

Answer to Reviewers

Reviewer 1: Minor revision

The topic is interesting, so a short meta-analysis definitely has a place. Overall, paper is well written and concise. However, several issues should be addressed prior to the publication:

1. From the clinical point of view the presented highlights and the discussion are incorrect. The authors statements that aggressive IV fluid therapy improves mortality in any AP patient and early aggressive IV fluid therapy is recommended are no longer true - see the last recommendations (JPN 2015, AGA 2018, WSES 2019). All guidelines advocate moderate and goal directed i/v fluid administration, although recognize that further analysis of volume and type of fluids is needed.
2. Methodology: what was the exact search strategy and terms used?
3. Methodology: how was the quality of included papers assessed.

ANSWERS: Thank you for your input and consideration.

1. We have corrected that in the manuscript and clarified that in the recent past most guidelines recommended early aggressive IV fluid therapy, but recent AGA guideline recommend cautious IVF administration.
2. Our search was conducted as follow: 3 electronic databases were used: PubMed, Cochrane, and Embase. Then we searched randomized controlled trials and cohort studies that evaluated aggressive IV fluid therapy in AP patients, from inception till 25 December 2018. The cohort studies as well as randomized controlled trials comparing aggressive fluid administration to non-aggressive fluid administration in patients with acute pancreatitis were included. Only articles published in the English language were screened. This meta-analysis was performed in concurrence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary I) and was registered on PROSPERO international prospective register of systematic reviews.
3. Only RCTs and Cohort studies were included and we used PRISMA AND PROSPERO guidelines

Thank you again for your insightful feedback, time and consideration.

Reviewer 2: Accept

Thank you.

Reviewer 3: Accept (High priority)

The authors have carried out a meta-analysis of aggressive fluid resuscitation in acute pancreatitis. This is an important topic and a means of treatment that is regularly taught by clinicians. The data supporting this approach is controversial and this study has aimed to address the subject. It is clear from their methodology that much of the published evidence is weak, with poorly designed studies and inadequate end points. The authors started with a large number of studies but ended having to include only 11 that fulfilled the study requirements. These data demonstrate that the use of aggressive fluid resuscitation versus goal directed fluid resuscitation could actually be harmful. The authors quite rightly suggest that

further data is required before a definitive answer can be given but the manuscript is certainly a very useful addition to the published literature.

Thank you for your input and your time reviewing our work, we truly appreciate it.

Reviewer 4: Major revision

The manuscript is a meta-analysis of the evidences on the intravenous fluid strategy for acute pancreatitis. The topic titled “Aggressive Intravenous Fluid Resuscitation Beneficial in Acute Pancreatitis” is indeed controversial in clinic, and some conclusions were drawn in this manuscript according to the analysis method.

Major revision

1. The heterogeneity in the study is relatively large. Though the reasons for such a great heterogeneity are discussed in the manuscript, it was not stated whether baseline data of enrolled patients (gender, age, presence of underlying disease, etc.) were provided in each reference included in the study or whether baseline data of intergroup patients were statistically analyzed in these references. The statistical **differences existed in baseline data?** In addition, a **quality assessment for the references** is required.
2. Clinical classification of acute pancreatitis has great influence on prognosis. Three subtypes of acute pancreatitis were mentioned, but it was not stated whether clinical classification of patients with acute pancreatitis was provided in the included references. I suggested that if the references included in the study provide the above data or data, it is recommended to conduct **subgroup analysis** according to **different baseline data and clinical classification** of acute pancreatitis, so as **to reduce heterogeneity** and improve the credibility. Or If the references included in the study did not provide the above data, a **more detailed explanation** should be given in the study.
3. Inclusion criteria for this study indicated that the study should be designed as a randomized controlled trial or cohort study, otherwise excluded. Randomized controlled trials and cohort studies are prospective studies and should generally be statistically analyzed using **relative risk values**. The random effects model and fixed effects model were also mentioned in the paper to analyze the corresponding relative risk, but all the forest pictures showed the corresponding odds ratio. whether it was a fault in the use of the analysis software, or author confused both of them? The difference affect the results and conclusions?
4. With a long time span of the literature inquired in this study, and development in the treatment of acute pancreatitis, **are the standards of intravenous fluid resuscitation consistent in the included references?** Is it **combined with other treatments?** The above questions should be checked and analyzed for their influence on the research results and should be extensively explained.

Minor revision 1. A funnel plot is required in the manuscript

ANSWERS: Thank you very much for your thorough review and insightful feedback. We have followed your great input and improved the manuscript as follow:

1. We do have the baseline characteristics collected in our raw data, and we have also explored the differences between baseline characteristics and we found differences on age, we then did a subgroup analysis for all outcomes according to AGE and ETIOLOGY of AP. No significant differences were found in both subgroup analysis (etiology and age). This material is available as supplemental. Thanks for this suggestion, it is very valuable.

In terms of quality assessment we have used Cochrane scale for RCTs and Newcastle scale for cohort studies.

2. As above, we did a subgroup analysis for all outcomes according to etiology of AP and age, to reduce heterogeneity. The severity of pancreatitis had lot of data missing and very heterogeneous, hence we could not do subgroup analysis for that and we have explained that in the manuscript. This material is available as supplemental II.

“We explored studying our outcomes in subgroups according to AP etiology and also according to age groups (older >55 years old vs. younger <55 years old). However, very few studies had data for us to include in the subgroup analysis and most studies did not report appropriate data for this analysis. From the available data, we did not find any significant differences in the subgroups analysis (supplemental II). Subgroup analysis by AP severity could not be studied due to lack of data”

3. Thank you for this correction, we have expressed all outcomes in relative risks instead of odds ratios. We have corrected the tables and manuscript.
4. This is a great question, we have clarified in the manuscript that the included studies were only performed to assess IV fluid amount and timing of administration in AP patients. The time and amount of IV fluid administered were the only outcomes of the studies, and also no other treatment was given. The focus of the studies was to assess the timing (usually fluid administered <24hrs vs >24hrs) and the amount (aggressive IV fluid, which the definition varied from 3ml/kg/hr. to 5ml/kg/hr. within first 24 hr. among studies). We have added this explanation to the manuscript to clarify this. (Method section, inclusion/exclusion criteria subsection)

- Minor: A funnel plot was created and included in the manuscript (available in supplemental II).

Thank you again for such great feedback, we really appreciate your time and we hope that all the hard work we have put on this manuscript and revisions will be optimal and satisfactory for you and the editorial board, and result in publication.

Best regards,

The authors