To the editor,

Congratulations to Suzie Ferrie and co-investigators for evaluating the protein dose recommendations in a randomized pragmatic study.[1] The studies' treatment allocation and blinding were conducted in a state-of-the-art design and multiple patient centered outcome variables were evaluated at fixed time points independent of ICU discharge status.
Higher amino acid intake -even though it didn't affect the primary outcome- apparently attenuated muscle wasting and weakness. This finding is in contrast with other recent RCT's, where even larger doses of intravenous amino acids did not improve functional outcome.[2] As the authors speculate, the moderate disease severity may explain attenuated anabolic resistance in their patients.[1] In both RCT's,[1, 2] the important mortality benefit with increased amino acid intake, predicted by several large observational prospective studies, was not confirmed.[3, 4] This is consistent with the general finding that results from non-randomized studies are less likely to be replicated in RCTs.[5]

Actually the number of patients who died in ICU was slightly higher in the high amino acid group 8 (14%) as compared to 6 (10%) in the lower amino-acid group, a difference reaching 10% at 6 months landmark mortality evaluation.[1] Could the authors clarify how non-surviving patients were dealt with in the evaluation of the primary and secondary functional outcome analyses? These mortality differences are not statistically significant and may well be independent of the high amino acid therapy, yet they may have affected functional outcomes as competing events.[6] As stated in the methods section "missing values for the primary outcome were assumed to be missing at random". In ICU however it is difficult to accept that patients who died would have been –if they survived- as strong as other patients, precluding the assumption of being "missed at random". The few additional deaths in the high amino acid arm may paradoxically have improved the results for the primary outcome, by eliminating two very low hand grip strength values in this group. Could the authors conduct a sensitivity analysis attributing the lowest hand grips strength values to patients who were dead at ICU discharge and likewise for patients dead at last hand grip assessment (day 7)? Could the authors also report the results for the secondary analyses after imputation of missing values, as these have been conducted but are actually not shown in the manuscript?

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