

## ANSWERS TO THE REVIEWERS

First of all, we'd like to thank the reviewers whose comments indeed contributed to improve the quality of the manuscript. All reviewers' requirements were fulfilled and the text was comprehensively reviewed by one of the authors who is a native English speaker.

### Reviewer 00214259

**1. This is a well-written manuscript about functional rehabilitation and muscle strength following an ICU admission.**

*AUTHORS: Thank you for these comments.*

**2. Authors should give more details about the way they screened participants, how much patients they excluded and for which reasons.**

*AUTHORS: We added more details on the patients screening process as follows: "Data was obtained from non-mechanically ventilated patients presenting with at least one of the following criteria: Katz score  $\geq 3$ , MRC  $\leq 48$ , diagnosis of pulmonary or cardiovascular disease, and cooperative (Richmond Agitation-Sedation Scale between 0 and 2) who stayed at least 48h at the ICU and underwent the mobilization protocol. Records of patients who died during the period of the study, with neuromuscular disease, returned to the ICU after discharge or with incomplete data were not included."*

**3. I understand that maybe patients who deceased during hospitalization were excluded. Compilations and comparisons of their data are important and should be provided.**

*AUTHORS: We agree that data from deceased patients could add some interesting information to the study. However, as we used secondary records and it was an exclusion criterion, these data were not available in the database. Because our study doesn't focus on mortality outcomes and it would be impossible to analyze their functional progress throughout all time points, we believe this information does not compromise our results. Nevertheless, a comment on it was added to the Discussion as a limitation of the study.*

**4. The major issues of this research ground on statistics descriptions. Amount of patients seem small related to the amount of factor that were analyzed. Justifications should be done. Who did the analysis? It should be mentioned to guaranty the validity of conclusions.**

*AUTHORS: Thank you for your comment. We enrolled 198 participants and considered 6 factors (gender; sepsis; COPD; dementia, previous stroke; cause of ICU admission) and 5 covariates (age; SAPS3; length of stay; Katz at admission; MRC at admission), summing up 10 degrees of*

freedom for statistical analysis. Thus the number of events per variable (EPV) is 19.8 in our study. Recommended EPV in literature ranges from 2 to 20 EPV<sup>1,2,3</sup>. Whilst some authors suggested relaxing the minimal 10 EPV<sup>4</sup>, other authors suggest that no single rule of EPV guarantees an accurate estimation of logistic regression parameters<sup>5</sup>. Therefore, we considered our study has a satisfactory number of EPV. This information was added to the Discussion in the revised version. Statistical analyses were conducted by one author (A.S.F.), who has both Ph.D. and M.Sc. in Biomedical Engineering besides M.Sc. in Physical Therapy. Such author is in charge of the Biostatistics course for both M.Sc. and Ph.D. courses at the Postgraduate Program at our Institution.

1 - Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. *J Clin Epidemiol.* 2015 Jun;68(6):627-36. doi: 10.1016/j.jclinepi.2014.12.014.

2 - Austin PC, Steyerberg EW. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat Methods Med Res.* 2014 Nov 19. doi: 0962280214558972

3 - Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* 1996 Dec;49(12):1373-9

4 - Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol.* 2007 Mar 15;165(6):710-8.

5 - Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *J Clin Epidemiol.* 2011 Sep;64(9):993-1000. doi: 10.1016/j.jclinepi.2010.11.012

**5. As age median is 80 years old, this study concerned elderly patients and this give some new data about that population. Is some more analysis can be made about that subgroup?**

*AUTHORS:* Thank you for your suggestion. As described in our manuscript, 80.3% of our sample is indeed composed by subjects aged  $\geq 65$  years. We consider that this characteristic reflects the regional characteristics of the population attending to the hospital, as well as all other control variables in our study. Because our study does not focus in elderly, hospitalized subjects, we initially conducted a complete-case analysis of the main outcomes regardless of age groups. In the revised version we included the descriptive analysis grouped by age ( $<65y$ ,  $\geq 65y$ ) alongside the comparative analysis using inferential statistics in Table 1. The Results and Discussion sections were amended accordingly.

**6. If longer total length of stay can be a predictor of good patients' functional progress because some patients could have been discharged too soon?**

*AUTHORS:* In our opinion this is one interesting finding of the study. In many services, patients' discharge relies only on clinical criteria, neglecting the functional status and independence of the patients. It is commented in the Discussion as follows: "This suggests that the in-hospital

*functional and muscle strength recovery may be time-dependent. Hence<sup>[12]</sup> the extent of improvements in functional outcomes during hospitalization should be incorporated in hospital discharge planning."*

**Reviewer 00502802**

**The article is well written but I have certain reservations.**

*AUTHORS: Thank you for this comment.*

**1. Introduction is very lengthy. It should be made more focused.**

*AUTHORS: We shortened the introduction as required. Indeed it is more objective now. The text and references were modified aiming at providing a background and making clear the rational of the study.*

**2. There are several grammatical and typographical error, which makes understanding difficult**

*AUTHORS: One of the authors is an English native speaker. We asked him to revise the manuscript again for this new version.*

**3. Exclusion criteria should be defined properly**

*AUTHORS: We added more details on the patients screening process as follows: "Data was obtained from non-mechanically ventilated patients presenting with at least one of the following criteria: Katz score  $\geq 3$ , MRC  $\leq 48$ , diagnosis of pulmonary or cardiovascular disease, and cooperative (Richmond Agitation-Sedation Scale between 0 and 2) who stayed at least 48h at the ICU and underwent the mobilization protocol. Records of patients who died during the period of the study, with neuromuscular disease, returned to the ICU after discharge or with incomplete data were not included."*

**4. Pts on mechanical ventilators were excluded, the impact of such an intervention should be properly addressed in discussion. It could be one of the limitations of the study.**

*AUTHORS: According to literature, the impact of mechanical ventilation on functional outcomes is unclear. We added a comment in the Discussion as follows: "As intubated and mechanically ventilated patients were not included in this study, it was not possible to analyse the influence*

*of this factor on muscle strength and functional progress during hospitalization. Although muscle weakness is associated with prolonged weaning from mechanical ventilation, there is large variability in the reported prevalence of ICU-AW among mechanically ventilated patients<sup>[31]</sup>. Therefore, future studies should address if mechanical ventilation is an independent predictor of peripheral muscle strength and functional progress in critically ill patients.”*

**5. Abbreviations, when used for first time, should be described eg. MRC score 6.**

*AUTHORS: The text was revised accordingly.*

**Reviewer 00029041**

**This paper is well-written. Several points should be clarified.**

*AUTHORS: Thank you for this comment.*

**1. Introduction should be shortened.**

*AUTHORS: We shortened the introduction as required. Indeed it is more objective now. The text and references were modified aiming at providing a background and making clear the rational of the study.*

**2. Were dead patients analysed?**

*AUTHORS: We agree that data from deceased patients could add some interesting information to the study. However, as we used secondary records and it was an exclusion criterion, these data were not available in the database. Because our study doesn't focus on mortality outcomes and it would be impossible to analyze their functional progress throughout all time points, we believe this information does not compromise our results. Nevertheless, a comment on it was added to the Discussion as a limitation of the study.*