TITLE PAGE

Title: Computed tomography measures of nutrition in patients with end-stage liver disease provide a novel approach to characterize deficits

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ESLD, end-stage liver disease; BMI, body mass index; MELD, model for end-stage liver disease; CT, computed tomography; ANOVA, analysis of variance; SPSS, Statistical package for the Social Sciences.

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Abstract

Aim: Patients with cirrhosis and end-stage liver disease (ESLD) develop severe nutrition deficits that impact on morbidity and mortality. Laboratory measures of nutrition fail to fully assess clinical deficits in muscle mass and fat stores. This study employs computed tomography imaging to assess muscle mass and subcutaneous and visceral fat stores in patients with ESLD.

Methods: This 1:1 case-control study design compares ESLD patients with healthy controls. Study patients were selected from a database of ESLD patients using a stratified method to assure a representative sample based on age, body mass index (BMI), gender, and model for end-stage liver disease score (MELD). Control patients were trauma patients with a low injury severity score (<10) who had a CT scan during evaluation. Cases and controls were matched for age +/- 5 years, gender, and BMI +/- 2.

Results: There were 90 subjects and 90 controls. ESLD patients had lower albumin levels ($p<0.001$), but similar total protein levels ($p=0.72$). ESLD patients had a deficit in muscle mass (-19%, $p<0.001$) and visceral fat (-13%, $p<0.001$), but similar subcutaneous fat (-1%, $p=0.35$). ESLD patients at highest risk for sarcopenia included those over age 60, BMI< 25.0, and female gender. We found degree of sarcopenia to be independent of MELD score.

Conclusions: These results support previous research demonstrating substantial nutrition deficits in ESLD patients that are not adequately measured by laboratory testing. Patients with ESLD have significant deficits of muscle and visceral fat stores, but a similar amount of subcutaneous fat.

INTRODUCTION

Frailty is a biologic syndrome of decreased physiologic reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes.[1] Sarcopenia, or muscle wasting, is an indicator of frailty in chronically ill and elderly patients. The theoretic etiologies of sarcopenia include malnutrition or malabsorption, increased myostatin (aging), abnormal use of protein as an energy source (cirrhosis), hormone deficiencies (cirrhosis), and reduced branched-chain amino acids (hepatic encephalopathy).[2] Liver disease is associated with many physiological changes such as altered metabolism and hormone imbalances resulting in a high risk for developing severe muscle wasting and frailty.[2-4] Sarcopenia is common among liver transplant candidates.[5, 6] Recent studies have shown an association between sarcopenia and adverse outcomes in chronically ill patients, including increased length of hospitalization, number of complications, health care costs, and mortality.[3, 7-13] Poor outcomes specific for ESLD patients include increased waitlist mortality, post-transplant mortality, length of post-transplant hospitalization, and infection.[8, 13-15]

There are multiple techniques to measure total body composition, including sarcopenia. Dual X-ray absorptiometry is the gold standard for measuring body composition in patients without fluid overload or ascites.[16-18] This tool, therefore, is not a reliable measure of total body composition in the patient with end-stage liver disease. Single slice axial computed tomography (CT) measurements of core muscle mass, visceral fat and subcutaneous fat have been shown to be accurate predictors of total body muscle and fat composition and may be used to predict changes in nutrition status in the transplant population.[19-23] MELD score, age, and BMI are all considered when deciding if a patient with ESLD is an acceptable candidate for transplantation. Frailty as a risk-factor of morbidity and mortality has largely been excluded from the discussion. This study was designed to quantify the severity of sarcopenia in ESLD patients, and to analyze the association between sarcopenia and BMI, age, gender, and MELD in ESLD patients.

METHODS

Records from a single center transplant database of 644 adults (≥18 years old) with ESLD who received a transplant between 2009-2014 were used for this study. Patients in this database were stratified by groups according to MELD, age and gender. Patients were first classified into three MELD groupings for scores <20, 20-30, and >30. Each of these MELD group was then stratified by age groups of 18-39, 40-49, 50-59, and 60+ years. Finally, 6 males and 6 females were randomly selected from each MELD-age group using a randomizer. If there were less than 6 males or 6 females in any group, then all of the available patients were chosen for study inclusion. This selection process resulted in a pool of 133 patients. Of the 133 randomly selected patients, 99 had an abdominal CT within 90 days before transplant, and 90 patients could be matched to a healthy control patient. Control patient data were extracted from a large trauma database within our health system, in order to perform a 1:1 case-control study design. Each anonymous qualifying control had an injury severity score less than 10 and received an abdominal CT scan during their initial trauma presentation and evaluation. Case-control matching criteria included the control being +/- 5 years, +/- 2.0 BMI, and the same gender as the case.

