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Handgrip strength adds more prognostic value to the MELD score than imaging-based measures of muscle mass in men with cirrhosis

Marie Sinclair, Brooke Chapman, Rudolf Hoermann, Peter W Angus, Adam Testro, Thomas Scodellaro, Paul J Gow

1. Victorian Liver Transplant Unit, 145 Studley Road, Melbourne, Victoria, Australia 3084
2. Department of Medicine, The University of Melbourne, Victoria, Australia 3052

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Corresponding author: Dr Marie Sinclair

Victorian Liver Transplant Unit, 145 Studley Road, Melbourne, VIC, AUSTRALIA, 3084

Ph: (+613)94965353. Fax: (+613)94963487. Marie.sinclair@austin.org.au

Abbreviations

DEXA: dual energy X-ray absorptiometry

MELD: model for end-stage liver disease

CT: computerized tomography

HR: hazard ratio

L: lumbar vertebra

BMD: bone mineral density

LM: lean mass

APLM: appendicular lean mass

HU: Hounsfield unit

IQR: interquartile range

sHR: subdistribution hazard ratio

CI: confidence interval

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Background: Sarcopenia is associated with mortality in cirrhosis but there is no gold standard for its diagnosis. The comparative utility of different diagnostic methods is unknown.

Methods: This single centre observational cohort study followed 145 men referred for liver transplant evaluation between 2005 and 2012. Muscle mass was estimated by handgrip

strength, Dual Energy Xray Absorptiometry (DEXA) lean mass and single slice CT scan at the 4th lumbar vertebra. Recorded outcomes included time-to-death or liver transplantation.

Results: The median age was 54 years [47; 59] and median MELD score 17 [14; 23]. Of 145 men, 56 died, with a median time-to-death of 7.44 months [3.48, 14.16]. Seventy-nine men were transplanted, with median time-to-transplant of 7.20 months [3.96, 12.84]. Prevalence of sarcopenia differed between diagnostic modalities, being 70.3% using CT-measured muscle, 45.9% using handgrip strength and 38.7% using DEXA. For each modality, muscle mass was inversely associated with waitlist mortality: HR 0.94 [0.90; 0.98], p=0.002 for CT-muscle, HR 0.99 [0.99; 0.99], p=0.003 for DEXA and HR 0.94 [0.91; 0.98], p=0.002 for handgrip. These results retained significance independent of the MELD score. In predicting mortality, the handgrip strength-MELD bivariable Cox model was superior to a MELD-CT-muscle Cox model (p<0.001).

Conclusion: Handgrip strength combined with MELD score was the superior predictive model in this novel study examining three commonly employed techniques to diagnose sarcopenia in cirrhosis. Handgrip strength has additional potential clinical benefits as it can be performed serially without the radiation dose, cost and access issues attributable to CT and DEXA.

BACKGROUND

Sarcopenia is associated with elevated mortality risk in cirrhosis, particularly for males (1), but there remains no gold standard for its diagnosis. Most published literature reports height-adjusted CT-estimates of muscle wasting; either psoas muscle thickness or transverse muscle area at the L3 vertebrae (1, 2). CT-based estimates have the drawbacks of radiation exposure, cost and need for additional software to analyse images, and there is no clear protocol for serial imaging. Lean mass as measured by dual-energy x-ray absorptiometry (DEXA) has more recently been correlated with mortality (3) as a lower radiation-dose option with high reproducibility (coefficient of variation <0.3% (4)), but DEXA is difficult to access in some centres and is limited by its inability to distinguish muscle from water.

Various simple, non-invasive, low-cost assessments of functional muscle strength exist that can be performed at the bedside or during outpatient consultations. Proposed methods include frailty measures extrapolated from the geriatric literature such as the Fried Frailty Index or the Short Physical Performance Battery (5), the 6-minute walk test (6) and handgrip strength (7), each of which have been validated in cirrhosis as independent predictors of

mortality. Concerns exist regarding patient cooperation with frailty measures in cirrhosis, but a recent multi-centre study suggests that frailty maintains its mortality risk independently of numbers connection test >45 seconds and the presence of ascites (8).

