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Comparing the performance of 3 sarcopenia definitions for predicting adverse events prior to liver transplant

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Abstract

Background: Sarcopenia is a syndrome of severe muscle wasting, associated with adverse outcomes related to liver transplantation (LT). There are several approaches used to identify sarcopenia. We aimed to investigate the prevalence of sarcopenia using 3 different criteria and determine how these performed in relation to clinical outcomes.

Methods: The cohort study included 237 adults with cirrhosis referred for LT. Sarcopenia was identified using (1) CT-defined; and the (2) original and (3) updated European Working Group on Sarcopenia in Older People criteria (EWGSOP1 and 2). Logistic regression was used to estimate OR and 95% CI for the relationships between sarcopenia and receiving an LT, unplanned admissions pre-LT, surgical complications, and length of stay for the LT admission. Fine-Gray competing risk analysis explored the impact of sarcopenia on receiving an LT and unplanned admissions. The AUC determined the predictive utility of the criteria.

Results: The prevalence of CT-defined sarcopenia (52%) was more than twice and 4-fold that of EWGSOP1-defined (22%) and EWGSOP2-defined (11%) sarcopenia, respectively. No criteria demonstrated a significant association with time to LT nor the time to unplanned admissions pre-LT. Similarly, none of the 3 criteria had superior predictive utility for the clinical outcomes for unplanned hospital admissions pre-LT of receiving an LT, with all 3 criteria having identical moderate AUCs for unplanned admissions (0.70) and similar weak AUCs ($\leq$0.55) for the likelihood of receiving an LT.

Conclusions: Sarcopenia in patients undergoing LT evaluation is prevalent. EWGSOP criteria appear to offer no advantage over CT-only criteria in

Abbreviations: BMI, body mass index; EWGSOP1, European Working Group on Sarcopenia in Older People original criteria; EWGSOP2, European Working Group on Sarcopenia in Older People updated criteria; HGS, hand grip strength; ICU, intensive care unit; LOS, length of stay; LT, liver transplantation; PPV, positive predictive value; QLTS, Queensland Liver Transplant Service; SMI, skeletal muscle index; SPPB, short physical performance battery; T2D, type 2 diabetes.

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identifying patients at increased risk of adverse LT outcomes. Bedside measures of muscle function may be of benefit in tracking the effectiveness of interventions targeting sarcopenia.

Keywords: advanced liver disease, cirrhosis, clinical risk assessment, low muscle mass, muscle wasting

INTRODUCTION

Sarcopenia is a syndrome characterized by progressive loss of skeletal muscle that can impact physical function.[1,2] Initially described in older adults as age-associated muscle disease, it is now recognized that sarcopenia can develop in chronic diseases such as cirrhosis, where accelerated aging occurs. A number of different criteria have been used to diagnose sarcopenia. The Global Leadership Initiative in Sarcopenia recently agreed that the components used to identify sarcopenia should (1) be consistent across clinical conditions and (2) incorporate aspects of muscle function in addition to muscle mass. Of the various criteria used to diagnose sarcopenia, those from the European Working Group on Sarcopenia in Older People (EWGSOP), which incorporate measures of muscle function in addition to muscle mass, have been the most widely used and are endorsed in guidelines for use in clinical and research settings.[3]

This contrasts with the majority of studies of patients with cirrhosis which have largely relied solely on measures of muscle mass, usually by CT. In these studies, the prevalence of sarcopenia varies from 22% to 70%,[4] and is associated with a number of adverse outcomes, including death, infection, and longer hospital length of stay.[5–8] In relation to liver transplantation (LT), in addition to the above impacts, sarcopenia has also been associated with reduced physical functioning and increased posttransplant mortality.[9,10] Because of the link with adverse outcomes, baseline sarcopenia assessments are recommended as part of the nutrition assessment for potential candidates of LT.[11–13] Another reason to diagnose sarcopenia in these patients is that it is potentially modifiable through diet and/or exercise interventions.[14,15]

The most widely used tool for liver disease severity and allocation of organs for LT is the MELD score.[16] A recognized limitation of this tool is the lack of objective measures of vulnerabilities in nutrition and physical status.[17] Current guidelines for sarcopenia diagnosis in patients with cirrhosis based on available literature recommend assessing muscle mass only, with CT the main modality used.[11,13,18–20] This contrasts with the initial EWGSOP criteria (EWGSOP1), which incorporated measurements of muscle strength and physical performance in addition to muscle mass.[21] Both muscle strength and physical performance have previously been shown to correlate with outcomes in patients with cirrhosis.[22,23] These criterion have been updated (EWGSOP2) with reordering of the diagnostic criteria placing the assessment of muscle strength as the first step in diagnosing sarcopenia.[1]

Currently, the hepatology community is out of step in how sarcopenia is defined compared with other patient groups, such as geriatric populations.[24] More importantly, the incorporation of measures of muscle function into the assessment of sarcopenia in patients with LT may improve the ability to identify those at greatest risk of adverse outcomes, who might benefit from diet and exercise interventions. Therefore, the aims of this study were to (1) determine the prevalence of sarcopenia in patients referred for LT using CT-only, and EWGSOP1- and 2-criteria and (2) compare these diagnostic criteria to determine which is best able to identify patients at increased risk of adverse clinical outcomes, including the impact of baseline sarcopenia on the likelihood of receiving an LT and unplanned hospital admissions prior to LT.