To assess for sarcopenia, CT imaging was used because it is standard practice for patients awaiting liver transplantation to receive an abdominal CT, and core muscle measurements from CT have been shown to be an acceptable indicator of total body muscle mass.[19-23] For each case and control, measurements of total psoas muscle area and subcutaneous fat area were taken at the most superior aspect of L3. Measurements at this level are accurate indicators of total body composition.[19, 22] Visceral fat is represented by perinephric fat and was measured at the hilum of the kidney. Three research assistants, who were trained in reading abdomen CT scans, made each measurement blind to the measurements of the other assistants and to the diagnosis and outcome of the patient. This was done to establish inter-rater reliability. Any measurement that differed by >15% of the mean (of the three readers) was re-examined until a consensus was reached. The mean of all three measurements was used to minimize the human error of each measurement. Total psoas area, total subcutaneous fat, and total visceral fat were scaled for the height of the patient by dividing the measured area (in cm^2) by the height (in $meter^2$). This created the

muscle index (derived from the total psoas area), subcutaneous fat index, and the visceral fat index (derived from perinephric fat) used in the comparison between case and control.

To make each measurement, the imaging software was set to "soft tissue" and the free hand drawing tool was used. [**Figure**] To measure the total psoas muscle area, the left and right psoas muscles were outlined at the most superior L3 CT slice and the two areas were summed to get the combined total psoas area. The subcutaneous fat area was obtained by subtracting the area of the outlined abdominal cavity (at the outermost muscle layer) from the area outlined just under the dermis. Visceral fat was assessed by measuring the perinephric fat. Since the level of the kidney within the abdominal cavity differed for each patient, the measurements were taken at the hilum of each individual kidney. This was done by outlining the kidney and vasculature and subtracting this area from the area obtained by outlining Gerota's fascia. Total visceral fat was calculated by summing the right and left perinephric fat values.

CT images were viewed and measured using Synapse picture archiving and communication system (PACS) software (FUJIFILM Holdings America Corporation, Valhalla, New York, USA). Data were analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics 24, IBM Corporation, Armonk, New York, USA). Retrospective analysis of patient data for this study were reviewed and approved by the Institutional Review Board of the Indiana University School of Medicine (study number 1011003619R005). Categorical variables in the analysis were compared using chi-square analysis, and continuous variable were compared using standard analysis of variance testing (ANOVA). Results with p-value <0.05 were considered statistically significant.

RESULTS

The median age and BMI of the 90 study patients was 45 and 27.2, respectively. Of these 90 patients, 52 of them were male. Likewise, the controls had a median age and BMI of 46 and 27.8, respectively. [**Table 1]** There was not a difference between the groups in total serum protein, but a deficiency in serum albumin was noted in ESLD patients (2.9 versus 3.6, $p<0.001$). A grouped analysis, comparing the medians between all cases and controls, was performed and showed a deficit in muscle mass index (42 ESLD versus 52 controls, $p<0.001$) and a deficit in visceral fat index (71 ESLD versus

114 controls, p<0.001). There was no difference in subcutaneous fat index (551 ESLD and 591 controls, p=0.35). Additionally, a matched analysis was done where the percent difference between each case and control was calculated. The median percent difference between each case and control included a 19% deficit in muscle mass index, a 13% deficit in visceral fat index, but an inconsequential 1 % difference in subcutaneous fat index.

