DR. MARIE SINCLAIR (Orcid ID : 0000-0003-0657-3048)

DR. PENELOPE HEY (Orcid ID : 0000-0002-5219-0382)

MS. BROOKE CHAPMAN (Orcid ID : 0000-0002-7251-8314)

Article type : Original Articles

Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk

Marie Sinclair^{1, 2}, Rudolf Hoermann², Adam Peterson², Adam Testro^{1, 2}, Peter W Angus^{1, 2}, Penelope Hey^{1, 2}, Brooke Chapman^{1, 2}, Paul J Gow^{1, 2}

1. Austin Hospital Liver Transplant Unit, VIC, 3084
2. University of Melbourne, Department of Medicine, Parkville, VIC 3000

Corresponding author:

Dr Marie Sinclair, Austin Hospital Liver Transplant Unit, Heidelberg, VIC, AUSTRALIA, 3084, pH (03)94965353, fax (03)94963487, marie.sinclair@austin.org.au

This work was supported by a NHMRC Early Career Fellowship awarded to Dr Marie Sinclair

No co-authors have conflicts of interest or financial disclosure to report

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/LIV.14071](https://doi.org/10.1111/LIV.14071)

This article is protected by copyright. All rights reserved

Project formulated by Marie Sinclair and Paul Gow. Data collection performed by Adam Peterson and statistics by Rudolf Hoermann. All authors collaborated in writing, editing and approved final manuscript

Abstract: 246 words

Manuscript: 3467 words

Tables: 2

Figures: 4

Abbreviations: DEXA (dual energy x-ray absorptiometry), MELD (model for end-stage liver disease), OR (odds ratio), BMD (bone mineral density), LM (lean mass), APLM (appendicular lean mass), TLM (total lean mass), HR (hazard ratio), sHR (subdistribution hazard ratio)

ABSTRACT

Introduction: Reduced muscle area on CT scan is an independent predictor of mortality in cirrhosis. We examine for the first time the relationship between Dual Energy X-ray Absorptiometry (DEXA) lean mass parameters on outcomes in cirrhotic men awaiting liver transplantation.

Materials and Methods: We retrospectively reviewed DEXA scans performed during transplant assessment between 2001 and 2016. Baseline data including presence of ascites and MELD score were recorded. DEXA lean mass measures were adjusted for height. The primary outcome was 12-month waitlist mortality.

Results: 420 men with median age 55.4 years [interquartile range 49.2; 59.4] and MELD 16 [12; 20] were studied. Median follow-up was 58.5 [28.8; 109] months. 12-month waitlist mortality was 12.4%. Appendicular lean mass was inversely associated with mortality (HR 0.78 [0.62; 0.98], $p=0.03$). Lean mass of arms (HR 0.37 [0.16; 0.83], $p=0.02$) rather than legs (HR 0.77 [0.58; 1.03], $p=0.08$) was responsible for this association. Upper limb lean mass showed a significant interaction with MELD score in predicting waitlist mortality, particularly within 4 months. Total lean mass was not associated with mortality but increased in conjunction with increasing ascites (OR for ascites 1.20 [1.15; 1.25], $p<0.001$ for each unit increase in MELD).

Conclusion: Upper limb lean mass by DEXA is strongly associated with mortality in men awaiting liver transplantation. The superiority of upper limb lean mass likely relates to confounding of lower limb measures by fluid retention. This DEXA parameter represents a novel and reproducible measure of sarcopenia in cirrhosis.

Abstract word count: 243

Key words: DEXA, sarcopenia, cirrhosis, mortality

LAY SUMMARY

Muscle wasting is associated with increased risk of death in liver disease, but the best method for measuring muscle is unknown. This study identifies a safe, accurate and reproducible measure of muscle in men with liver disease, employing technology more traditionally used to measure bone strength. Reduced muscle mass of the arms by this technique was associated with an increased risk of death.

-

INTRODUCTION

Sarcopenia is common in cirrhosis and increases in prevalence with advancing severity of liver disease (1, 2). Sarcopenia is now a well-established risk factor for adverse outcomes in patients awaiting liver transplantation (3). However, there is still no gold standard for its diagnosis. Height-adjusted muscle area at the L3 level on CT scan is the most widely employed measure to quantify muscle mass in cirrhotics. Utilising this method sarcopenia has been linked with increased pre-transplant mortality, pre and post-transplant infection risk, and post-transplant hospitalization (4-6). However, the associated radiation dose limits the appeal of serial CT scans to measure change in muscle mass over time and analysing scans requires specialized computer software.