METHODS

Study design

This was a single-center, cohort study, including patients from the Queensland Liver Transplant Service (QLTS), Brisbane, Australia. The study was approved by the Metro South Human Research Ethics Committee (HREC/2018/QMS/46728) and the University of Queensland Human Research and Ethics Centre (2019002997) and was conducted in line with the Declaration of Helsinki and Istanbul. Data were collected as part of routine care, with a waiver of consent provided by the abovementioned Ethics Committees. The STROBE checklist was used to guide the reporting of your this cohort study. Checklist in Supplementary file The STROBE checklist, http://links.lww.com/HC9/C26.

Study cohort

Adults (above 18 y) who were referred for LT at the QLTS between March 28, 2018, to September 18, 2022

and had a baseline assessment with the hepatologist and pre-LT dietitian were included in the study. Physical therapists are not part of the QLTS, and therefore to the knowledge of the authors, no patients were undergoing supervised physical therapy during their pre-LT evaluation. Inpatients were excluded unless admitted specifically for LT assessment and were medically stable. Otherwise, their baseline appointment was classified as when they had their first visit to the outpatient pre-LT clinic. Patients were eligible if they had an abdominal CT available within 6 months of their baseline dietetic appointment and excluded if they did not have cirrhosis or were being considered for retransplant or multiple simultaneous organ transplantation. Patients with overt HE ($\geq$ grade 2) as assessed by the treating hepatologist using the West Haven Criteria[25] were excluded from data collection due to the known impact this may have on the ability to perform physical assessments.[20]

Baseline clinical data

Electronic medical records were accessed to obtain clinical and laboratory data, including dietetics assessments and clinical outcomes. Baseline clinical data collection included age, sex, etiology of liver disease, presence of HCC, MELD score,[16] presence of ascites, and documented diagnosis of type 2 diabetes (T2D). Anthropometric assessments included weight in kilograms (digital scales, Tanita, Japan), height in centimeters (wall-mounted stadiometer), and body mass index (BMI; kg/m^2). If ascites were present, dry weight was estimated from the last weight post-paracentesis or by subtracting 5%, 10%, or 15% of total body weight for mild, moderate, or severe ascites, respectively. An additional 5% was subtracted if edema was present.[5] Malnutrition (well nourished, moderately or severely malnourished) was determined by the modified subjective global assessment for liver cirrhosis.[26]

Pretransplant and early posttransplant outcomes data

Pre-LT data included outcomes of receiving an LT and of having an unplanned hospital admission prior to LT. The duration of pre-LT involvement with the QLTS was collected, including the time to LT, or in those not proceeding to LT, when they were discharged from the service along with the reasons for not proceeding to LT. These reasons were grouped into 3 outcomes: (1) waitlist mortality (defined as death prior to LT or delisting/discharge due to disease progression, as previously defined),[27] (2) discharge due to an improvement in liver disease, and (3) other reasons (patient choice whereby the patient elected not to proceed to LT, relapse to drug or alcohol use or still awaiting LT at study endpoint).

If patients had an unplanned admission, the time to first unplanned admission was recorded. Indications for unplanned hospital admissions included (1) HE, (2) gastrointestinal bleeding, (3) fluid imbalance (both fluid overload and dehydration), (4) infection, or (5) other reasons. A diagnosis of infection required a clinical diagnosis based on the presence of symptoms, pathology results (blood/urine/ascites microscopy and culture, full blood count, biochemistry), and imaging that was treated with i.v. antibiotics. Other reasons for unplanned admission included bowel perforation; incarcerated umbilical hernia; hepatorenal syndrome; acute kidney injury; fevers with no other evidence of infection as defined above; severe coryzal symptoms; diarrhea; fecal loading; abdominal pain cause not identified, fractured neck of femur, and extensive thrombosis. Scheduled admissions for prebooked surgical or medical procedures, including paracentesis booked by the treating hepatologist for patients requiring regular paracentesis, were not included.

For patients who received an LT, collected data included the durations of intensive care unit (ICU), total hospital length of stay (LOS), and the presence of major surgical complications during their transplant admission.[28] ICU and hospital LOS were grouped into $\leq$4 days and $>$4 days and $\leq$18 days and $>$18 days, respectively, as per proposed benchmarks for LT.[29] Complications were categorized according to the Clavien-Dindo grading system for postoperative surgical complications.[28]

CT-defined sarcopenia

CT-defined sarcopenia was based on muscle mass assessment via abdominal CT using Slice-O-Matic V5.0 software (Tomovision, Montreal, Canada) by a trained clinician, as described.[30] In brief, the cross-sectional area of muscle at the superior-inferior midpoint of the third lumbar vertebra was measured.[17,25] Once the skeletal muscle area was determined, skeletal muscle index (SMI) was calculated by dividing skeletal muscle area by height in meters squared (cm^2/m^2). Sarcopenia was defined using cut-points specific to advanced liver disease (SMI $<$ 50 cm^2/m^2 for men and $<$ 39 cm^2/m^2 for women).[4,31]

EWGSOP-defined sarcopenia

Sarcopenia was also defined using the original EWGSOP1 and updated (EWGSOP2) criteria.[1,21] EWGSOP1-defined sarcopenia includes (1) CT assessment of low SMI, utilizing the abovementioned method and cut-points; and (2) the presence of either low hand grip strength (HGS) or poor physical function. HGS was

measured using a calibrated digital Jamar dynamometer. The highest measurement of 3 readings from the dominant hand was used for analysis. Low HGS was defined as per the EWGSOP criteria as <30 kg of force for males and <20 kg of force for females.[21] Poor physical function was identified using the short physical performance battery (SPPB).[32] A deficit in function was diagnosed if the SPPB score was $\leq 9/12$ as per liver cirrhosis literature.[33] According to EWGSOP1 criteria, the presence of low muscle mass alone is classified as pre-sarcopenia. Patients with all 3 components (low muscle mass, strength, and physical function) were classified as having severe sarcopenia.