This study was designed to analyze muscle mass and fat differences among patients stratified by BMI, gender, age and MELD score. The first subgroup analysis was stratified by BMI groupings (<25, 25-29, 30-34, 35+). [**Table 2**] Muscle mass index, subcutaneous fat index, and visceral fat index all differed among BMI groups with each index increasing with increased BMI (p= 0.03, <0.001, 0.02 respectively). BMI <25 had the most profound sarcopenia with a 29% muscle mass index deficit when compared to age-gender-BMI-matched controls. Muscle mass deficits also existed in the 25-29 and 30-34 BMI groupings with a -22% and -16% difference when compared to controls. The muscle mass index for ESLD patients was 9% higher than controls in the highest grouping of BMI ≥35. The highest BMI group also showed ESLD patients with a 7% higher subcutaneous fat and 34% less visceral fat than controls. While the visceral fat index increased with increasing BMI (56, 74, 83, 110), the matched analysis showed greater deficits in visceral fat among increasing BMI groupings. BMI groupings of 30-34 and ≥35 showed greater deficiencies in visceral fat than those with BMI <30 (-27% and -34% versus -12%). There were only minimal differences in the laboratory measures (serum albumin and protein) between BMI groups, which failed to reach significance.

Subgroup analysis by gender included data on 52 males and 38 females. [**Table 3**] Both genders had a similar deficit in serum albumin compared to controls (p=0.25), but females with ESLD had a higher serum protein level when compared to ESLD males and the combined control group (p<0.01). The ESLD female group had significantly lower muscle mass when compared to both the combined control group and to the ESLD male group (p<0.001). The female group also had a higher subcutaneous fat index (p<0.001) and a lower visceral fat index (p<0.001).

Subgroup analysis by age included comparison of four age groups (18-39, 40-49, 50-59, ≥60). [**Table 4**] The serum albumin and total protein were similar among all age groups, with all ESLD patients having low albumin levels compared to the control group. The psoas area index was lower for all age groups when compared to the control group (p=0.05). Among ESLD patients, the group over age 60 had a markedly lower muscle mass index when compared to all other patients. Differences in the subcutaneous fat index were insignificant between age groups. Visceral fat index increased with each age group starting at 53 for the ages 18-39 grouping and rising to 90 in the ≥60 age group (p= <0.001). Patients over age 60 also had the greatest visceral fat deficits when compared to matched controls, with ESLD patients in the ≥60 age group having a 48% deficit in visceral fat (compared to the 18-39 ESLD patients with only an 8% deficit (p= <0.01)).

Patients were grouped into three MELD groups (6-19, 20-30, 31-40) with approximately equal number of patients in each group (32, 33, and 25). [**Table 5**] Only serum albumin differed significantly between MELD groups, with more severe disease correlating with lower serum albumin (p<0.001). Muscle mass, subcutaneous fat, and visceral fat indices were not significantly different between MELD groups.

DISCUSSION

The present study supports previous research that there are substantial nutritional deficits in the ESLD population that are not adequately measured by laboratory testing. Sarcopenia, or decreased muscle mass, is an important predictor of patient outcomes in the ESLD patient population.[8, 13-15] Studies have recently proposed cut-off values for specific populations to define and quantify the severity of sarcopenia using CT or magnetic resonance imaging.[5, 8, 14, 15, 24-28] These cut-off ranges are often ambiguous, such as the lowest quartile, and not based on clinical outcomes. The present study avoids the ambiguity of population specific cut-offs by using a case-control design where each ESLD patient is compared to a healthy gender-age-BMI-matched control. This study demonstrates that ESLD patients experience sarcopenia and decreased visceral fat while maintaining a comparable amount of subcutaneous fat when compared to healthy age-gender-BMI-matched controls.

The subgroup analyses suggest that the groups at risk for the most profound sarcopenia are females, the elderly, and patients with BMI <25. A previous study suggested the presence of gender specific body compositional changes showing that muscle wasting may be more severe in males, while females have more severe fat deficits with preserved muscle volume.[6] In the present study females had a lower muscle mass index and visceral fat index; however, the percent difference between male cases and controls and female cases and controls was not significantly different for all three indices. This suggests that body compositional changes may actually be similar among women and men with ESLD. Other studies have recognized this by reporting gender specific sarcopenia cut-off values for males and females. Though sarcopenia may not be as prevalent in women as originally thought, the risk for complications in sarcopenic women may be greater than in sarcopenic men. One study found that 43% of women classified as sarcopenic experienced major complications, while only 10% of non-sarcopenic women experienced complications ($p<0.01$).[29]

The elderly were also identified as a population at high risk for developing severe sarcopenia. ESLD patients over the age of 60 had the lowest muscle mass index of any age group and the greatest deficit of visceral fat when compared to healthy controls. One explanation for the increased risk of sarcopenia may be an additive affect of multiple physiological mechanisms such as malnutrition and increased myostatin thought to be associated with aging, as well as the mechanisms associated with liver failure. The visceral fat index trended upward with increasing age, though the visceral fat deficit for diseased patients trended downward. Patients with ESLD may not store as much visceral fat as healthy individuals as they age, or this reserve may be mobilized more readily in the elderly in response to disease.