Dual energy x-ray absorptiometry (DEXA) is frequently performed in cirrhotic patients to assess bone mineral density (BMD), as cirrhotic osteodystrophy remains common (7). DEXA body composition scans can be performed simultaneously with no additional time or radiation. This creates a comprehensive, compartmentalized, 3-dimensional assessment of

the whole body, stratified into bone mass, fat mass and lean mass (LM) and allows assessment of functionally important muscle groups and individual body compartments.

The chief limitation of DEXA is its inability to differentiate muscle from water. This may be responsible for the finding from one study that DEXA can underestimate sarcopenia in cirrhosis (8). However, other groups reported that DEXA is a useful measure to quantify sarcopenia even in the presence of ascites (9). The use of appendicular lean mass (APLM) (sum of the LM of arms and legs) as opposed to total lean mass (TLM) has been proposed to minimize confounding by ascites (10). However, this measurement may still be impacted by lower limb oedema. Our group previously demonstrated the utility of serial DEXA measurements to assess the anabolic effect of testosterone therapy in men with cirrhosis (11). Treatment group subjects demonstrated a significant increase in DEXA-quantified APLM, TLM and bone mass, with a corresponding reduction in fat mass.

In this study, we aimed to differentiate the relative clinical utility of individual components of DEXA LM in assessing risk of mortality in cirrhotic men awaiting liver transplantation to identify the most suitable location for measuring sarcopenia in men awaiting liver transplantation.

MATERIALS AND METHODS

This study is a retrospective analysis of prospectively collected data in a longitudinal cohort of patients assessed for liver transplantation. Subjects were assessed at a single tertiary centre in Melbourne, Australia from September 2001 to November 2016. The variable of interest was lean mass (LM), as an indicator of sarcopenia, measured in all body compartments using DEXA whole body composition performed during work-up for the primary purpose of bone mineral density assessment. This study was approved by the Human Research Ethics Committee, Austin Health.

Patients

Inclusion criteria

This study was confined to men given they comprise the majority of transplant referrals in our centre (>80%), and the data pertaining to sarcopenia and mortality is strongest in males

(3). All men over 18 years who proceeded to formal transplantation assessment in the study period were included.

Exclusion criteria

Patients without DEXA body composition were excluded. DEXA was not performed during work-up for fulminant liver failure or rapid decompensation (including acute-on-chronic liver failure) as was deemed to be clinically inappropriate as our DEXA scanner is off-site. These patients represent a different cohort of patients who we believe should be excluded from this study regardless given the acute nature of their illness. A further 3 patients were excluded due to the unavailability of blood tests to calculate a Model for End Stage Liver Disease (MELD) score within a 4-week window of assessment and 1 further patient was excluded due to being lost to follow-up shortly after transplant assessment.

Baseline investigations

Routine biochemistry including bilirubin, creatinine and international normalized ratio (INR) to calculate MELD score was performed in-house at Austin Hospital within 4 weeks of the baseline DEXA scan. Most commonly (>85%), all investigations were performed in a 3-day window period. All results are expressed in international scientific units (SI). Quoted MELD scores are native and unadjusted.

Demographics

Age and disease aetiology were recorded for all subjects.

Body composition

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 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 (8) and all parameters reported in this study are height-adjusted. The previously reported cut-off for APLM of $<7.26\text{kg/m}^2$ for men was used to diagnose sarcopenia (12).

Ascites assessment

The treating transplant hepatologist recorded the presence of ascites at the time of transplant assessment in three possible categories: none, diuretic-controlled, or requiring abdominal paracentesis.

Waitlist mortality

All major clinical outcomes are prospectively recorded in the existing liver transplant database by dedicated liver transplant nurses who are responsible for retrieving data from both within the Austin Hospital and external institutions. Mortality data were extracted retrospectively from this database for the purpose of this study. Mortality within 12 months was chosen as this is a relevant and commonly reported timeframe for liver transplant waitlist mortality (13). Patients who were transplanted were censored at the time of transplant for the purpose of mortality analysis.

Statistical analysis

Data are reported as median and interquartile ranges (25th and 75th percentiles). Wilcoxon rank sum test was used to test between-group difference of continuous variables and chi-squared test that of frequencies. Variables were not corrected for multiple testing and considered exploratory. Kendall's rank correlation was used to test associations between continuous variables.

