

## Peer Review File

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### Reviewer A:

The authors investigated physical activity (PA) in patients awaiting LT in a country with long waiting times. The topic is of interest. However, there are a few methodological and descriptive critical problems as follows.

1) Sample size was too small to draw any definite conclusions. Especially, sample size in subgroup analyses according to sex or nutritional support was too small.

**Reply 1:** Thank you for pointing out this aspect. This clear limitation is now more explicitly discussed in the manuscript, particularly with regard to subgroups.

**Changes in the text:** We have modified the text as advised and have added sentences in which the limitations of our sample size, particularly in the subgroup analyses, are clearly stated. (page 16, lines 252-257)

2) As for nutritional support, the authors showed only that nutritional support was defined as receiving regular counseling by a dietician and oral supplementation either with branch-chained amino acids or other protein-rich supplements prescriptions and/or placement of a nasojejunal feeding tube. This description is too vague. Please show details of pretransplant nutritional support for the patients.

**Reply 2:** Thank you for mentioning this aspect. In light of the small sample size (see comment above) in-depth description and analysis was considered to result in the same statistical sample size restrictions, which is why we did not go into depth in the manuscript. A corresponding sentence has been added to the manuscript.

**Changes in the text:** The paragraph clinical definitions was expanded “Placement of a nasojejunal feeding tube was usually done as an inpatient procedure with enteral feeding started in a hospital setting and once established a supported by the patient, continued as an outpatient with support from community nurses. Frequency of outpatient consultations were carried out based on the individual needs of each patient.” (page 9, lines 133-137)

Additionally, “As such which type of nutritional support might result in the most benefit for the patient in this setting could not be assessed.” has been added (page 17, lines 275-276).

3) Nowadays, muscle function including muscle strength as well as physical activity is considered important in evaluating sarcopenia. How about the change of muscle function in patients on the liver transplant waiting list?

**Reply 3:** Thank you for mentioning other parameters for evaluating sarcopenia, which we absolutely agree with. Some parameters including handgrip strength at inclusion are shown in Table 1 and in the text, page 11. In-depth analysis of changes of these parameters over time was beyond the aims and objectives of this manuscript. But we agree, that further studies will benefit if these parameters are studied over time, particularly in patients with an excessively long waiting time.

**Changes in the text:** none.

4) It is well known that preoperative sarcopenia is closely related to postoperative complications such as infection due to impaired immune function. How about the impact of pretransplant PA on infection after transplant?

**Reply 4:** We thank the reviewer for this very important point. As a surrogate marker for this aspect we included emergency hospitalization in the composite adverse outcome, most of which were for infections. With regard to the sample size (first comment of Reviewer A), the power for a more in-depth outcome analysis this outcome is unfortunately not given.

**Changes in the text:** It has been added to the manuscript: “In-depth analysis of adverse outcome endpoints (such as infections) was not feasible due to inadequate power due to the small sample size.” (page 17, lines 276-277)

5) In patients undergoing liver transplantation, the implementation of exercise intervention is difficult due to decompensated liver cirrhosis and co-morbidities. Are there any efficient ways to perform exercise therapy or increasing PA for patients undergoing liver transplantation?

**Reply 5:** This is a highly relevant question albeit not easy to provide a quick-fix solution! The group from Peter Reese published a trial *Liver Transplantation* (Serper M, Jones LS, Clement T, Reddy RK, Reese PP. A randomized, controlled, prehabilitation intervention to maximize early recovery (PRIMER) in liver transplantation. *Liver Transpl* [online ahead of print]. 2023 Jun 29) in which they show that providing the patients with incentives (in this case financial and text-based “motivation nudges”), may indeed be efficient in getting this very sick group of patients to stick to PA. We have expanded on this in the manuscript accordingly.

**Changes in the text:** The manuscript has been expanded: “This lack of finding might also be confounded by not having identified the beneficial exercise intervention or prehabilitation program so far in these patients.” (page 15, lines 238-240)

### **Reviewer B:**

I carefully reviewed the manuscript entitled “Physical Activity Decreases in Patients on the Liver Transplant Waiting List and Influences Postoperative Outcome - A Prospective Cohort Study”. This paper investigated physical activity (PA) in patients awaiting LT (liver transplantation) in a country with long waiting times and showed that moderate PA (MPA) decreased over time in patients listed for LT, which was associated with adverse outcome. This study had an interesting intervention in which patients were fitted with a wrist tracker (FitBit) to monitor PA. The results obtained support the need for routine prehabilitation practices in patients awaiting LT. Despite some limitations, such as patient sample size, as the authors describe in the text, the paper is potentially worthy of publication in *Hepatobiliary Surgery and Nutrition*. There are descriptions in the text that suggest some logical inconsistency. My comments are below.