EWGSOP2-defined sarcopenia involved an initial assessment for low muscle strength. HGS was measured using the method above, but low HGS was defined using updated cut-points of <27 kg of force for males or <16 kg of force for females.[1] If low HGS was present, sarcopenia was confirmed with CT using the methodology described above. Following this, physical function was assessed via SPBB, and if a score of $\leq 9/12$ was present, this was classified as severe sarcopenia. If low HGS was present, without low SMI, this was classified as pre-sarcopenia.

Data analysis

Descriptive analyses were used with demographic and clinical variables. Data are presented as n (%), mean $\pm$ SD for normally distributed data, or median (IQR). Normality was assessed using Shapiro Wilks test with visual interpretations of normality plots. For statistical analysis of EWGSOP1 and 2 criteria, sarcopenia was grouped into sarcopenia, including severe sarcopenia, versus no sarcopenia, including pre-sarcopenia. For CT-defined sarcopenia, this was either present or not present. χ^2 tests or Fisher exact tests (categorical) and Mann-Whitney *U* tests (continuous) were used to separately explore associations between receiving an LT or not, pre-LT unplanned admissions, surgical complications during the transplant admission as well as LOS in ICU and hospital for this admission. Univariable and multivariable binary logistic regression analyses were individually performed for the 3 sarcopenia definitions with the above clinical outcomes, described as adjusted odds ratios (aORs) with 95% CI. Multivariable analyses were adjusted for age, sex, presence of HCC and MELD score, and presence of ascites as potential confounders.

Survival analysis of the primary outcomes included competing risk analysis with cumulative incidence curves. This examined the relationship with each of the sarcopenia definitions and time from baseline clinic appointment until (1) LT and (2) first unplanned admission pre-LT using the confounders of age, sex, MELD score, presence of ascites, and HCC presence. Fine-Gray competing risk analysis was performed with waitlist mortality, discharge from the service due to improvement in liver disease, or discharge from the service for other reasons for not proceeding to LT as competing risks. These competing risk estimates were described as subhazard ratios (sHRs), with 95% CIs. A Cox regression analysis was performed to determine the risk of waitlist mortality for the 3 separate sarcopenia definitions.

To assess the predictive utility of the 3 separate sarcopenia definitions, the AUROC was calculated. The AUC for the 3 sarcopenia definitions was used independently as well as in addition to the MELD score, to determine if any of the definitions added value in predicting unplanned hospital admissions or the likelihood of receiving a LT. The DeLong test was performed to assess if the AUC models were significantly different from one another. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value analyses were also conducted to determine the best diagnostic accuracy of the definitions independently, as well as the added value of each definition to the MELD score. Statistical analyses were carried out using IBM SPSS Statistics, version 28.0 (IBM: IBM Corp) and R Statistical Software (v4.1.2; R Core Team 2021). Significance was set at $p < 0.05$.

RESULTS

Demographic and clinical characteristics of patients with sarcopenia assessment

From a total of 274 potential candidates of LT assessed (2 patients assessed as inpatients), 237 patients had a valid CT available and were included in the study. There were no significant differences across demographic or clinical characteristics for those who did and did not have a CT available for sarcopenia assessment (Supplemental Table S1, http://links.lww.com/HC9/B974). From this total, 235 had complete data for the EWGSOP1- and 2-definitions for sarcopenia (n = 2 had either missing HGS or SPPB data to complete sarcopenia diagnosis). As seen in Table 1, the median age (IQR) was 58 (50–62) years, and 75% of the patient group was male. Alcohol-associated liver disease was the most prevalent underlying etiology, followed by chronic viral hepatitis. Fifty-nine percent of the cohort (139/237) received an LT. Of the remaining patients, 23% were in the waitlist mortality group, 9% were not transplanted as their liver disease improved, and 10% left the service for other reasons or were still awaiting LT at the end of the study.

Sarcopenia prevalence

The prevalence of CT-defined sarcopenia was highest at 52%, followed by 22% for EWGSOP1-defined

TABLE 1 Demographic and clinical characteristics of the total cohort with sarcopenia assessment

	Study population (n = 237) n (%), mean ± SD or median (IQR)
Age (y)	58 [50–62]
Sex, male	177 (75)
MELD score	16 [11–20]
Estimated dry weight (kg)	83 [71–98]
BMI kg/m^2	27 [24–32]
BMI categories (based on estimated dry weight[a])	
Underweight (≤ 18.49 kg/m^2)	7 (3)
Healthy weight (18.5–24.9 kg/m^2)	76 (32)
Overweight (25-29.9 kg/m^2)	79 (33)
Obese (≥ 30 kg/m^2)	75 (32)
Etiology of liver disease	
Alcohol-associated liver disease	91 (38)
Chronic viral hepatitis (HCV/HBV)	54 (23)
MASLD	41 (17)
PBC/PSC	32 (14)
AIH	5 (2)
Cryptogenic	3 (1)
Other[c]	11 (5)
Those with HCC	69 (29)
T2D	60 (25)
Ascites present	83 (35)
Edema present	76 (32)
SGA score	
A (well nourished)	158 (67)
B (moderately malnourished)	70 (29)
C (severely malnourished)	9 (4)
SPPB score (n = 232)[b]	
Score out of 12	11 [9-12]
SPPB deficit (≤ 9/12 = deficit in function)	75 (32)
Hand Grip Strength (kg of force)	33 ± 10

