

Thank you for the opportunity to revise this manuscript. My reply to the reviewer's queries are outlined below:

The review written by Lim AKH summarizes the potential approaches to distinguish primary liver injury from muscle injury in severe rhabdomyolysis. The conclusion is that the typical pattern and trajectory of the levels of creatine kinase and aminotransferases and a concurrently elevated bilirubin or  $\gamma$ -glutamyl transferase could help make the differential diagnosis between muscle injury from genuine liver injury. The issue is often problematic in a clinical setting and the manuscript is thus important.

Minor points:

1. Given the impact of the conclusion, the review seems too long. It should be more concise.

**Reply:** I have shortened the paper as suggested. Any information deemed unnecessary have been removed. This includes removing the detailed description of the case example but retaining Figure 1 and using an expanded figure legend. I have reduced the word count by ~20%. As part of improving conciseness, the headings have been simplified and some paragraphs have been relocated to different areas or integrated into others.

2. In severe rhabdomyolysis, it seems uncommon that the patient is accompanied with severe liver injury or acute hepatic failure. Therefore, it is unclear that how important to distinguish primary liver injury from muscle injury in severe rhabdomyolysis. The authors should make a comment on that point.

**Reply:** I completely agree that severe liver injury is generally not a feature of this association. This is where the quantitative analysis of this association is useful to demonstrate this fact. We have recently published a paper examining the functional relationship between CK and ALT (Lim AKH, Arumuganathan C, Lau Hing Yim C, Jellie LJ, Wong EWW, Junckerstorff RK. A Cross-Sectional Study of the Relationship between Serum Creatine Kinase and Liver Biochemistry in Patients with Rhabdomyolysis. *J Clin Med* 2020; 9(1): 81. doi:10.3390/jcm9010081). I have added a new figure (*Figure 2*) to the paper which should help readers visualise the magnitude of the association, and included the citation to this publication. In short, our study indicated that an ALT above 800 U/L would be unusual in this context. This additional information is added under the subheading *Quantitative analysis and potential confounders*. I have modified that *Core tip* as well to mention this point.

As to the second point whether it is important to distinguish liver injury from muscle injury, I would argue that it still very relevant, given that our group also found that excessive testing for liver disease (serology, imaging, etc.) remained a feature in this clinical context. I have also added mention of the new findings from this publication in the current submitted paper (page 6, *Unnecessary testing or missed diagnosis*). The other reasons why it is important to distinguish the two conditions has already been elaborated in detail under *Potential implications* on page 6-7. I have modified the *Conclusion* slightly to reflect the additional information.

**Note for the Editor:**

The new reference mentioned above is being processed by PubMed and does not have a PMID number yet. This should be available in the next week or so. May I leave it for the copyeditors to insert when it becomes available?