

Peer Review File

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Reviewer A

Comment 1 predictor of severe acute pancreatitis (SAP). The authors conclude that cardiac injury may be an earlier event relative to respiratory, renal and circulatory injury in SAP. They should clarify that “circulation” mentioned in MMS system to diagnosis of SAP deals with cardiac function or not, since circulatory system including cardiovascular system relates to cardiac function and blood vessel function. As a single center retrospective study, small sample size and lack of CK-MB trace data are limitations and shortcomings of the manuscript.

Reply 1 Thanks for your kind suggestion. We added the clarification that “circulation mentioned in MMS system to diagnosis of SAP cannot deals with cardiac function” in the second paragraph of discussion part. We deem that the circulation variables of MMS cannot directly deal with the cardiac function due to the preload and postload of heart can be almost ignored but the cardiac dysfunction is mainly characterized with decreased stroke volume and cardiac output in the early stage of SAP. We also agree with your comments of our limitation.

Comment 2 CK-MB should be listed in Key Words.

Reply 2 Thanks for your helpful suggestion. We added CK-MB into the list of Key words in the revised manuscript.

Comment 3 Line 148, “273 of them were enrolled and divided into Mild AP (mild n=59), Moderate SAP (n=123) and SAP (n=56)”, in which 273 should be 238.

Reply 3 We are sorry for this mistake which has been corrected in the revised manuscript. Thanks a lot!

Comment 4 Where is Table 3? Why the numbers in Figure Legends do not match the attachment Figures?

Reply 4 We are sorry for this mistake. In the revised manuscript, Table 3 was referred in paragraph 4, line 323 of Result section. We rechecked all the tables and figures as well as their figure legends, and corrected the mistakes. Thanks a lot!

Comment 5 References should be in standard format.

Reply 5 We appreciate your kind suggestion. The references were reformatted in the revised manuscript.

Comment 6. The language errors are far too many and need to correct.

Reply 6 We are sorry our language mistake. The language has been improved with help of native English speaker.

Reviewer B

Comment 1 Why were the structural heart markers elevated in patients with a severe clinical course? Was there increased rhabdomyolysis or heart failure? The cause of the cardiac markers should be described more in detail. Have functional heart assessments been performed?

Reply 1

We appreciate your thoughtful questioning. The increase of heart markers in the early stage of SAP is mainly due to the inflammatory cytokine or reactive oxygenase specie which can cause direct damage of heart cell. The role of rhabdomyolysis on cardiac markers in SAP patients was mentioned by Alessandra, et al (*Pancreas*, 44(4), 678-80. doi:10.1097/MPA.0000000000000320), but they showed the cTNT and CK, but not CK-MB were higher in severe acute pancreatitis compared to mild acute pancreatitis.

The role of heart preload and postload might was supposed to be little as the hypovolemia. We have added a more specific discussion in the paragraph 1 of discussion section. Besides, the functional heart assessment such as echocardiography were regularly performed but not at the time point of admission. Therefore, we did not add these data into this manuscript. The echo performance in the early stage of SAP are warrant in the future prospective study.

Comment 2 A major limitation of the study is the absence of serial measurements in order to monitor cardiac marker levels in the AP cohort. How did the markers look in the progress? Have there been changes in serum levels depending on the clinical course? Please discuss.

Reply 2

We agree with your opinion on the limitation of study. We did not provide more data on the trend of CK-MB due to the respective design. According to study of Ragesh, et al (Pancreas, 46(5), 626-630. doi:10.1097/MPA.0000000000000820), the CK-MB were mildly elevated on Day 1 and normalized in Day 3 in a cohort of severe acute pancreatitis which admitted within 7 days after disease onset. it is speculated that the peak level of CK-MB appears in the early stage and then decreases. In our study, we enrolled the cohort of patients who were admitted from onset to admission within 48 hours which might be the time point of peak level of CK-MB with the convincing predictive ability. We add this discussion into the limitation part of Discussion section

Comment 3 Was the predictive value of CK-MB associated with a poor long-term outcome? A Kaplan-Meier survival analysis is missing here.

Reply 3 Thanks for your kind suggestion. The Kaplan-Meier survival analysis between SAP and non-SAP was provided as supplemental figure 6.

Comment 4 Though the authors demonstrated a certain prognostic benefit of analyzing the cardiac marker activity, they made no comparison with other biomolecules, which have recently discussed to be useful for patients with AP (Int. J. Mol. Sci. 2020, 21, 338). Do assessments of cardiac markers provide an advantage (e.g. resulting in a more

precise diagnosis or detecting patients at risks?

Reply 4 Thanks for your kind suggestion. Among the biomarker and scoring systems mentioned in the paper you provided (Int. J. Mol. Sci. 2020, 21, 338), serum level of CRP and PCT as well as APACHE II, SOFA, BISAP and MCTSI were compared to CK-MB in the aspect of predictive ability for SAP or POF occurrence. The results were separately showed in Figure 2 and 3.

Comment 5 What role do age and gender play? Many biomarkers vary in their reference values, i.e. physiological range, particularly depending on these two variables?

Reply 5 Thanks for your kind suggestion. The CK-MB was reported to be influenced by gender (*Braz J Med Biol Res.* 2011;44(3):236-239. doi:10.1590/s0100-879x2011007500007) or age (*Can J Appl Physiol.* 2000;25(6):419-429. doi:10.1139/h00-027). In our study, there were no significant difference among mild, moderate and severe acute pancreatitis in age and gender. We reanalyzed the difference between non-SAP and SAP group and find there were still no significant difference in age [median (IQR), 49 (39.25, 63) vs 47 (37.75, 60.25), P=0.5817] and gender (male/total, 13/56 vs 113/182, P=0.053).