[a]Dry weight was estimated from post-paracentesis weight if available, otherwise or by subtracting 5%, 10%, or 15% of total body weight for mild, moderate, or severe ascites, respectively, as described.[5] An additional 5% was subtracted for bilateral pedal edema.
[b]5 patients did not have SPPB complete.
[c]Other causes of liver disease: hepatic sarcoidosis, alpha1-antitrypsin deficiency, Budd-Chiari cirrhosis.
Abbreviations: AIH, auto-immune hepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SGA, subjective global assessment; SPPB, Short Physical Performance Battery; T2D, type 2 diabetes.

sarcopenia, while EWGSOP2-defined sarcopenia was present in 11% of patients. Using EWGSOP1 criteria, 29% of patients had pre-sarcopenia (low SMI only), while using EWGSOP2, 3% had pre-sarcopenia (low HGS only). Supplemental Table S2, http://links.lww.com/HC9/B975, details the various prevalence rates for presarcopenia, sarcopenia, and severe sarcopenia across the 3 definitions.

Various clinical characteristics of those with and without sarcopenia using the 3 criteria for sarcopenia were explored (Table 2). For CT-defined sarcopenia there were significantly higher prevalence of sarcopenia in males versus females (56% vs. 40%, $p = 0.03$), and nonobese versus obese patients (65% vs. 25%, $p < 0.001$). Related to this, patients with CT-defined sarcopenia had a lower BMI than those without (dry BMI 25 [22–28] kg/m^2 vs. 30 [26–34] kg/m^2, $p < 0.001$), with a similar finding when EWGSOP1 criteria were used to diagnose sarcopenia (dry BMI 25 [23–30] kg/m^2 with vs. 28 [24–32] kg/m^2 without EWGSOP1-defined sarcopenia, $p = 0.02$).

Using EWGSOP1- and EWGSOP2-criteria, the prevalence of sarcopenia was higher in malnourished versus well-nourished patients (39% vs. 15% $p < 0.001$ when EWGSOP1-criteria were used; 20% vs. 6%, $p < 0.001$ for EWGSOP2). MELD scores were higher in patients with sarcopenia versus those without (18 [15–23] in those with sarcopenia diagnosed with EWGSOP1 criteria versus 15 [10–18] in those without, $p < 0.001$; and 20 [16–24] in those with EWGSOP2-defined sarcopenia versus 15 [10–19] in those without, $p < 0.001$). There the prevalence of sarcopenia using EWSOP criteria was generally lower in patients with HCC versus those without (using EWGSOP1-criteria, the prevalence of sarcopenia was 12% in patients with HCC vs. 26% in those without, $p = 0.02$; while with EWGSOP2-criteria these figures were 4% vs. 13%, $p = 0.04$).

Sarcopenia and clinical outcomes

Tables 3, 4, and 5 show the univariable and multivariable binary logistic regression analyses for each of the 3 sarcopenia definitions and clinical outcomes.

Sarcopenia and the likelihood of receiving a liver transplant, having an unplanned admissions pretransplant or waitlist mortality

During a median of 133 (IQR 77–224) days of person follow-up 139 patients (59%) received a liver transplant, while 97 patients (41%) had an unplanned hospital admission. Supplemental Figures S1–5, http://links.lww.com/HC9/B973 demonstrate the cumulative incidence curves for those with and without sarcopenia using the 3 sarcopenia definitions.

Table 6 presents the results of the Fine-Gray competing risk analyses. We found that no sarcopenia definition was statistically significantly associated with time to liver transplant or with time to unplanned hospital admissions pretransplant after competing risks were

TABLE 2 Associations between sarcopenia (CT, EWGSOP1, and EWGSOP2 defined) and various clinical characteristics

	n = 237			n = 235			n = 235		
Characteristic grouping	**CT-defined sarcopenia n (%)**	**No sarcopenia n (%)**	***p* n (%)**	**EWGSOP1 Sarcopenia n (%)**	**No sarcopenia n (%)**	***p* n (%)**	**EWGSOP2 sarcopenia n (%)**	**No sarcopenia n (%)**	***p* n (%)**
HCC	35 (29)	34 (30)	—	8 (16)	61 (33)	—	3 (12)	66 (31)	—
No HCC	88 (72)	80 (70)	0.8	43 (84)	123 (67)	**0.02**	22 (88)	144 (69)	**0.04**
Male	99 (81)	78 (68)	—	41 (80)	135 (73)	—	20 (80)	156 (74)	—
Female	24 (19)	36 (32)	**0.03**	10 (20)	49 (27)	0.31	5 (20)	54 (26)	0.53
Well nourished	75 (61)	83 (73)	—	20 (39)	136 (74)	—	9 (36)	147 (70)	—
Malnourished	48 (39)	31 (27)	0.1	31 (61)	48 (26)	< **0.001**	16 (64)	63 (30)	< **0.001**
Liver transplant	75 (61)	64 (56)	—	25 (49)	112 (61)	—	13 (52)	124 (59)	—
No liver transplant	48 (39)	50 (44)	**0.45**	26 (51)	72 (39)	**0.13**	12 (48)	86 (41)	0.50
Obese BMI ≥ 30 kg/m^2	19 (15)	56 (49)	—	12 (24)	63 (34)	—	7 (28)	68 (32)	—
Nonobese < 30 kg/m^2	104 (85)	58 (51)	< **0.001**	39 (76)	121 (66)	0.15	18 (72)	142 (68)	0.66
BMI (kg/m^2)	25 [22–28]	30 [26–34]	< **0.001**	25 [23–30]	28 [24-32]	**0.02**	25 [22-32]	27 [24-32]	0.1
MELD score	16 [11-19]	15 [11-19]	0.3	18 [15-23]	15 [10–18]	< **0.001**	20 [16–24]	15 [10–19]	< **0.001**
Age (y)	59 [50–62]	58 [50-63]	0.7	59 [51-62]	58 [50–62]	0.8	59 [52-62]	58 [50–62]	0.9

Bold values indicate statistically significant.

