle Index: A Simple and Reliable Method of Sarcopenia Assessment on Computed Tomography Scan in Chronic Liver Disease and its Impact on Mortality. *J Clin Exp Hepatol.* 2023;13(2):196-202.
21. Ritz A, Froeba-Pohl A, Kolorz J, et al. Total Psoas Muscle Area as a Marker for Sarcopenia Is Related to Outcome in Children With Neuroblastoma. *Front Surg.* 2021;8:718184.
22. Lurz E, Patel H, Lebovic G, et al. Paediatric reference values for total psoas muscle area. *J Cachexia Sarcopenia Muscle.* 2020;11(2):405-414.
23. Castiglione J, Somasundaram E, Gilligan LA, Trout AT, Brady S. Automated Segmentation of Abdominal Skeletal Muscle on Pediatric CT Scans Using Deep Learning. *Radiol Artif Intell.* 2021;3(2):e200130.
24. Baracos VE. Psoas as a sentinel muscle for sarcopenia: a flawed premise. *J Cachexia Sarcopenia Muscle.* 2017;8(4):527-528.
25. Rutten IJG, Ubachs J, Kruitwagen R, Beets-Tan RGH, Olde Damink SWM, Van Gorp T. Psoas muscle area is not representative of total skeletal muscle area in the assessment of sarcopenia in ovarian cancer. *J Cachexia Sarcopenia Muscle.* 2017;8(4):630-638.
26. Khan S, Benjamin J, Maiwall R, et al. Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis. *J Clin Transl Res.* 2022;8(3):200-208.
27. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol.* 2012;10(2):166-173, 173 e161.
28. Tantai X, Liu Y, Yeo YH, et al. Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *J Hepatol.* 2022;76(3):588-599.
29. Woolfson JP, Perez M, Chavhan GB, et al. Sarcopenia in Children With End-Stage Liver Disease on the Transplant Waiting List. *Liver Transpl.* 2021.
30. Montano-Loza AJ. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. *Liver Transpl.* 2014;20(11):1424.
31. Hassan EA, Makhlouf NA, Ibrahim ME, et al. Impact of Sarcopenia on Short-Term Complications and Survival After Liver Transplant. *Exp Clin Transplant.* 2022;20(10):917-924.
32. Artru F, Miquet X, Azahaf M, et al. Consequences of TIPSS placement on the body composition of patients with cirrhosis and severe portal hypertension: a large retrospective CT-based surveillance. *Aliment Pharmacol Ther.* 2020;52(9):1516-1526.
33. Jahangiri Y, Pathak P, Tomozawa Y, Li L, Schlansky BL, Farsad K. Muscle Gain after Transjugular Intrahepatic Portosystemic Shunt Creation: Time Course and Prognostic Implications for Survival in Cirrhosis. *J Vasc Interv Radiol.* 2019;30(6):866-872 e864.
34. Tsien C, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. *Eur J Gastroenterol Hepatol.* 2013;25(1):85-93.
35. Gioia S, Ridola L, Cristofaro L, et al. The improvement in body composition including subcutaneous and visceral fat reduces ammonia and hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Liver Int.* 2021;41(12):2965-2973.
36. Holt RI, Baker AJ, Jones JS, Miell JP. The insulin-like growth factor and binding protein axis in children with end-stage liver disease before and after orthotopic liver transplantation. *Pediatr Transplant.* 1998;2(1):76-84.
37. Kyrana E WJ, Wells JC, Dhawan A. Sarcopenia and Fat Mass in Children With Chronic Liver Disease and Its Impact on Liver Transplantation. *JPGN Reports.* 2022;3(2):e200.
38. Selberg O, Burchert W, vd Hoff J, et al. Insulin resistance in liver cirrhosis. Positron-emission tomography scan analysis of skeletal muscle glucose metabolism. *J Clin Invest.* 1993;91(5):1897-1902.
39. Holt RI, Jones JS, Baker AJ, Buchanan CR, Miell JP. The effect of short stature, portal hypertension, and cholestasis on growth hormone resistance in children with liver disease. *J Clin Endocrinol Metab.* 1999;84(9):3277-3282.

40. Wells JCK. *The evolutionary biology of human body fatness : thrift and control.* Cambridge, UK ; New York: Cambridge University Press; 2010.
41. Wells JCK. Body composition of children with moderate and severe undernutrition and after treatment: a narrative review. *BMC Med.* 2019;17(1):215.
42. Bartz S, Mody A, Hornik C, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab.* 2014;99(6):2128-2137.
43. Loeb N, Owens JS, Strom M, et al. Long-term Follow-up After Pediatric Liver Transplantation: Predictors of Growth. *J Pediatr Gastroenterol Nutr.* 2018;66(4):670-675.
44. Ee LC, Noble C, Fawcett J, Cleghorn GJ. Bone Mineral Density of Very Long-term Survivors After Childhood Liver Transplantation. *J Pediatr Gastroenterol Nutr.* 2018;66(5):797-801.
45. Rangaswamy C, Mailer RK, Englert H, Konrath S, Renne T. The contact system in liver injury. *Semin Immunopathol.* 2021;43(4):507-517.
46. Zhao JC, Lu SC, Yan LN, et al. Incidence and treatment of hepatic artery complications after orthotopic liver transplantation. *World J Gastroenterol.* 2003;9(12):2853-2855.