1. The authors state in their paper as follow, “our data show that nutritional supplementation was associated with improved MPA between weeks 20 and 40 in patients awaiting liver transplantation, suggesting a clear benefit of this intervention”. However, Table 4 seems to indicate that from 20 to

40 weeks MPA improved significantly not only in the yes group ( $p=0.045$ ) but also in the no group ( $p=0.024$ ) for "nutritional support before LT". Although there was no significant difference between the two groups, is it appropriate to state that "nutritional supplementation was associated with improved MPA"?

**Reply 1:** We agree with the reviewer, that this is misleading and have adapted the manuscript accordingly.

**Changes in the text:** Changes have been made, as suggested (page 16, line 252)

The limitations have also been expanded upon: "The non-significance within the nutritional vs. no nutritional support group may be due to under-powering regarding this factor." (page 17, lines 278-279).

2. After week 40, a significant decrease ( $p<0.001$ ) of MPA over time was noted only in the group with nutritional support, but not in the group without nutritional support. Considering the impact on MPA after Week 40, it is more beneficial for the patient not to provide nutritional support. Do the data from this paper really suggest a benefit of nutritional support?

**Reply 2:** Thank you for mentioning this aspect. The interpretation of the necessity of nutritional support is a double-edged sword. These patients typically are more frail and receive nutritional support due to their sarcopenia. This results in a selection bias of patients receiving nutritional support. Resultingly, they tend to have decreased capacities. The interpretation aspects are therefore comparable to MELD scoring for waitlisted patients.

**Changes in the text:** We have expanded the manuscript accordingly: "The clinical interpretation is challenging, as there is likely to be a selection bias in as much as that severe sarcopenic patients are typically those receiving nutritional support. Nutritional support may thus be considered a surrogate marker for the extent of the disease severity in waitlisted patients. The interpretation in this sense is comparable to the restrictions of the interpretation of the Model End-Stage Liver Disease in these frail patients." (page 16, lines 253-256)

### **Reviewer C:**

This paper is a cohort study of the association between preoperative physical status and postoperative outcomes. The patients on the LT waiting list are frail and critically ill, and their situation is unique. In this context, the changes in physical status, the effects of preoperative rehabilitation and nutritional support, and the impact of LT on outcome were very interesting and important. The topic of this study is of great value. However, the data presented were too complex to interpret and understand. Furthermore, the main findings of this study, the significant association between MPA and post-LT outcomes, and the changes in MPA on the waiting list are difficult to understand. The organization of this paper should be revised.

The following items should be corrected.

(1) How did you support the patients' nutrition? The details of nutritional support should be described in Method.

**Reply 1:** We thank you for pointing out this important aspect, which we fully agree with. Details of how nutritional support is provided, is already mentioned, as suggested by the reviewer, in the

methods section (methods section page 9, point “2.4 Clinical Definitions”). We have added a few more clarifications in the text.

**Changes in the text:** “Placement of a nasojejunal feeding tube was usually done as an inpatient procedure with enteral feeding started in a hospital setting and once established a supported by the patient, continued as an outpatient with support from community nurses. Frequency of outpatient consultations were carried out based on the individual needs of each patient.” Was added (page 9, lines 133-137)

(2) Table 2: Outcomes during the transplantation period. How about infection, rejection, and other non-surgical complications? Only one case? How long was the length of hospital stay and ICU stay? The outcome of LT should be analyzed and described in more detail.

**Reply 2:** We thank the reviewer for this valid comment. For in-hospital complications we only included data of major complications (i.e Dindo-Clavien >3). Simple infections, such as urinary tract infections only requiring antibiotics without organ failure or other non-surgical complications < grade 3 are not included in the table. We did not have any case of rejection in the observed period. As a surrogate marker for infections, rejections and other complications the composite adverse endpoint was defined to allow further statistical analysis.