Abbreviations: BMI, body mass index; EWGSOP1, European Working Group on Sarcopenia in Older People original criteria; EWGSOP2, European Working Group on Sarcopenia in Older People updated criteria; T2D, type 2 diabetes.

TABLE 3 Binary logistic regression analysis (univariable and multivariable) for CT-defined sarcopenia (independent variable) with pretransplant unplanned admissions and posttransplant surgical complications, and length of stay

	Univariable analysis				Multivariable analysis	
	Yes n (%)	No n (%)	aOR (95% CI)	*p*	aOR (95% CI)	*p*
CT-defined sarcopenia n = 237[a]	123 (52)	114 (48)				
Pretransplant unplanned hospital admissions[a] n = 97	54 (44)	43 (38)	1.29 (0.77–2.17)	0.33	1.05 (0.59–1.87)	0.89
Recipients of LT n = 139 Early posttransplant complications[b]	75 (54)	64 (46)				
Grade ≥ 3 post-op complication	39 (52)	32 (50)	1.08 (0.56–2.11)	0.81	1.02 (0.50–2.07)	0.96
ICU LOS > 4 d	5 (7)	8 (13)	0.50 (0.15–1.61)	0.24	0.51 (0.15–1.72)	0.27
LOS > 18 d	11 (15)	19 (30)	0.40 (0.18–0.93)	0.03	0.39 (0.17–0.92)	0.03

Note: Multivariable analysis was adjusted for confounders of age, sex, presence of HCC, MELD score, and presence of ascites.
[a]Pretransplant unplanned admissions in 237 patients.
[b]Post-transplant surgical complications data is based on n = 139 and includes n = 2 patients who died at the time of transplant; LOS data are based on the remaining 137 patients.
Abbreviations: aOR, adjusted odds ratio; ICU, intensive care unit; LOS, length of stay.

taken into account. When exploring the impact of sarcopenia on waitlist mortality, all definitions demonstrated an increased risk of waitlist mortality. CT-defined (HR 1.32, 95% CI: 0.75–2.33, $p = 0.34$), EWGSOP-2 defined (HR 1.74, 95% CI: 0.81–3.76, $p = 0.16$); however, only patients with EWGSOP1-defined sarcopenia had a statistically significantly increased risk (HR 2.47 95% CI: 1.25–4.85) compared to those without sarcopenia ($p = 0.008$) as seen in (Figure 1).

Sarcopenia and early post-LT outcomes

Of those who received a transplant, 51% (71/139) of patients experienced a major surgical transplant complication, including 2 patients who died at the time of transplant. For the remaining 137 transplant recipients, the median LOS in the ICU was 1 (0.9–2) day, while LOS in the hospital during LT admission was 12 (9–17) days. Thirteen patients (9%) had an ICU LOS > 4 days, while 30 (21%) had a hospital LOS > 18 days. ICU and hospital LOS were not significantly different for those with or without sarcopenia, irrespective of the definition used. However, a relationship with LOS was only seen in patients who were sarcopenic using CT criteria who were less likely to have prolonged hospital LOS (> 18 d) at the time of LT (adjusted OR 0.39, 95% CI: 0.17–0.92), Table 3. A similar but not statistically significant trend was seen when sarcopenia was present using EWGSOP1 and 2 criteria (Tables 4 and 5, respectively).

The predictive utility of sarcopenia and likelihood of LT, and unplanned hospital admissions prior to LT

Supplemental Table S3, http://links.lww.com/HC9/B976, shows the comparisons of the AUC from the ROC, the sensitivity, specificity, the PPV, and negative

TABLE 4 Binary logistic regression analysis (univariable and multivariable) for EWGSOP1-defined sarcopenia (independent variable) with pretransplant unplanned admissions and posttransplant surgical complications, and length of stay

	Univariable analysis				Multivariable analysis	
	Yes n (%)	No n (%)	aOR (95% CI)	*p*	aOR (95% CI)	*p*
EWGSOP1-defined sarcopenia n = 235[a]	51 (22)	174 (78)				
Pretransplant unplanned hospital admissions n = 96[a]	27 (53)	69 (40)	1.88 (1.00–3.51)	0.04	0.90 (0.43–1.88)	0.78
Recipients of LT n=137 Early-posttransplant complications[b]	*25 (18)*	*112 (82)*				
Grade ≥ 3 post-op complication n = 69	17 (68)	52 (46)	2.45 (0.98–6.15)	0.06	2.52 (0.87–7.29)	0.09
ICU LOS > 4 d n = 13	1 (4)	12 (11)	0.36 (0.04–2.90)	0.34	0.31 (0.03–2.86)	0.30
LOS > 18 d n = 29	7 (28)	22 (20)	1.67 (0.62–4.51)	0.32	1.62 (0.52–5.12)	0.41

Note: Multivariable analysis was adjusted for confounders of age, sex, presence of HCC, MELD score, and presence of ascites.
[a]Pretransplant unplanned admissions in n = 235 patients.
[b]Posttransplant surgical complications data is based on n = 137 and includes n = 2 patients who died at the time of transplant; LOS data are based on the remaining 135 patients.
Abbreviations: aOR, adjusted odds ratio; EWGSOP1, European Working Group on Sarcopenia in Older People original criteria; ICU, intensive care unit; LOS, length of stay.