Risk of mortality was estimated by cause specific hazards using Cox model censored at the event of transplantation and conventionally displayed by survival curves. In measuring mortality, patients were censored at the time of transplantation and thus pre-transplant deaths within 12 months were the assessed outcome (waitlist mortality). Analysis relied on Cox Proportional Hazards (Cox PH) model with continuous covariates where the proportionality assumption was met. The assumption of proportional hazards was verified by means of Schoenfeld's test and plot (14). When violated and hazards rates were non-proportional, as was the case with MELD score for observation periods >4 months, a weighted estimation of Cox regression was reported instead of the simpler proportional model (15). Truncation was introduced at the 95th percentile to further reduce the influence of potential outlying events. Significance testing relied on the robust Lin-Wei covariance matrix (15). To define a potential threshold in the risk of sarcopenia, Cox models with restricted cubic splines with five knots, allowing for non-linearity testing and visualisation of a threshold effect were fitted (16). They were statistically compared with the simpler linear Cox model by both likelihood ratio test and Akkaike's information criteria (14).

For markers of sarcopenia, univariate Cox analysis was complemented by multivariable analysis, adjusting for clinically relevant pre-specified influences, namely age and MELD score (14). To assess potential supra-additive effects between upper limb LM and MELD score interactive multivariable Cox models were fitted. In the presence of both significant interaction between the covariates upper limb LM and MELD score and non-proportionality of the 12-month risk, time varying Cox models with a step function were fitted (17). The resulting complex risk profiles and predictive plots are displayed for clinically chosen levels of interest.

We also assessed subdistribution hazards (sHR), modelling the probability of an event of death as a competing risk to transplantation according to the method of Fine and Gray (18). The cumulative incidence for the sHR is shown for patients with and without sarcopenia, as defined by adjusted upper limb LM. As the optimum cut point for upper limb LM was not previously known, a cut-point analysis was performed following a method described by Williams et al (19). For discriminatory power, the concordance index was derived at various time points according to Uno's method (20). Two-sided p values <0.05 conferred statistical significance for all tests. The R statistical software environment (version 3.5.1 for Mac) (21) was used for all analyses including survival base package (14, 22) and added packages rms (version 5.1-2) (16), survminer (version 0.4.3) (23), coxphw (version 4.0.1) (15), survC1 (version 1.0.2) (20) and cr17 (version 0.1.0) (24).

RESULTS

Between September 2001 and November 2016, 803 adult patients underwent assessment investigations for transplantation including 571 who had DEXA body composition scans (147 women and 424 men), of which 420 men were included in this study. Median follow-up time was 58.5 [28.8; 109] months (range 0.8 to 200 months), 78.5 [50.9; 126] in patients who survived and 12.3 [4.7; 29.8] months in patients who died.

Baseline demographics

Median age of patients was 55.4 [49.1; 59.4] and median MELD score 16 [12, 19]. The primary indication for transplant assessment was hepatocellular carcinoma in 119 (28.3%) subjects, Hepatitis C in 102 (24.3%), alcoholic cirrhosis in 53 (12.6%), Primary sclerosing

cholangitis in 43 (10.2%), NAFLD in 26 (6.2%) and other aetiologies including autoimmune and metabolic conditions in 77 (18.3%).

At baseline, 193 patients (46.0%) had no ascites, 94 (22.4%) had diuretic-controlled ascites and 133 (31.7%) patients required paracentesis. The median baseline adjusted APLM was 7.81kg/m^2 [7.06;8.59] (range 4.57 to 13.81kg/m^2). Using the cut-off of $<7.26\text{kg/m}^2$, 30.9% were classified as sarcopenic (25). Baseline variables are displayed in Table 1.

Overall, 124 men died (29.5%), with a median time-to-death of 12.3 [4.65;29.8] months. 62 died within 12 months (14.8%), with 52 deaths occurring pre-transplantation. The 12-month waitlist mortality was 12.4% and 4-month wait-list mortality 6.2%. For the purpose of this study, only 12-month pre-transplant mortality is reported.

312 (74.1%) men received a liver transplantation (all from deceased donors), with a median time to transplant of 6.6 months [37.2, 11].

