Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Ulinastatin in the Treatment of Severe Acute Pancreatitis: a single-center randomized controlled trial" (MS No: 81071). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made a correction which we hope meets with approval. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript, Title page, abstract et. Point by point responses to the reviewers' comments is listed below this letter. Thank you! We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Suqin Wang

We would like to express our sincere thanks to the reviewers for their constructive and positive comments.

Replies to Reviewers

Specific Comments

Responds to the reviewer's comments:

Reviewer #1:

Introduction 1) Introduction is redundant. Please make it a little shorter and reduce the number of irrelevant citations.

Author Response: Thank you very much for your important comments. We had made it a little shorter and reduce the number of irrelevant citations, Thank you very much for your good comments.

Method

1. "In addition, 100 ml of saline solution with a concentration of 0.9% was

administered to individuals with fluid restriction"; What does this mean? Do you mean dissolving the UTI in 100ml of saline?

Author Response: Thank you very much for your important comments. We had deleted it to avoid misunderstandings. Thank you!

2. The authors should provide a definition of "clinical efficacy".

Author Response: Thank you very much for your important comments. We had provided a definition of "clinical efficacy" in the Outcome assessment section. Thank you!

3. It is difficult to tell whether the total daily dose is 800,000 units (400,000 units administered twice) or 400,000 units, so please state clearly.

Author Response: Thank you very much for your important comments. We had re-write it and state clearly, total daily dose is 800,000 (400,000 units administered twice) units thank you!

4. Mortality at 7 days is associated with management of systemic inflammation, including SIRS and multiple organ failure. In previous reports of acute pancreatitis, the main outcome was death during hospitalization. If possible, authors should show in-hospital mortality.

Author Response: Thank you very much for your important question. As previous studies and our clinical experience showed that Ulinastatin can significantly reduce the early mortality of severe patients, included Severe AP. Hence, we want to explore the effective of early Ulinastatin treatment in Severe AP patients. So, the primary endpoint of this study was 7-day mortality in the present study. Long-term outcome follow-up need to explore in the future. We also stated this limitation in the discussion. Thank you very much for your good comments.

5) " (1) patients who were unlikely to be salvaged upon admission" "(6) multi-organ dysfunction"; The authors excluded fatal cases and multiple organ failure. This raises

concerns about selection bias. What criteria did you use to diagnose them? In general, patients with multiple organ failure and high risk of mortality should be admitted to the ICU. In particular, many of the patients who died within 7 days should have multiple organ failure or a high risk of death, so this selection criterion is very important.

Author Response: Thank you very much for your important question. This may be an inaccuracy of our description. We mean that fatal cases and multiple organ failure before illness. We had revised it. Thank you!

6) Also, the status of organ damage in pancreatitis should be presented according to the Modified Marshall scoring system.

Author Response: Thank you very much for your important question. This may be an inaccuracy of our description. We mean that fatal cases and multiple organ failure before illness. We had revised it. Thank you!

7) "Extended hospital stays and greater healthcare costs have previously been recorded for individuals who have severe multiple traumas or who need intensive critical care. This study thus compared the two groups in terms of how long they stayed in the hospital and how much their treatment ultimately cost." Authors should cite previous literature on multiple trauma.

Author Response: Thank you very much for your important question. I am sorry, it was our mistake, we had revised it. Thank you!

8）It is a single-center study, and it seems that the treatment policy for pancreatitis is unified. So the authors should describe the standard of care for severe pancreatitis at your hospital such as fluid replacement, sandostatin and management of pain relief.

Author Response: Thank you very much for your important comment. The treatment strategy of severe AP according to the severe AP guideline[1-3]. As the treatment policy for pancreatitis was to more, and all treatment policy, such as drugs and continuous

hemodiafiltration were same between two groups. We had stated it in the backgrounds and methods. Then, we did not describe the standard of care for severe pancreatitis in the present study. Thank you very much.

Results

1) "From October to December 2021, we assessed 217 elderly patients. In total, 181 participants were randomized at a 1:1 ratio and given either UTI treatment (n=91) and receiving a placebo (n=90)." Why were only elderly patients included in the study? I believe that this study also included younger patients.

Author Response: Thank you very much for your important comment. I am sorry, it was our mistake, we had deleted “elderly”, and revised it. Thank you!

2) page 7; "Inpatient expenditures and length of stay after surgery" The current study did not involve surgery.

Author Response: Thank you very much for your important comment. I am sorry, it was our mistake, we had deleted “after surgery”, and revised it. Thank you!

Conclusion 1) Costs were not significantly different between the two groups.

Author Response: Thank you very much for your important comment. We had revised it. Thank you!

Minor 1) In Tables, UTI is misspelled as TUI. Please correct. 2) There are many errors in this manuscript. Therefore, please make sure to thoroughly revise the document once again.

Author Response: Thank you very much for your important comment. We had revised it. Thank you!