ESLD patients with lower BMI had more severe sarcopenia. This finding is contrary to the idea of sarcopenic obesity that has been described in many populations. The present study suggests that sarcopenic obesity is not present in the adult ESLD population. Increased BMI may have a protective effect on the development of sarcopenia. This finding of increased muscle mass with increasing BMI may also help to explain the obesity paradox, where obese, or overweight, patients with end organ failure

have better post-surgical outcomes. Visceral fat was found to be significantly different between the different BMI and age groups (p=0.02, <0.001, respectively). One study found that the ratio between visceral and subcutaneous fat might be an important predictor of mortality with increased visceral fat being associated with increased post-transplant mortality.[26] This also supports the obesity paradox, as those with higher BMI were more deficient in visceral fat and less deficient in subcutaneous fat.

MELD did not correlate well with muscle mass, subcutaneous fat, or visceral fat indices. A previous study also suggested that muscle mass was not associated with MELD.[12] One study suggests sarcopenia may only be associated with mortality in less severe liver disease (MELD<15).[15] Utilization of sarcopenia as a prognostic factor, in addition to MELD, may be an important clinical indicator of successful transplantation and wise allocation of organs. However, muscle quality as measured by strength or stamina may be more predictive of mortality than simple muscle mass. Several measure of strength have been reported including hand grip strength, Short Physical Performance Battery, and muscle density, the six minute walk test and the 5 meter walk test. Unfortunately, the present study did not address the issue of muscle quality or mortality.[30]

In conclusion, this study uses a carefully matched case-control design to assess nutritional deficits in the ESLD population using objective CT measures. CT measures provide novel insight into frailty and sarcopenia that cannot be understood with the standard serum markers of nutrition, albumin and protein. Objectively assessing a patient's level of sarcopenia may assist in clinical management, as well as risk stratification in choosing patients as transplant candidates. This appears to be especially true in certain patient populations such as the elderly, morbidly obese, female and those with low BMI.

Figure legend.

A. Cross sectional image of the abdomen at the L2-L3 disc interspace. The picture illustrates the location of the measures taken to assess (B) psoas area, and (C) visceral (perinephric) and (D) subcutaneous fat.

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Table 1. Comparison of patients with end-stage liver disease and healthy controls.

	Controls	End stage liver disease	p-value
OVERALL (number (%))	90	90	
Demographics			
MELD (mean)		22	
Gender: Male	104 (58%)	104 (58%)	1
Age (years, median(range))	46	45	0.84
Body mass index (median)	27.8	27.2	0.87
Laboratory measures			
Serum albumin (g/dL)	3.6	2.9	<0.001
Total protein (g/dL)	6.5	6.5	0.72
Sarcopenia (group comparison)			
Psoas area index (median)			
Grouped comparison	5.2	4.2	<0.001
Matched comparison (% difference)		-19%	
Measures of body fat (group comparison)			
Subcutaneous fat index (median)			
Grouped comparison	59.1	55.1	0.35
Matched comparison (% difference)		-1%	
Perinephric fat index (median)			
Grouped comparison	11.4	7.1	<0.001
Matched comparison (% difference)		-13%	

Table 4. Comparison of patients with end-stage liver disease and healthy controls stratified by MELD score

	Controls	End stage liver disease				p-value*
		Study patient age				
		18 to 39	30 to 49	50 to 59	>60	
Number	90	64	48	46	22	
Laboratory measures						
Serum albumin (g/dL)	3.6	2.7	2.9	3.1	2.6	0.56
Total protein (g/dL)	6.5	6.4	6.3	6.5	6.7	0.33
Sarcopenia (group comparison)						
Psoas area index (median)						
Grouped comparison	5.2	4.3	4.1	4.4	3.6	0.05
Matched comparison (% difference)		-21%	-26%	-8%	-25	0.19
Measures of body fat (group comparison)						
Subcutaneous fat index (median)						
Grouped comparison	59.1	48.1	55.8	62.7	51.7	0.81
Matched comparison (% difference)		4%	8%	-2%	-11	0.66
Perinephric fat index (median)						
Grouped comparison	11.4	5.3	6.8	8.7	9	<0.001
Matched comparison (% difference)		-8%	-26%	-12%	-48	<0.01