This study aims to identify the sarcopenia tool that best predicts mortality, by reporting on the use of three commonly employed modalities and their respective prognostic abilities: L4 transverse CT, DEXA body composition and handgrip strength. We also aim to assess their prognostic ability in combination with the MELD score, given that a MELD-sarcopenia score may better predict waitlist mortality than the MELD score alone (9).

METHODS

This study represents the extension of a previously reported retrospective observational study examining the relationship between low testosterone and sarcopenia as measured by CT scan in men with cirrhosis (10). The examined cohort was identified from the database of the Victorian Liver Transplant Unit to retrieve records of all men referred for transplant evaluation between 2005 and 2012 who had a CT scan encompassing the L4 level and serum testosterone available at the time of transplant assessment. Serum biochemistry including MELD score was recorded at the time of transplant assessment, and patients were followed for the outcomes of death or transplantation.

The methods of this study are as described previously. Additional data from the time of assessment was manually retrieved and added to the initial dataset for the purpose of this study.

Measurement of muscle mass by CT scan

Quadruple phase Computerised Tomography (CT) is performed during transplant assessment to assess vasculature and liver parenchyma. Tomovision SliceOmatic software (version 5.0, Toronto, Canada) was used to reformat transverse CT scans at the L4 region into fat, muscle and bone planes using Hounsfield unit (HU) thresholds. The threshold of 0 to +100 HUs for identifying skeletal muscle was the most accurate and reproducible using this software version, which allowed for calculation of skeletal muscle area as previously described (11). Muscle area was adjusted for patient height as previously described in other cohorts, with a cut-off of 52.4cm²/m² used to diagnose sarcopenia (1, 11). This height-adjusted skeletal muscle area is expressed as cm²/m² and for the purpose of this paper will be referred to as

CT-muscle mass. All CTs were analysed by a single trained observer. Intra-observer variation in our cohort was less than 2% on multiple testings.

Measurement of muscle mass by DEXA scan

DEXA scans are routinely performed at our centre during transplant assessment. Bone mineral density (BMD) and total body composition (compartmental fat mass, lean mass (LM) and bone mass) are quantified automatically during DEXA scans. Scans were all performed at the Austin Hospital on a single machine using the Prodigy DEXA scanner (GE Lunar, Madison, WI). The software was upgraded 4 times during the study period (versions 5.0, 7.51, 9.30, 10.51 and 13.60). Patient height was recorded to allow adjustment for patient stature (12) and all muscle parameters reported in this study are height-adjusted. Appendicular lean mass (APLM=lean mass of arms + lean mass of legs) has been proposed as the most appropriate method in cirrhosis to minimise confounding by ascites (3). The previously reported cut-off for APLM of $<7.26\text{kg/m}^2$ for men was used to diagnose sarcopenia (13). For the purpose of this paper, APLM as measured by DEXA will be referred to as DEXA-muscle mass.

Handgrip strength

Handgrip strength was recorded in the patient's non-dominant hand and was the average of 3 attempts using a calibrated Jamar Hand Dynamometer. The most commonly used cut-off for sarcopenia in men is $<30\text{kg}$ (14).

Outcome measures

Date of death and date of transplant were retrieved from the existing liver transplant database

Statistical analysis

Descriptive statistics included median and interquartile ranges (IQR, 25th and 75th percentiles). Differences between two groups were analysed by means of non-parametric Wilcoxon rank sum test or chi-squared test in case of frequencies. Demographic tables were considered explanatory and not corrected for multiple testing. Correlations were based on Kendall's tau rank correlation.