As suggested by the reviewer, hospital and ICU stay have been added and details expanded in the manuscript.

**Changes in the text:** The suggested changes have been expanded upon in Table 2.

(3) Physical activity (3.2), Table 3, Figure 2, and Figure 3

This section is the most important, but the description is complicated and it is difficult to grasp the main points. It needs to be deliberately organized; overall changes in MPA should be analyzed, and changes in weekly MPA by gender and nutritional support should be added to Figure 2. Figures 3C-F present detailed data but are too complex. These graphs can be presented as supplementary data.

**Reply 3:** We thank the reviewer for this critical analysis of the data. We agree that in its current form, appreciation of the data may not be ideal. We have made the suggested changes.

**Changes in the text:** As suggested by the reviewer, we have moved Figures 3c-f to supplemental. Material. According changes in were made (Files Figures, Supplementary Appendix). References in text were adapted accordingly (page 13, line 195 and 211; page 32, lines 521-524). An explanation in text has been added as follows “The visual presentation of the median distribution of continuous factors (Age, Child Pugh Score, liver frailty index and quality of life) with regard to MPA and temporal changes are shown using heatmaps in Supplemental Figure 2” (page 13, lines 195-197).

(4) Nutritional support improved MPA during the waiting period, and MPA was significantly associated with the outcomes after LT. The association between nutritional support and LT outcomes needs to be analyzed directly.

**Reply 4:** We thank you for highlighting this relevant aspect. As correctly noted by another reviewer, all patients, irrespective of nutritional support, showed a significant association between reduced MPA and adverse outcomes. Indeed, continuing nutritional support after week 40, seemingly resulted in a worse outcome, compared to patients without nutritional support. However, to conclude that nutritional support may indeed result in a more detrimental outcome is tackling the problem from the wrong end: only patients doing really badly, ie, patients with persistent and severe

sarcopenia and patients unable to maintain sufficient oral intake by themselves, continued to be reliant on additional nutritional support. Thus, the need for nutritional support has to be understood as a surrogate marker for the extent of disease severity of the waitlisted patient. We have adapted and explained this accordingly.

**Changes in the text:** “On crude univariate logistic regression analysis nutritional support did not significantly reduce the occurrence of adverse clinical endpoint (OR 0.848, 95%CI 0.179-3.740,  $P=0.829$ ).” has been added to text on page 12, line 199.

In the discussion this has been expanded upon with “The clinical interpretation is challenging, as a selection bias through that severe sarcopenic patients are typically those receiving nutritional support. This factor can be considered as a surrogate marker for the extent of the disease severity in waitlisted patients.” (page 16, lines 253-256)

(5) The association between changes in MPA and LT outcome should be statistically analyzed. Figures 4A and 4B suggest that increased MPA is associated with favourable outcomes.

**Reply 5:** We thank the reviewer for the valuable and very valid comment. We are confused as we have no Figure 4A and assume the reviewer is referencing to Figure 3A and 3B and therefore have revised according to these aspects.

We agree with the reviewer, that Figure 3A and B suggest that increased MPA is associated with favourable outcome also in the subgroups of factors for sex and nutritional support. To recapitulate, summarize and display these relevant findings, as suggested by the reviewer, we depicted previously the results in the forest plot in Figure 4.

This figure shows the effect on combined adverse outcome by changes of MPA in units of 10 minutes-weekly. We have emphasized this important point more clearly in the actual text of the body and the discussion.

**Changes in the text:**

Figure 3C to 3F were moved to supplementary Appendix to bring to the readers attention the findings of Figure 3A & B as well as existent Figure 4. (File ‘Figures’ to File ‘Supplementary Appendix’).

The manuscript text has been expanded: “Figure 3A and 3B display the temporal changes of MPA for the *a priori* chosen categorical factors sex and nutritional support for stratified outcome. Figure 4 depicts a univariate logistic regression with subsequent presentation in a Forest Plot to assess for significance.” (Page 13, lines 210-212)

#### **Reviewer D:**

The authors presented an innovative prospective study analyzing the role of Physical activity in patients waiting for liver transplantation.

The study included 35 patients, 28 were transplanted.

The study is well conducted and presented. Statistical analysis is clearly performed.

**Reply:** We thank the reviewer for taking the time to review our manuscript and supporting its publication.

**Changes in the text:** none.