Predictors of waitlist mortality within 12 months

Univariate analysis by Cox PH modelling demonstrated that MELD score was positively associated with waitlist mortality (HR 1.09 [1.05; 1.14], $p<0.001$) and APLM inversely associated (HR 0.76 [0.59; 0.97], $p=0.03$).

The mortality risk associated with APLM was strongly associated with upper limb LM (HR 0.27 [0.11; 0.66], $p=0.004$) but not lower limb LM (HR 0.77 [0.56; 1.04], $p=0.09$). TLM (HR 1.02 [0.91; 1.15], $p=0.71$) was not a significant predictor of mortality. Factors associated with waitlist mortality are displayed in Table 2.

To define a potential threshold effect, a non-linear Cox PH model with restrictive cubic splines was fitted (Figure 1). While visually supporting the existence of a threshold, the nonlinear model was not significantly superior to the simpler linear model (likelihood ratio test, $p=0.20$), nor was it more informative based on Akaike's criteria (AIC difference -1.35). We therefore relied on the simpler linear model for further analyses.

Short versus medium-term mortality

While the mortality risk associated with upper limb LM was proportional over the 12-month observation period, the risk for MELD was non-proportional, displaying a relatively high and proportional hazard ratio of 1.15 [1.10; 1.21] over the first 4 months, and a lower averaged HR of 1.04 [0.91; 1.19] from 4 to 12 months. We therefore relied on weighted Cox regression

when reporting adjusted 12-month risk involving MELD together with other covariates. MELD was a better predictor of early mortality than late mortality, with a concordance index for MELD of 85% for 3 months, 79% for 4 months and only 66% for 12 months.

Proposed definition of sarcopenia using upper limb lean mass

A cut point analysis revealed the optimum risk-based cut-off for adjusted upper limb LM to be at 1.6 kg/m². Mortality risk levelled off above 2.3kg/m². These values are subsequently used for survival curves to represent low and robust muscle mass. Table 1 represents the baseline demographics for patients falling above and below the newly identified upper limb LM sarcopenia threshold of 1.6kg/m².

Interaction between upper limb lean mass and MELD score

In a multivariable weighted Cox model, age-adjusted upper limb LM conferred a supra-additive 12-month mortality risk at a low MELD score (adjusted multiplicative HR 1.23, [95% CI 1.03, 1.49], p=0.03). It interacted significantly with MELD score in predicting short-term (<4 months) and 12-month mortality. Again, sarcopenic measurements of upper limb LM significantly (p=0.04) interacted with MELD score, thereby substantially increasing the relatively low risk associated with a MELD score below 15 as well as impacting mortality risk at a high MELD score. The complex risk profile resulting from a non-proportional hazards rate over the 12-month period and significant modulatory impact of upper limb LM on MELD score-associated risk was fitted by Cox regression with a step function, showing a significant three-way interaction (HR 0.70 [95%CI 0.52, 0.94], p=0.02) between continuous upper limb LM, continuous MELD score and two discrete time groups (<4 months and 4-12 months). Figure 2 displays this risk profile, using two clinically selected levels of MELD score and upper limb LM.

Competing risks of mortality and liver transplantation

Using the cut-off for upper limb sarcopenia of 1.6kg/m², we assessed both conventional survival curves according to the method of Kaplan Meier (Figure 3a) and the competing risks of mortality with the chance of transplantation over 12 months in patients with (n=79) and without sarcopenic upper limbs (n=341), plotting the cumulative incidence functions of the subdistribution risks for each group according to the method of Fine Gray (Figure 3b). While the two groups had the same chance of receiving a transplant (p=0.61), they differed sharply in their mortality risk (p<0.001).

Association between ascites and MELD score

The prevalence of ascites rose with increasing MELD score (OR for ascites 1.20 [1.15; 1.25], $p < 0.001$ for each unit increase in MELD). Only 29.7% of patients with a MELD < 15 had ascites, as opposed to 80% of those with a MELD of 20 or above ($p < 0.001$).

Association between ascites and DEXA body composition

Individual components of DEXA LM displayed differing relationships with the presence of ascites. TLM was increased in patients with ascites as compared to those without (median 19.7 kg/m^2 [18.1; 21.5] vs 18.7 kg/m^2 [17.1; 19.9] $p < 0.001$), but comparable lower limb LM readings were seen in patients both with and without ascites 5.9 kg/m^2 [5.2; 6.6] vs 5.9 kg/m^2 [5.4; 6.4], $p = 0.89$ respectively). Upper limb LM was lower in patient with ascites than in those without (median 1.8 kg/m^2 [1.6; 2.0] vs 2.0 kg/m^2 [1.9; 2.2]), $p < 0.001$) as was APLM (median 7.7 kg/m^2 [7.0; 8.6] vs 8.0 kg/m^2 [7.3; 8.7], $p = 0.04$).