Survival analysis was used to follow up patients until they had died, received a transplant, or their observation period had ended. Patients still alive were censored at the time their status

has last been confirmed. Patients who were transplanted were censored at the time of transplant.

Survival curves were derived according to the method of Kaplan-Meier. Analysis of predictive factors for mortality was conducted on all patients who died or were transplanted within a 2-year follow-up period and relied on cause specific hazards using Cox proportional hazards model. The assumption of proportional hazards was verified by means of Schoenfeld's test and plot. Statistical differences in frequencies were compared by log rank test. Classification accuracy was assessed with the integrated Brier score (range 0 to 1), and the discriminatory power with the concordance index (c index).

For competing predictors of interest, such as MELD score and muscle mass, both crude and adjusted hazard ratios were analysed to ascertain their independent significance. To compare outcomes of nested models sharing the same sample, a likelihood ratio test was used. To account for transplantation as a competing event with mortality, we also analysed competing risks and subdistribution hazards (sHR) using the method of Fine Gray (15). Two-sided P values < 0.05 conferred significance for all tests. The statistical software package R 3.5.1 for Mac with the added packages survival 2.43-3 and pec 2018.07.26 was used for the analyses (16-18).

RESULTS

Baseline demographics

Complete liver transplant evaluation including serum testosterone and single slice CT at the L4 level was performed for 145 men with cirrhosis and decompensated liver disease during the study period, out of a total of 370 men assessed for transplant. Baseline demographics are as previously described (10). The median age was 54 years [interquartile range, 47; 59] and median MELD score was 17 [14; 23]. The majority of patients had Child Pugh C cirrhosis (71.7%) with smaller numbers of Child Pugh B and A (21.4% and 6.9% respectively). Baseline demographics are displayed in Table 1

The median follow-up duration was 8.30 months [4.08, 14.16] with median time-to-transplant of 7.20 months [3.96, 12.84] and time to death of 7.44 months [3.48, 14.16]. Of the 145 men undergoing transplantation evaluation, 59 died, 79 were transplanted and 7 remain alive at last censor date in July 2018, 5 of whom were delisted, 1 who was rejected and 1 who remains active on the waitlist.

Prevalence of sarcopenia according to diagnostic method of sarcopenia

Using the previously described cut-off for CT-muscle mass of 52.4 cm²/m², the prevalence of sarcopenia was 70.3% (102/145). The median CT-muscle mass was 48.0 cm²/m² [43.8; 54.1]. Using the cut-off for sarcopenia for DEXA-muscle mass of <7.26kg/m², the prevalence of sarcopenia was 38.7% (46/119). The median DEXA-muscle mass was 7.52kg/m² [6.87; 8.36]. Using the cut-off for handgrip strength of <30kg, the prevalence of sarcopenia was 45.9% (50/109). The median handgrip strength was 30.9kg [25; 38].

Correlation between diagnostic methods of sarcopenia

CT-muscle mass correlated only moderately with DEXA-measured APLM (tau 0.41, p<0.001), with similar correlations observed for arms lean mass by DEXA (tau 0.39, p<0.001), legs lean mass by DEXA (tau 0.37, p<0.001) and total lean mass by DEXA (tau 0.38, p<0.001). The correlation between CT-muscle and handgrip strength was present but weak (tau 0.24, p<0.001). Handgrip strength was modestly correlated with DEXA-measured APLM (tau 0.34, p<0.001) and DEXA-measured arms lean mass (tau 0.39, p<0.001).

Patients meeting criteria for sarcopenia by any diagnostic method had an associated increased mortality risk

Patients with sarcopenia as defined by pre-established cut-offs for each method were more likely to die than those without sarcopenia. Transplant-free survival is displayed using Kaplan Meier curves in sarcopenic versus non-sarcopenic patients in Figure 1.

Univariable analysis for mortality (censored for transplant)

Factors associated with mortality were derived by Cox PH model using the continuous variables of the various muscle measurements and are displayed in Table 2. For each 1kg increase in handgrip strength, mortality was reduced by 6%, and for each 1 point increase in MELD score, mortality was increased by 11%.