TABLE 5 Binary logistic regression analysis (univariable and multivariable) for EWGSOP2-defined sarcopenia (independent variable) with pretransplant unplanned admissions and posttransplant surgical complications, and length of stay

	Univariable analysis				Multivariable analysis	
	Yes n (%)	No n (%)	aOR (95% CI)	*p*	aOR (95% CI)	*p*
EWGSOP2-defined sarcopenia n = 235[a]	25 (11)	210 (89)	—	—	—	—
Pretransplant unplanned hospital admissions n = 96[a]	11 (44)	85 (41)	1.16 (0.50–2.67)	0.74	0.47 (0.18–1.25)	0.13
Recipients of LT n = 137 Early-posttransplant complications[b]	*25 (18)*	*112 (82)*	—	—	—	—
Grade ≥ 3 post-op complication	7 (54)	62 (50)	1.17 (0.37–3.67)	0.79	0.86 (0.24–3.09)	0.82
ICU LOS > 4 d	1 (8)	12 (10)	0.76 (0.09–6.40)	0.80	1.14 (0.11–11.62)	0.91
LOS > 18 d	2 (15)	27 (22)	0.64 (0.13–3.06)	0.64	0.54 (0.10–2.86)	0.54

Note: Multivariable analysis was adjusted for confounders of age, sex, presence of HCC, MELD score and presence of ascites.
[a]Pretransplant unplanned admissions in n = 235 patients.
[b]Posttransplant surgical complications data is based on n = 137 and includes n = 2 patients who died at the time of transplant; LOS data are based on the remaining 135 patients.
Abbreviations: aOR, adjusted odds ratio; EWGSOP2, European Working Group on Sarcopenia in Older People updated criteria; ICU, intensive care unit; LOS, length of stay.

predictive values for the predictive utility for the likelihood of LT and unplanned admissions. This investigated the 3 different sarcopenia definitions independently and in combination with the MELD scores to determine if the addition added to the predictive utility of MELD.

The 3 sarcopenia definitions all performed poorly in identifying patients at risk of not receiving an LT. All AUCs indicated a weak predictive performance. There was no improvement when the MELD was added. The De-long test (Supplemental Table S4, http://links.lww.com/HC9/B977) confirmed no sarcopenia definition was superior in identifying patients at increased risk of not proceeding to LT.

In relation to identifying patients at increased risk of unplanned hospital admissions, the 3 sarcopenia definitions individually showed moderate positive predictive value; however, AUC scores indicated overall weak predictive performance. When the definitions were combined with the MELD score, the PPV improved slightly (Figure 2), with the combination of MELD + EWGSOP2 criteria having the highest PPV (76%). AUCs across all definitions increased with the addition of the MELD, indicating good predictive performance (AUCs were 0.72 [95% CI 0.66–0.79] for CT-defined and similarly 0.72 [95% CI: 0.66–0.79] for EWGSOP1-defined with 0.73 [95% CI: 0.66–0.79] for EWGSOP2); however, this was not a clinically meaningful improvement over the AUC for MELD alone. The De-Long test indicated a superior albeit weak predictive power of EWGSOP1 in identifying patients at increased risk of unplanned admissions, but this lost significance when MELD was added (Supplemental Tables S3, http://links.lww.com/HC9/B976 and S4, http://links.lww.com/HC9/B977).

DISCUSSION

This is the first study to compare the prevalence of sarcopenia in patients referred for LT using CT and EWGSOP1 and 2 criteria, comparing the predictive utility of each for clinical outcomes. The first observation was the impact of the different sarcopenia criteria on the prevalence rates. CT-defined sarcopenia was present in over half of the patient cohort, more than twice the prevalence identified with EWGSOP1 and 4 times the number identified by EWGSOP2. The prevalence of CT-defined sarcopenia in the current study was similar to other advanced liver disease cohorts,[19,34] while the prevalence of sarcopenia using EWGSOP1 and 2 criteria is similar to another study in a population with cirrhosis,[35] and other chronic diseases.[36] Because both EWGSOP criteria require an additional measure of muscle strength beyond CT-defined low muscle mass, it is expected that there are lower prevalence rates as they represent a subset of those with CT-defined sarcopenia.

In the current study, the aim was to determine whether the additional rigor of the EWGSOP criteria was superior to CT-assessed low muscle mass–only approach in

TABLE 6 Competing risk analysis for receiving a liver transplant and unplanned admission across 3 sarcopenia definitions

Outcome	CT-defined sarcopenia sHR (95% CI)	*p*	EWGSOP1-defined sarcopenia sHR (95% CI)	*p*	EWGSOP2-defined sarcopenia sHR (95% CI)	*p*
Liver transplantation	1.18 (0.84–1.65)	0.33	0.66 (0.41–1.06)	0.09	0.80 (0.42–1.50)	0.48
Unplanned admissions	0.92 (0.61–1.39)	0.69	0.86 (0.49–1.49)	0.58	0.55 (0.26–1.18)	0.12