Association between DEXA body composition and MELD

Upper limb LM fell with rising MELD score ($\text{tau} = -0.20$, $p < 0.001$) (Figure 4a). TLM increased with rising MELD score in this cohort ($\text{tau} = 0.15$, $p < 0.001$) (Figure 4b).

DISCUSSION

This study assesses the differential prognostic impact of lean mass, as measured by DEXA, at various locations. Our study confirmed that reduced muscle mass is associated with increased mortality and identified upper limb lean mass as a novel measure of sarcopenia in cirrhotic men awaiting liver transplant. This new marker adds prognostic value to the MELD score. Given the low cost, reproducibility and reduced radiation dose of DEXA compared to CT, this is a promising technique for both the initial diagnosis of sarcopenia as well as serial monitoring of muscle mass in cirrhotic patients. Our analysis of various components of lean mass found that upper limb was most strongly associated with waitlist mortality as compared to other body compartments, with a suggested cut-off for sarcopenia of less than 1.6 kg/m^2 .

Although MELD score is most commonly used to prioritise patient for liver transplantation, it does not take into account extra-hepatic comorbidities such as physical frailty. Although sarcopenic men did have more severe liver disease than non-sarcopenic men in this cohort, in patients with either a MELD score of 10 or of 20, having reduced LM in the upper limb was associated with significantly reduced survival (Figure 1a and 1b). Information on lean mass

was supra-additive and interactive, resulting in more complex risk profiles when using combinations of the two markers, and was not due to modification of survival by the competing event of transplantation. The subdistribution hazard and mortality risk for men with sarcopenic upper limbs was significantly greater compared to the non-sarcopenic group, while the two groups had the same chance of receiving a transplant. This suggests that sarcopenia may independently confer mortality risk, which is particularly clinically useful in patients with low MELD score who would otherwise be considered to have low mortality risk. This is in keeping with CT-based data that demonstrated that sarcopenia adds value to MELD score (26) and that a MELD-sarcopenia score may be a better prognostic tool than MELD alone in patients with cirrhosis (27).

Our data is similar to the only other cohort study to our knowledge examining DEXA body composition in cirrhosis (10) that demonstrated a link between APLM and mortality (HR 0.44 [0.21; 0.92], $p=0.029$). Only our study dissected APLM into upper and lower limb LM components, which allowed us to ascertain that upper and not lower limb LM was responsible for the utility of APLM readings. The superiority of upper limb LM appears to be driven by confounding of DEXA measures of TLM and lower limb LM by fluid retention. In support for this explanation, we observed a strong positive association between the presence of ascites and TLM by DEXA, strongly suggesting that DEXA TLM can be inaccurate in cirrhotics. Although we did not quantify peripheral oedema, DEXA would also overestimate lower limb LM in the presence of oedema and thereby falsely elevate APLM readings, whereas fluid retention in the upper limb is rare. This is apparent in the lack of a significant relationship between lower limb LM and mortality (HR 0.77 [0.58; 1.03], $p=0.08$), with a much stronger and statistically significant association observed for upper limb LM (HR 0.37 [0.16; 0.83], $p=0.02$).

Most studies examining the impact of sarcopenia in cirrhosis have used CT-based methods; either muscle area on a single transverse slice at the L3 level or psoas muscle thickness (3, 6). However, CT techniques are limited by radiation dose, the need for specialized computer software and manpower to analyse images and the difficulty in selecting precise scanning planes to ensure comparability between patients. There is also no clear protocol for serial CT imaging, with potential inaccuracies if patient position or image plane is not reproduced (28). Improving technology in DEXA scanning has resulted in high accuracy, with a coefficient of variation of 0.3% (29). In combination with the negligible radiation dose of 0.0042

millisieverts (30) and instant results, this makes DEXA an attractive option for both point-in-time and serial measurements of muscle mass.