Age was not associated with mortality. Handgrip strength was a numerically stronger predictor for mortality than any other factor, including MELD score (concordance 0.71± 0.09 for handgrip strength versus 0.67 ± 0.09 for MELD score). The superior predictive value of handgrip strength as compared to MELD was significant in a shared sample (likelihood ratio test, p< 0.001).

Multivariable model including MELD score

Given the significant findings on univariable analysis, bivariable models including MELD score were studied to assess whether the impact of sarcopenia was independent of severity of liver disease. We found that muscle contributed independent significant mortality risk to MELD using multivariable Cox models and this was true for each individual measure of muscle mass or function. Adjusted hazard ratios are reported in Table 3.

In predicting mortality (time-to-death as a continuous variable) in the shared sample where both CT scan and handgrip strength were performed (n=109), the handgrip strength-MELD bivariable Cox model was superior to a MELD-CT Cox muscle model (likelihood ratio test, $p < 0.001$)

Looking at the binary outcome (discrimination) of pre-transplant mortality within 12 months, classification accuracy for MELD-handgrip strength was comparable to MELD-CT muscle overall in classifying events and non-events (Brier score 0.151 versus 0.154), but MELD-handgrip strength had the highest concordance as a model (0.73 as compared to 0.63 for the MELD-CT model), but this difference was not statistically significant ($p = 0.16$).

MELD score was associated with chance of transplantation, but muscle mass was not

There was no significant association between any of the muscle measures and chance of transplantation. MELD score was significantly associated with transplantation (HR 1.05 [1.01; 1.09], $p = 0.007$).

Competing risk analysis

When taking the competing risks of mortality with the event of transplantation into account, as shown in Figure 2, patients with sarcopenia had a higher subdistribution mortality risk, although their chances of receiving a transplant were similar.

DISCUSSION

This study for the first time examines the relative prognostic value of three commonly employed measures of muscle in men waitlisted for liver transplantation. We demonstrate for the first time that handgrip strength used in combination with MELD score was the best

predictor of waitlist mortality. This was significantly superior to a model incorporating muscle as measured by transverse CT scan, which has more commonly been reported in sarcopenia studies in this cohort. Our findings suggest that functional muscle strength may be a more accurate predictor of mortality than muscle mass in this population.

This study confirms what is now well-established in the literature: that a single measure of reduced muscle mass or function is an independent risk factor for mortality in men with cirrhosis. We identified a widely ranging prevalence of sarcopenia using the standardised cut-offs for sarcopenia, from 38.7% using DEXA to 70.3% using single slice CT. Despite these differences, sarcopenia by each of the three techniques correlated with waitlist mortality. Previously published studies demonstrating such a link have examined the 6-minute walk, handgrip strength, short physical performance battery, subjective global assessment, psoas muscle thickness on CT, transverse muscle area on CT, and DEXA lean mass measures (1-3, 5, 6, 19). This study is unique in its analysis of different diagnostic methods in a single cohort of patients, with most previous studies employing single slice CT scans at the L3 level (1, 9, 20, 21).

A major advantage of studying different diagnostic methods in a single cohort is to assist in selecting the most accurate but also the most appropriate diagnostic method of sarcopenia. There is a clinical need for a frequently reproducible diagnostic method for sarcopenia, as the majority of patients awaiting liver transplant demonstrate a progressive deterioration in muscle function, and this deterioration itself is associated with increased mortality (22, 23). Early identification of this decline would allow for implementation of more aggressive nutritional therapies and more frequent medical assessments, as well as adding important prognostic information. Given recent studies have suggested that a MELD-sarcopenia score could better predict waitlist mortality as compared to the MELD score alone (9, 24), the allocation of organs may be improved by incorporating a measure of muscle mass or function into the MELD score. Such a measure would need to be performed on a regular basis at the same time as the MELD score to allow for a dynamic assessment of patient risk and subsequent adjustment of waitlist priority. Validated serial measures of muscle would also aid in the development of clinical trials of future sarcopenia therapies.