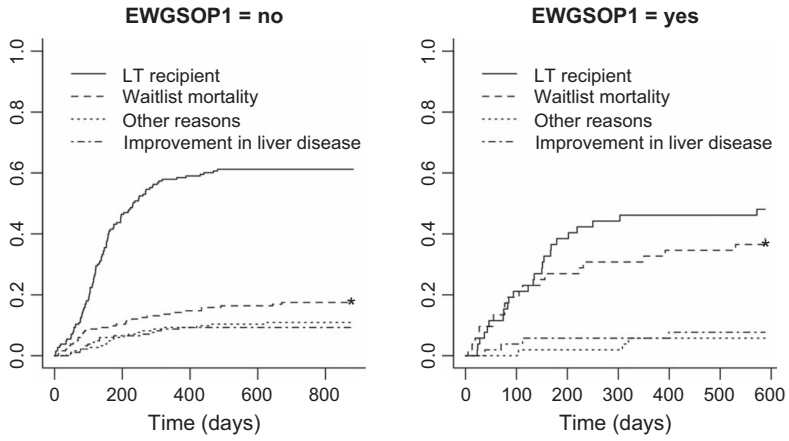

FIGURE 1 Cumulative incidence curves including competing risks for study end point of liver transplantation for those with and without EWGSOP1-defined sarcopenia. *sHR 2.72, 95% CI: 1.34–5.51, $p < 0.001$. Abbreviations: EWGSOP, European Working Group on Sarcopenia in Older People; LT, liver transplantation.

identifying patients at increased risk of adverse outcomes. This was examined in relation to 2 outcomes: the likelihood of receiving an LT, and the likelihood of experiencing an unplanned admission pre-LT. None of the 3 sarcopenia definitions demonstrated significantly increased risks for these 2 outcomes in competing risk analysis. Additionally, the predictive utility of each sarcopenia criteria was modest at best both on their own and when added to the MELD score.

Previous studies provide strong evidence that sarcopenia is linked to adverse outcomes in LT.[19] There is a complex interplay between sarcopenia, liver disease severity, physical frailty, and clinical outcomes that need to be better understood.[13,20] Metabolic

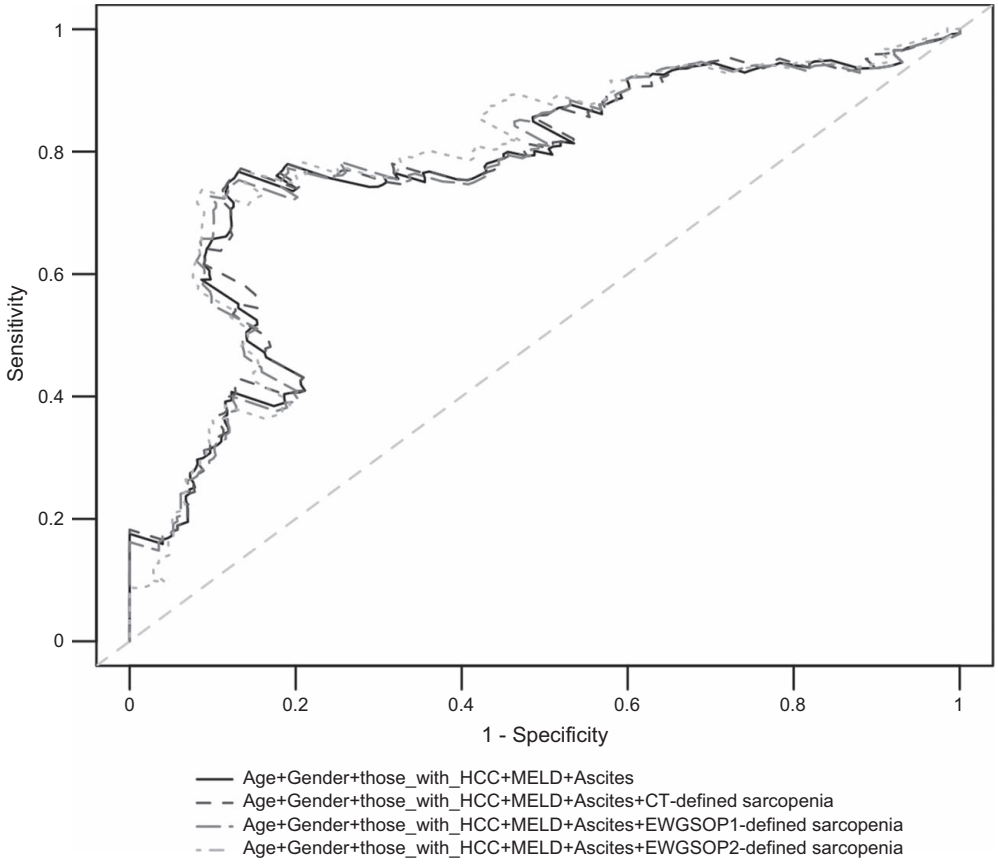

FIGURE 2 ROC analysis for unplanned admission predictions. The 4 lines indicate the AUROC with MELD alone and are adjusted to include each of the 3 sarcopenia definitions.

disturbances such as hyperammonemia influencing muscle protein synthesis and breakdown, and nutritional impairments in advanced liver disease are prevalent and contribute to reduced muscle mass. While the current study did not find predictive utility in using EWGSOP1 or 2 definitions of sarcopenia beyond that of CT diagnosis in relation to specific pre-LT outcomes, there were relevant associations with EWGSOP criteria. Patients with EWGSOP1 and 2 defined sarcopenia, but not CT-defined, were more likely to be malnourished and have significantly higher MELD scores than those without. This appears to be because the addition of measures of muscle function identifies patients with more severe disease and a greater likelihood of malnutrition. Patients with low muscle mass and impaired muscle function (EWGSOP1 and 2) were also less likely to have HCC. This may be related to the association between sarcopenia and more severe liver disease, as a significant proportion of patients referred for LT with the primary indication of HCC have relatively well-compensated cirrhosis. This further emphasizes a relationship between liver disease severity, nutritional status and physical performance.