The need for better serial monitoring of sarcopenia on the transplant waitlist is driven by accumulating findings that deterioration in physical condition is associated with increased waitlist mortality. Hanai et al (31) reported that a reduction of muscle mass by >3.1% per year was significantly associated with increased mortality (HR 2.73 [1.43; 5.44] $p<0.001$) while the FRAILT study reported that patients who were able to increase handgrip strength had an 11% reduction in mortality for each 1kg increase in handgrip strength ($p<0.01$) (32). Furthermore, frailty predicts delisting from the liver transplant waitlist (32) as well as being associated with poorer post-transplant outcomes including mortality and post-transplant length-of-stay (5, 33). The ability to more accurately and objectively quantify changes in muscle mass may therefore improve allocation of organs to those who will benefit most and help identify patients for early intervention.

Deterioration in muscle strength may just be an epi-phenomenon of worsening liver disease, although studies have clearly identified a mortality risk associated with sarcopenia that is independent of the MELD score (3). Our group's clinical trial of testosterone therapy in cirrhotic men demonstrated an increase in muscle mass (11), with numerically fewer deaths in the treatment arm, but the study was underpowered to assess the impact on survival. An observation study of transjugular intrahepatic portosystemic shunts in cirrhotics however found that survival was improved in patients whose muscle mass increased (34), however randomised trial data is still lacking.

This study represents the largest cohort of cirrhotics awaiting liver transplantation with comprehensive DEXA body composition analysis. The completeness of data, with only 4 patients excluded out of 424, adds strength to our results but this work still needs confirmation in other populations. We acknowledge that we have not validated DEXA against CT in this cohort, and did not have the patient numbers to evaluate DEXA in women. Ideally, a large, multi-centre prospective study would perform DEXA body composition at transplant assessment and serially on the waitlist in both genders to allow us to assess the impact of changes in upper limb LM on outcomes including mortality, sepsis, waitlist dropout and post-transplant outcomes. This would also allow us to assess the utility of DEXA at identifying patients that need to be prioritized and would also address the important

question of whether there is a threshold of sarcopenia below which transplantation becomes futile.

CONCLUSION

This study examines for the first time the clinical utility of a range of DEXA lean mass parameters and mortality in a large cohort of male cirrhotics assessed for liver transplantation. Reduced upper limb lean mass, as opposed to total or lower limb LM, was most strongly associated with waitlist mortality in this cohort, and represents a novel, reproducible means of assessing sarcopenia in this population. Upper limb LM added prognostic value to the MELD score with a suggested cut-off for sarcopenia of less than 1.6 kg/m². Given the low cost, and reduced radiation dose of DEXA compared to CT scans, this is a promising technique for both the diagnosis of sarcopenia as well as serial monitoring of muscle mass in cirrhotic patients on the liver transplant waitlist.

LEGENDS

Figure 1. Linear (A) vs non-linear (B) Cox PH model for the relative hazard of mortality according to upper limb LM.

The non-linear Cox model was fitted with five knots restrictive cubic splines. While visually supporting the possible existence of a threshold, statistically, the two models were similarly likely (likelihood ratio test, $p=0.20$) and equally informative (see Results).

Figure 2. Interactive influence of the covariates MELD and upper limb LM in predicting probability of 12-month survival.

The time dependent and interactive risk profile of the two continuous covariates was estimated by Cox regression with a step function (see Methods and Results). The distinct risk profiles for clinically relevant levels of upper limb LM and MELD are shown here. (A) shows the survival curves for a patient with a low MELD score of 10 and an upper limb LM

of either 1.6 or 2.3kg/m² whereas (B) predicts survival for these levels of upper limb LM in combination with a high MELD score of 20.

Figure 3. (A) Kaplan Meier plot of 12-month survival in patients with (n=79) and without sarcopenic upper limbs (n=341). (B) Competing risk of 12-month mortality with the chance of transplantation in patients with (n=79) and without sarcopenic upper limbs (n=341). Shown are cumulative incidence curves for the subdistribution hazards (sHR) of each group, as derived by the method of Fine Gray (18). While the sHR for transplantation was similar between the two groups, sHR for mortality was much higher ($p<0.001$) in men with sarcopenic upper limbs. The 95% confidence limits of the curves are indicated at 4 months.