In our study, although patients with sarcopenia were significantly more likely to die pre-transplant, muscle strength was similar in transplanted and non-transplanted individuals,

reflecting that these patients were not prioritised for transplantation. This contrasts with MELD score which was higher in both transplanted patient and patients who died, in keeping with current guidelines that use MELD or MELD-Na alone to prioritise patients for transplantation, and do not take into account muscle wasting. Some studies have reported that sarcopenia may also predict post-transplant length of stay, infection and mortality (11), hence prior to consideration of a MELD-sarcopenia score it must be established whether there is a point below which muscle wasting or weakness is so severe that transplantation becomes futile. An easily reproducible measure of muscle mass would therefore also be useful to perform large-scale observational studies in waitlisted cirrhotics to follow both pre- and post-transplant outcomes that would add further value to this current study using only a single point-in-time measurement. This would ultimately allow for allocation of organs to those for whom there would be most benefit.

Computerised tomography is poorly suited to serially measurements given its radiation dose and associated cost and is therefore unlikely to be incorporated into a MELD-sarcopenia score. DEXA scans expose the patient to minimal radiation and have a high accuracy with a coefficient of variation <0.3% (25), but still incur cost and availability is not widespread. Furthermore, DEXA lean mass cannot differentiate fluid from muscle so oedema can falsely elevate readings, which may explain why DEXA lean mass appeared to underestimate the prevalence of sarcopenia in this cohort (at only 38.7%). Given the superiority of the handgrip-MELD predictive model, handgrip strength may therefore be the most appropriate diagnostic tool to improve clinical decision making in cirrhotics. It can be performed at the bedside or during an outpatient consultation in a matter of minutes without additional risk or cost and has been well validated in previous cirrhotic populations as a predictor of mortality (7, 19).

In the geriatric literature reduced handgrip strength is also strongly associated with mortality (26), and similarly appears to be a better predictor of outcomes than imaging measures of muscle mass (27). Muscle function may therefore universally be a more clinically useful tool than muscle mass, which is plausible given that many imaging-based modalities cannot comment on muscle quality and muscle mass correlates only modestly with muscle strength (28). Muscle strength also tends to decline prior to muscle wasting (29), hence handgrip strength will identify patient deterioration earlier than imaging-based methods. The limitation to muscle function assessment is the requirement for patient cooperation and

susceptibility to fluctuations in the context of acute illness, however our experience is that serial handgrip strength monitoring can be performed reliably in patients awaiting transplant. A multi-centre study of cirrhotics in the United States also found that functional measures of frailty retain their significance independent of the presence of encephalopathy or ascites (8). Whether concerns regarding the objectivity and reproducibility of functional methods will limit their use for a possible MELD-sarcopenia score remains unknown.

The strengths of this study include the comprehensive analysis of muscle mass and function using different methodologies, and the complete observation to death, transplantation or delisting in all patients. Limitations include our modest sample size, but despite this we were still able to demonstrate statistically significant associations between each modality and mortality, and demonstrate superiority of the MELD-handgrip strength predictive model as compare to MELD-CT. The inclusion of only patients who had an available CT may further undersell the value of handgrip strength, which can be performed in all patients on a frequent basis, without concern for cost, radiation and accessibility, and is indeed performed in every one of our patients undergoing transplant assessment on a 1 to 3 monthly basis. We also analysed only men; thus these findings are not generalizable to women. Repeating a similar study in a larger population including men and women across multiple centres would further validate our results, and ideally a comparison should be performed with other functional measures of muscle strength such as the Liver Frailty Index, which has specifically been shown to have value in women as well as men (8). Analysis of post-transplant outcomes would also be a valuable target of future research to identify whether severe sarcopenia should preclude patient from transplant.