There may be an issue with the cutoffs employed by the various criteria to define sarcopenia. While there are cut-points for CT-defined sarcopenia specific to advanced liver disease,[31] this is not the case for functional measures such as HGS. The EWGSOP criteria are validated in older community dwelling adults.[37] The translation into other chronic disease cohorts may require further refinement,[24] such as inclusions of muscle-specific strength (muscle strength/muscle size).[24,38] Younger patients referred for LT who do not have age-related muscle dysfunction would need to lose a disproportionately greater amount of muscle strength to meet low HGS criterion as recommended for EWGSOP2 criteria in particular. A small number of studies have provided recommendations for HGS cut-points in cirrhosis.[22,23,39] There is some support for the original EWGSOP1 HGS cut-point of <30 kg force for males, with an Australian study identifying a HGS of <30 kg as a strong predictor of LT waitlist mortality for men,[23] and a study from India identifying a HGS <31 kg of force as the optimal cut-point for screening sarcopenia in cirrhosis.[39] The EWGSOP2 criteria would miss a proportion of these male patients as it uses a cut-point of <27 kg of force for HGS. A study investigating the predictive utility of HGS alone in patients with cirrhosis, demonstrated a HGS of <19.5 kg of force (in males and females) saw an almost 8-fold higher mortality risk.[22] The EWGSOP2 HGS cut-points for women (<16 kg of force) would miss a proportion of these patients. While attempts have been made to determine the most appropriate HGS cut-point for LT cohorts[40,41] further research is needed for clinical translation.

There are some clinical benefits related to the different approaches used to diagnose sarcopenia in other settings. An advantage of using the updated EWGSOP2-criteria in clinical practice is that it provides an option for clinicians without access to CT/MRI, or in circumstances where this is contraindicated, to progress onto management if a patient has *probable* sarcopenia based on low HGS.[3] LT cohorts are unique in that cross-sectional imaging is frequently performed as part of LT surgical evaluation and for HCC monitoring (although muscle mass quantification is not typically reported in these scans in practice). Thus, diagnostic criteria modified to avoid unnecessary CT exposure are not as relevant in this population. An additional benefit in LT cohorts is that there is a large body of evidence demonstrating the relationship between CT-defined sarcopenia and patient outcomes.[13,20] Finally, in pre-LT patients, using CT-defined criteria provides an accurate and objective measure not influenced by acute illness or alterations in cognitive function such as HE, both of which could influence performance on functional assessments.

Our group has a long-term interest in nutrition and exercise interventions in liver disease.[15,42–45] An aim of the study was to determine the predictive utility of these established sarcopenia criteria in identifying patients referred for LT at increased risk of adverse clinical outcomes. The intention was for the information to potentially be used to improve outcomes by enhanced surveillance or potentially prehabilitation interventions. All 3 criteria used to define sarcopenia require cross-sectional imaging, which may be repeated for HCC management but is not necessarily part of the management algorithm for patients with decompensated disease who are the most unwell. The powerful influence of measures of muscle strength or function on clinical outcomes in advanced liver disease, independent of their use in EWGSOP-criteria, have been shown.[23,33,46] If intervening to ameliorate or reduce the impact of sarcopenia, accessible and repeatable measures are required, and in this case, functional measures such as HGS or the SPPB may still have a role.

The lack of observable significant associations between sarcopenia and clinical outcomes in this study could be due to 2 factors. While in large cohort studies, there is strong evidence of the impact of reduced muscle mass (CT-defined sarcopenia) on clinical outcomes, the utility of identifying sarcopenia for an individual patient is less clear. First, interactions between liver disease severity and comorbidities are likely to impact the outcome for an individual patient with sarcopenia. Second, the strict criteria used in the EWGSOP1, and 2 definitions of sarcopenia meant that there were a large proportion of patients who experienced adverse events were categorized as nonsarcopenic. Conversely, CT-defined sarcopenia was present in $>50\%$ of the study cohort and so

was not sufficiently discriminatory in identifying patients at increased risk.

We therefore acknowledge the limitations of the study. This was a single-center study of 237 patients, so may have been underpowered to identify some associations with the sarcopenia definitions, although our power analysis suggested otherwise. Nonetheless, we found very little evidence or even trends in the data to support the inclusion of EWGSOP-defined sarcopenia into the baseline assessment of patients referred for LT to identify those at increased risk of adverse outcomes. As a result of the study design, we only analyzed muscle mass and function at baseline during LT assessment. However, this was a deliberate decision as we wanted to determine the predictive clinical utility of diagnosing sarcopenia on a patient's first visit to the clinic. Additionally, due to the pragmatic nature of data collection within a clinical setting at a patient's first visit to the service, formal assessment of minimal and overt (grade 1) HE was not undertaken. This is an important area for future studies. Additionally, Future studies should consider examining the impact of changes in muscle strength or measures (specifically HGS and/ or SPPB) on patient outcomes.

CONCLUSIONS

The present study demonstrated that CT-defined sarcopenia is a prevalent issue in pre-LT populations. As expected, this method identifies a far greater proportion of pre-LT cohorts as sarcopenic compared to EWGSOP definitions. When evaluating the predictive utility of these individual sarcopenia definitions, none were superior in identifying patients at increased risk of adverse clinical outcomes. In pre-LT settings, abdominal CTs performed for surgical evaluation could offer an opportunity for objective measures of muscle mass to be incorporated into standard reporting of these scans. Further research is required to determine if simple bedside measures such as HGS would be useful in tracking the trajectory of patients and monitoring the effectiveness of interventions targeting sarcopenia. To facilitate this, future work to validate appropriate muscle strength cut-points for an advanced liver disease population is needed.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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