Figure 4. Relationship between MELD score and lean mass parameters of (A) the upper limb and (B) total body. The locally weighted scatterplot smoothed line is indicative only, correlations are given in the text

REFERENCES

1. Sinclair M, Grossmann M, Angus PW, Hoermann R, Hey P, Scodellaro T, et al. Low testosterone as a better predictor of mortality than sarcopenia in men with advanced liver disease. *J Gastroenterol Hepatol*. 2016;31(3):661-7.
2. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl*. 2017;23(5):625-33.
3. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2012;10(2):166-73, 73 e1.
4. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186990.
5. DiMartini A, Cruz RJ, Jr., Dew MA, Myaskovsky L, Goodpaster B, Fox K, et al. Muscle mass predicts outcomes following liver transplantation. *Liver Transpl*. 2013;19(11):1172-80.
6. Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Belghiti J, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *J Hepatol*. 2014;60(6):1151-7.
7. Guanabens N, Pares A. Osteoporosis in chronic liver disease. *Liver Int*. 2018;38(5):776-85.

8. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. *Eur J Gastroenterol Hepatol*. 2015;27(3):328-34.
9. Strauss BJ, Gibson PR, Stroud DB, Borovnicar DJ, Xiong DW, Keogh J. Total body dual X-ray absorptiometry is a good measure of both fat mass and fat-free mass in liver cirrhosis compared to "gold-standard" techniques. Melbourne Liver Group. *Ann N Y Acad Sci*. 2000;904:55-62.
10. Belarmino G, Gonzalez MC, Sala P, Torrinhas RS, Andraus W, D'Albuquerque LA, et al. Diagnosing Sarcopenia in Male Patients With Cirrhosis by Dual-Energy X-Ray Absorptiometry Estimates of Appendicular Skeletal Muscle Mass. *JPEN J Parenter Enteral Nutr*. 2017;148607117701400.
11. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. *J Hepatol*. 2016;65(5):906-13.
12. Messina C, Maffi G, Vitale JA, Ulivieri FM, Guglielmi G, Sconfienza LM. Diagnostic imaging of osteoporosis and sarcopenia: a narrative review. *Quant Imaging Med Surg*. 2018;8(1):86-99.
13. Fink MA, Berry SR, Gow PJ, Angus PW, Wang BZ, Muralidharan V, et al. Risk factors for liver transplantation waiting list mortality. *J Gastroenterol Hepatol*. 2007;22(1):119-24.
14. Therneau T, Grambsch P. Modeling survival data: Extending the Cox Model. Springer-Verlag. 2000.
15. Dunkler D, Ploner M, Schemper M, Heinze G. Weighted cox regression using the r package coxphw. *J Stat Software*. 2018;84.
16. Harrell FE, Jr. S functions for biostatistical/epidemiologic modeling, testing, estimation, validation, graphics, and prediction. Programs available from biostat.mc.vanderbilt.edu/rms. . 2009.
17. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6(7):121.
18. Fine J, Gray R. A proportional hazards model for the subdistribution of competing risks. *Journal of the American Statistical Association*. 1999;94:496-509.
19. Williams B, Mandrekar J, Mandrekar S, Cha S, Furth A. Finding optimal cutpoints for continuous covariates with binary and time-to-event outcomes. Mayo Clinic Technical Report. 2006;1:27.
20. Uno H, Cai T, Pencina M, D'Agostino R, Wei L. On the c-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med*. 2011;30:1105-17.

21. team R. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>. 2018.
22. Therneau T. A Package for Survival Analysis in S. version 2.38. 2015.
23. Kassambara A, Kosinski M. survminer: Drawing Survival Curves using 'ggplot2'. R package version 0.4.3. <https://CRAN.R-project.org/package=survminer>. 2018.
24. Mlynarczyk M, Biecek P. cr17: Testing Differences Between Competing Risks Models and Their Visualisations. R package version 0.1.0. <https://CRAN.R-project.org/package=cr17>. 2017.
25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412-23.
26. van Vugt JLA, Alferink LJM, Buettner S, Gaspersz MP, Bot D, Darwish Murad S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. *J Hepatol*. 2017.
27. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, et al. Inclusion of Sarcopenia Within MELD (MELD-Sarcopenia) and the Prediction of Mortality in Patients With Cirrhosis. *Clin Transl Gastroenterol*. 2015;6:e102.
28. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. *Am J Clin Nutr*. 2002;76(2):378-83.
29. Bilsborough JC, Greenway K, Opar D, Livingstone S, Cordy J, Coutts AJ. The accuracy and precision of DXA for assessing body composition in team sport athletes. *J Sports Sci*. 2014;32(19):1821-8.
30. Damilakis J, Adams JE, Guglielmi G, Link TM. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. *Eur Radiol*. 2010;20(11):2707-14.
31. Hanai T, Shiraki M, Ohnishi S, Miyazaki T, Ideta T, Kochi T, et al. Rapid skeletal muscle wasting predicts worse survival in patients with liver cirrhosis. *Hepatol Res*. 2016;46(8):743-51.
32. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant*. 2014;14(8):1870-9.
33. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg*. 2010;211(2):271-8.
34. Tsien C, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. *Eur J Gastroenterol Hepatol*. 2013;25(1):85-93.