In conclusion, we report for the first time on the use of three common methods of measuring muscle mass and function in a cohort of men with cirrhosis on the liver transplant waitlist. For the first time, we have shown that a model using handgrip strength in combination with MELD appears to be the best predictor of waitlist mortality. Given that handgrip strength is simple, cheap and can be performed serially, we propose it as the method of choice for monitoring sarcopenia in cirrhotics awaiting liver transplant. Future large-scale studies are required to assess the potential benefit of a MELD-handgrip strength score in improving organ allocation, as well as identifying whether a threshold exists below which transplant may be futile.

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Table 1

Child Pugh score:	
A	6.9%
B	21.4%
C	71.7%
MELD score	
≤12	14.5%
13-19	44.8%
≥20	40.7%
Age	
Median	54 years
Interquartile range	47 to 59 years
BMI	
Median	25.7kg/m ²
Interquartile range	23.3 to 30.4kg/m ²
Hepatoma:	
Yes	27.6%
No	72.4%

Cirrhosis aetiology:	
Hepatitis C	43.4%
Alcohol	17.9%
Hepatitis B	8.3%
PSC	10.3%
NASH	6.9%
Other	13.2%

Table 2. Univariable analysis for mortality

	HR [95% CI]	P value	Concordance (CI)
Handgrip strength (kg) n=109	0.94 [0.91; 0.98]	0.002	0.71± 0.09
DEXA-muscle (kg/m ²) n=119	0.99 [0.99; 0.99]	0.003	0.68 ± 0.09
MELD score n=145	1.11 [1.06; 1.16]	<0.001	0.67 ± 0.09
Serum sodium (mmol/L) n=145	0.94 [0.88; 0.99]	0.04	0.62 ± 0.10
CT-muscle (cm ² /m ²) n=145	0.94 [0.90; 0.98]	0.002	0.65 ± 0.08
Testosterone (nmol/L) n=145	0.93 [0.87; 0.98]	0.008	0.66 ± 0.08

Hazards Rates (HR) were derived by Cox PH model.

HR: hazard rate. CI: confidence interval. DEXA: dual energy x-ray absorptiometry. MELD: model for end-stage liver disease score. CT: computerized tomography.

Table 3. Bivariable MELD-muscle models for transplant-free survival

Model	Variable	Adjusted HR [IQR]	p value
CT-muscle and MELD	MELD score	1.09 [1.05; 1.14]	<0.001
	CT scan (cm ² /m ²)	0.95 [0.91; 0.99]	0.02
DEXA-APLM and MELD			

	MELD score	1.11 [1.05; 1.17]	<0.001
	DEXA-APLM (kg/m ²)	0.99 [0.99; 0.99]	0.008
Handgrip strength and MELD			
	MELD score	1.08 [1.02; 1.15]	<0.001
	Handgrip strength (kg)	0.95 [0.91; 0.99]	0.007

Legend: CT: computerized tomography, DEXA: dual energy x-ray absorptiometry, APLM: appendicular lean mass, MELD: model for end-stage liver disease, kg: kilograms, m²: metres squared, HR: hazard ratio, IQR: interquartile ratio

Figure 1. Transplant-free survival is reduced in patient with sarcopenia

Legend: Kaplan Meier curves demonstrate survival in sarcopenic and non-sarcopenic individuals as measured by (a) CT-muscle <52.4 (cm²/m²) (b) DEXA-muscle (appendicular lean mass) <7.26 (kg/m²) and (c) Handgrip strength <30 (kg).

Figure 2. Cumulative incidence curves for the competing risk of mortality versus transplant for sarcopenia according to handgrip strength (A) and MELD score (B).

Legend: sHR: subdistribution hazard, HGDS: handgrip strength, MELD: model for end-stage liver disease, CIC: cumulative incidence curves