To the editors and reviewers

Re: Manuscript 74772: Hey et al. DEXA and post transplant outcomes

We thank you for your feedback. We have made changes to the manuscript. Please find below a point-by-point response to queries raised.

Kind regards

Dr Penelope Hey and colleagues
Liver Transplant Unit
Austin Health

Reviewer #1:

#It is known from the literature, that differing definitions of sarcopenia, modalities used for muscle mass assessment, severity of liver disease and inadequate power of some studies to adequately assess mortality are one of the problems, why sarcopenia does not yet have more evidence and why clear recommendations for prioritization or cut-off values for liver transplantation cannot yet be given. Era of transplantation may also be a factor as advancements in peri-operative care and immunosuppressive agents have improved post-transplant survival in the modern era, which is also problematic for generalisations, as you mentioned in the Discussion section. So, my question is, how did you respect "era of transplantation" in your patient cohort? Could you give a short overview about the perioperative standard of care / immunosuppression etc.. Was this the same for the whole cohort? And why didn`t you incorporate muscle function, as it is required for the definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP), which gained even more importance comparing the 2010 and 2019 diagnostic criteria for sarcopenia? It is known that sarcopenia should not be the sole criterion for listing/non-listing, i.e. muscle mass does not necessarily correlate with muscle strength and functionality with willpower being far more important.

Reply: We thank reviewer 1 for these comments. We have added in a paragraph in the Materials and Methods Section (Entitled "Peri-operative and early post-operative management") to address this question. This details the standard transplant protocols, organ allocation and immunosuppressive regimens used over the period. A comment on switching to mycophenolate from azathioprine in 2012 has also been added.

We have added in data on mortality rates, demonstrating an improvement in the latter half of the time period examined. This can be found in the results section under "Mortality and graft failure". A brief discussion of these findings has been included in the Discussion section where "Era of transplantation" is discussed (Paragraph 2): *The higher 12-month post-transplant survival observed in the latter half of the period likely reflects improvements in medical care, despite the increasing medical complexity and older age of transplant recipients.*

We understand that a major limitation of this study is that it does not report functional measures of muscle strength as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP). Given the retrospective nature of this study, measures of handgrip strength were not available consistently on patients included in this study over the timeframe assessed. A sentence in the final paragraph has been added acknowledging this limitation. *"A major limitation of this study is that muscle strength was not included due to the lack of available data over the timeframe described."*

#The general demand is to that effect that a common transplant candidate index reflecting sarcopenia/frailty should be established as a standard in all transplant centers to facilitate comparability. Even just quantifying muscle mass is a challenge. The most common method is performance of a standardized CT at the level of LWK 3 and determination of the SMI as a muscle cross section. But there are different limits in the literature, and also different limits for men and women. You proposed a relatively rarely used method for determining sarcopenia. Have any limits been described in the literature? Are there also known different limits for men and women?

Reply: We have amended paragraph 4 in the discussion to address these concerns. We have discussed the utility of DEXA over CT in more depth and examined the lack of available data on the use of DEXA in this cohort. We have also included cut off values recommended by one previous single centre cohort in men only.

*The influence of pre-transplant sarcopenia and frailty on early post-transplant ACR is also uncertain with conflicting reports in the literature[14, 15]. This study found no association between pre-transplant sarcopenia and early ACR. This provides reassurance that optimising sarcopenia pre-transplant does not appear to result in higher rates of ACR.*

*While muscle area measured on transverse abdominal CT is often considered gold standard for quantifying muscle mass in cirrhosis, practice guidelines recommend against the use of CT for the sole purposes of sarcopenia assessment due to high radiation doses[16]. In addition to CT, DEXA and bioelectrical impedance (BIA) are recommended by the European Working Group for Sarcopenia in Older People for assessment of muscle mass[1]. DEXA has advantages over CT due to its reproducibility, low cost and radiation and no requirement for further analysis. However, the inability of DEXA to differentiate fluid and lean tissue is particularly problematic in decompensated cirrhosis where the occurrence of ascites and peripheral oedema are high.*

*Current guidelines recommend the use of APLM for defining sarcopenia using DEXA[1] with cut-off values extrapolated from non-cirrhotic cohorts for both men and women[7]. In a small*

*prospective series of men with cirrhosis, APLM did not change following large volume paracentesis suggesting this is not confounded by ascites[17]. However, the influence of peripheral oedema in this population has not been well described.*

#Why was the endpoint rejection (ACR) chosen? Which conclusions should be drawn from this when treating sarcopenic patients?

Reply: ACR was chosen as an endpoint as available literature has shown a conflicting association with sarcopenia and frailty. A discussion regarding this and the implications on treating sarcopenia have been added into paragraph 2 of the discussion.

*The influence of pre-transplant sarcopenia and frailty on early post-transplant ACR is also uncertain with conflicting reports in the literature[14, 15]. This study found no association between pre-transplant sarcopenia and early ACR. This provides reassurance that optimising sarcopenia pre-transplant does not appear to result in higher rates of ACR.*

**Reviewer #2:**

**Specific Comments to Authors:** The assessment of patients waiting for liver transplantation is one of the challenges of the transplant teams, has many standards in the application, but there are certain limitations. This article evaluates from the perspective of upper limb muscle atrophy and has certain application significance. However, the limitations are more obvious, and it is still not widely used in clinical. I hope to continue to explore in the later clinical work.

Reply: We thank reviewer 2 for their comments. We have added in a longer discussion about the merits and limitations of DEXA vs CT for the diagnosis of low muscle mass to address these concerns.

## EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

***(1) Science editor:***

The authors included more than 400 patients and confirmed that sarcopenia was an independent and potentially modifiable predictor of bacterial infection and increased hospital stay in patients with liver cirrhosis after transplantation. The evaluation of muscle loss is still a problem. Muscle quality, size and gender are all influencing factors. **The validation queue is missing**. The format of the table should use the three line table format. Self Citation Count: 2

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade C (Good)

Reply: The format of the table has been changed.

***(2) Company editor-in-chief:***

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Transplantation, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the

author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Reply: Amendments have been made to the tables. The figures have been resubmitted in powerpoint form. Copyright statement on the figures has been added.