Table 1. Baseline demographics according to proposed definition of sarcopenia of upper limb lean mass <1.6kg/m²

	All	Sarcopenic	Non-sarcopenic	P value
Age (years)	55.4 [49.2; 59.4]	53.2 [45.5; 58.8]	55.7 [49.2; 59.7]	0.048
MELD score	16 [12, 19]	18 [15; 22]	15 [11; 19]	<0.001
Upper limb lean mass (kg/m²)	1.90 [1.67; 2.10]	1.5 [1.39; 1.55]	2.0 [1.82; 2.16]	<0.001
Lower limb lean mass (kg/m²)	5.87 [5.28;6.56]	4.97 [4.47; 5.50]	6.08 [5.50; 6.68]	<0.001
APLM (kg/m²)	7.81 [7.06;8.59]	6.43 [5.95; 7.05]	8.09 [7.46; 8.75]	<0.001
Total lean mass	19.1 [17.5;20.7]	17.8 [16.3; 19.2]	19.5 [17.9; 20.9]	<0.001
Ascites present	64.0%	78.2%	48.5%	<0.001
Sodium (mmol/L)	136 [133; 139]	133 [128; 135]	137 [134; 140]	<0.001
Creatinine (μmol/L)	81 [66; 105]	93 [71; 139]	79 [65; 100]	0.02
Bilirubin (μmol/L)	49 [28; 89]	72 [43; 129]	46 [25; 82]	0.002
INR	1.4 [1.2; 1.7]	1.6 [1.4; 1.9]	1.4 [1.2; 1.6]	<0.001
Albumin (g/L)	29 [25; 34]	29 [26; 35]	29 [25; 34]	0.81
Haemoglobin (g/L)	122 [101; 138]	99 [90; 110]	125 [110; 140]	<0.001
Platelets (x10⁹/L)	90 [67; 133]	95 [74; 125]	90 [63; 134]	0.98
Vitamin D (nmol/L)	54 [35; 95]	45 [32; 71]	57 [36; 97]	0.07

--	--	--	--	--

Table 2. Univariate hazard ratio of various factors for 12-month waitlist mortality

Variable	HR	95% confidence interval	P value
MELD score ¹	1.09	1.05; 1.14	<0.001
APLM (kg/m ²)	0.77	0.59; 0.97	0.03
Upper limb LM (kg/m ²)	0.27	0.11; 0.66	0.004
Lower limb LM (kg/m ²)	0.77	0.56; 1.04	0.09
TLM (kg/m ²)	1.02	0.91; 1.15	0.71
Presence of ascites	2.17	1.21; 3.88	0.009
Sodium (mmol/L)	0.85	0.81; 0.90	<0.001
Albumin (g/L)	0.95	0.91; 0.99	0.03
Vitamin D (nmol/L)	0.98	0.97; 0.99	<0.001

¹The Cox model with MELD violated the proportional hazard (PH) assumption and was therefore adjusted by weighted Cox regression. All other variables were fitted with Cox PH model (see Methods).

liv_14071_f1a.tiff

liv_14071_f1b.tiff

liv_14071_f2a.tiff

MELD score 20

liv_14071_f2b.tiff

liv_14071_f3a.tiff

liv_14071_f4a.tiff

liv_14071_f4b.tiff

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Sinclair, M;Hoermann, R;Peterson, A;Testro, A;Angus, PW;Hey, P;Chapman, B;Gow, PJ

Title:

Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk

Date:

2019-06-01

Citation:

Sinclair, M., Hoermann, R., Peterson, A., Testro, A., Angus, P. W., Hey, P., Chapman, B. & Gow, P. J. (2019). Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk. LIVER INTERNATIONAL, 39 (6), pp.1089-1097. <https://doi.org/10.1111/liv.14071>.

Persistent Link:

<http://hdl.handle.net/11343/285488>