* For difference among age groups

Table 5. Comparison of patients with end-stage liver disease and healthy controls stratified by MELD score

	Controls	End stage liver disease				p-value*
		Body mass index				
		< 25	25 to 29	30 to 34	>35	
Number	90	64	60	36	20	
Laboratory measures						
Serum albumin (g/dL)	3.6	2.9	2.9	3.1	2.5	0.37
Total protein (g/dL)	6.5	6.5	6.5	6	6.8	0.49
Sarcopenia (group comparison)						
Psoas area index (median)						
Grouped comparison	5.2	3.2	4.4	4.8	4.9	0.03
Matched comparison (% difference)		-29%	-22%	-16%	9%	0.08
Measures of body fat (group comparison)						
Subcutaneous fat index (median)						
Grouped comparison	59.1	37.1	51.4	77.2	121.5	<0.001
Matched comparison (% difference)		-11%	7%	-8%	7	0.29
Perinephric fat index (median)						
Grouped comparison	11.4	5.6	7.4	8.3	11	0.02
Matched comparison (% difference)		-12%	-12%	-27%	-34%	0.29

* For difference among body mass index groups

Table 2. Comparison of patients with end-stage liver disease and healthy controls stratified by MELD score

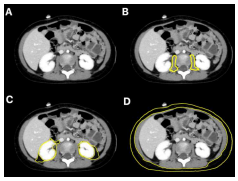
	Controls	End stage liver disease			p-value*
		MELD Score			
		6 to 19	20 to 30	30 to 40	
Number	90	32	33	25	
Laboratory measures					
Serum albumin (g/dL)	3.6	3.1	2.7	2.6	<0.001
Total protein (g/dL)	6.5	6.5	6.8	5.7	0.28
Sarcopenia (group comparison)					
Psoas area index (median)					
Grouped comparison	5.2	4.2	4.1	4.2	0.66
Matched comparison (% difference)		-28%	-19%	-19%	
Measures of body fat (group comparison)					
Subcutaneous fat index (median)					
Grouped comparison	59.1	66.6	52.6	49.5	0.54
Matched comparison (% difference)		-10%	5%	15%	
Perinephric fat index (median)					
Grouped comparison	11.4	7.1	5.8	7.3	0.76
Matched comparison (% difference)		-12%	-13%	-23%	

* For difference among MELD score groups

Table 3. Comparison of patients with end-stage liver disease and healthy controls stratified by MELD score

	Controls	End stage liver disease		p-value*
		Gender		
		Male	Female	
Number	90	52	38	
Laboratory measures				
Serum albumin (g/dL)	3.6	2.8	2.9	0.25
Total protein (g/dL)	6.5	6.1	6.9	<0.01
Sarcopenia (group comparison)				
Psoas area index (median)				
Grouped comparison	5.2	4.7	3.5	<0.001
Matched comparison (% difference)		-19%	-17%	0.56
Measures of body fat (group comparison)				
Subcutaneous fat index (median)				
Grouped comparison	59.1	51.4	69.1	<0.001
Matched comparison (% difference)		-1%	1%	0.38
Perinephric fat index (median)				
Grouped comparison	11.4	8.4	6.3	<0.001
Matched comparison (% difference)		-19%	-11%	0.17

* For difference among gender groups



Research Highlights

Key Points

1. Compared to healthy controls, patients with end-stage liver disease have marked sarcopenia and loss of visceral fat, but similar subcutaneous fat.

2. End-stage liver disease patients at highest risk for sarcopenia include the elderly, patients with low body mass index, and females.

3. Severity of liver disease, as measured by model for end-stage liver disease score, is not correlated with degree of sarcopenia.

4. The severity of nutritional deficits associated with end-stage liver disease are not adequately represented by serum albumin and protein levels, though serum albumin does correlate with model for end-stage liver disease score.