Reviewer #2:

Specific Comments to Authors: The authors in this study aimed to investigate whether ulinastatin (UTI) could be used to improve the outcomes of patients with severe acute pancreatitis (AP). This study is clinically relevant and well conducted. The core limitation is its single center design and we agree with the authors that further studies to further explore the efficacy of UTI. Peer review criteria checklist 1 Title. Does the title reflect the main subject/hypothesis of the manuscript or need modification? - YES 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript or need modification? - YES 3 Key Words. Do the key words reflect the focus of the manuscript? -YES 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? - YES 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc) in adequate detail? - No. Will require further revision - please refer to additional questions below 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? - YES 7 Discussion. Does the manuscript discuss the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Need modification 8 Illustrations and tables. Are the figures, diagrams, and tables sufficient, good quality and appropriately illustrative, with labeling of figures using arrows, asterisks, etc, and are the legends adequate and accurately reflective of the images/illustrations shown? - YES 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? - YES 10 Units. Does the manuscript meet the requirements of use of SI units? - YES 11 References. Does the manuscript appropriately cite the latest, important and authoritative references in the Introduction and Discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? - YES, the references are adequate 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and

grammar accurate and appropriate? - YES. However, there are certain questions and corrections that the author will have to address. Please refer to additional comments below Additional questions for the authors to address - Under the results section, the authors should change "From October to December 2021" to "From October 2018 to December 2021" as this would clarify the study period. - The authors mentioned that 217 elderly patients were assessed, however the inclusion criteria of the trial states that patients from the ages of 25-75 were included in the study. - The authors need to further describe what constitutes the endpoint of efficacy, including cure, effective and ineffective - The authors conclude that UTI treatment could enhance kidney, hepatic and coagulation function however this does not appear to be reflect in their data. - The authors conclude that UTI treatment could decrease the risk of death with hyperinflammation after severe AP but this does not appear to be reflected in their data - In the trial profile, further details of why patients who did not meet the trial inclusion criteria could be added - In table 1, the percentages for smoking history is missing - In the tables, the treatment group should be named UTI group instead of TUI group - The authors conclude that the associated costs with hospitalization dropped significantly but this is not reflected in their data

Author Response: Thank you very much for your important question. We have studied comments carefully and have made a correction which we hope meets with approval. We had described what constitutes the endpoint of efficacy, including cure, effective and ineffective. The data of kidney, hepatic and coagulation function laboratory indicators can be seen in the table 3. The data of 7-day mortality and hyperinflammation can be seen in the table 2 and table 3. Patients who did not meet the trial inclusion criteria could be seen in the figure 2. We had added the data of percentages for smoking history. We haad revised the TUI to UTI. Thank you very much for your comments again.

Reviewer #3:

The diagnostic criteria for severe acute pancreatitis are unknown in this study. Please indicate the revised Atlanta classification, APACHE II score, and necrotizing

pancreatitis rate at diagnosis. Please indicate the period from the onset of acute pancreatitis to the time of diagnosis. In this study, cholelithiasis accounted for many of the causes, which is different from the usual patient background. Please indicate the percentage of patients who underwent endoscopic bile duct drainage.

Author Response: Thank you very much for your important question. We had revised and added it in the text and table 1. Thank you very much for your good comments again! cholelithiasis accounted for many of the causes maybe related to the Chinese population.

Reviewer #4:

The paper is very interesting and presents a novel treatment for severe pancreatitis with very good results. The paper is well written, the introduction is well organized and the methods are also well described. The results are overwhelming and suggest that UTI might become an important treatment for severe acute pancreatitis. I have only some questions to be answered: Did you performed a sub analysis of UTI according to the cause of pancreatitis? Does alcoholic pancreatitis have better or worse response to UTI? The 2 major adverse events were abnormal liver enzymes and granulocytopenia. What were the mean values of liver enzymes? Did they recover after? Did you need to reduce dose or suspend? And about granulocytopenia..did that fact increase the risk of infection? Did you perform a sub analysis at day 30 and day 90 to see the prognosis? How common was walled-off necrosis in both groups? In the first sentence of the results I would change to: "From October 2018 to December 2021..."

Author Response: Thank you very much for your important question. In the present study, we just to explore the clinical efficacy of UTI after all type SAP. So, we did not performed a sub analysis of UTI according to the cause of pancreatitis. But it's a very good idea and we'll consider it in the future study. The mean values of liver enzymes in the table 3, all patients recover after treatment, not reduce dose. As previous studies and our clinical experience showed that Ulinastatin can significantly reduce the early mortality of severe patients, included Severe AP. Hence, we want to explore the

effective of early Ulinastatin treatment in Severe AP patients. So, the primary endpoint of this study was 7-day mortality in the present study. Long-term outcome follow-up need to explore in the future. We also stated this limitation in the discussion. Thank you very much for your good comments. We had added the rate of necrosis SAP. We had revised according to your comments. Thank you!

Thank you very much for your comments again.

Suqin Wang
14-May-23

1. Jaber S, Garnier M, Asehnoune K, Bounes F, Buscail L, Chevaux J, et al. Guidelines for the management of patients with severe acute pancreatitis, 2021. 2022; 41:101060.
2. Bai X, Jin M, Zhang H, Lu B, Yang H, Qian JJPojotIAoP. Evaluation of Chinese updated guideline for acute pancreatitis on management of moderately severe and severe acute pancreatitis. 2020; 20:1582-6.
3. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. 2019; 14:27.