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# Effect of aggressive versus conservative hydration for early phase of acute pancreatitis in adult patients: A meta-analysis of 3,127 cases

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ABSTRACT

*Background:* The advantages of aggressive hydration compared to conservative hydration within 24 h for acute pancreatitis (AP) remain controversial in adult patients. A meta-analysis was undertaken to investigate whether aggressive strategies are more beneficial.
*Methods:* We searched (on February 1, 2021) PubMed, Embase, and the Cochrane Library for eligible trials that assessed the two therapies and performed a meta-analysis. The primary endpoint was in-hospital mortality. Secondary outcomes were adverse events (e.g., renal failure and pancreatic necrosis) within 24 h of treatment.
*Results:* Five randomized controlled trials and 8 observational trials involving 3127 patients were identified. Patients with severe pancreatitis showed significant difference of in-hospital mortality (OR 1.75; 95% CI 1.32–2.33) in aggressive hydration group, which were less susceptible to study type and age. Patients with severe pancreatitis were likely to develop respiratory failure (OR 5.08; 95% CI 2.31–11.15), persistent SIRS (OR 2.83; 95% CI 1.58–5.04), renal failure (OR 2.58; 95% CI 1.90–3.50) with significant difference. A longer hospital stay was observed in patients with severe pancreatitis (WMD 7.61; 95% CI 5.51–9.71; $P < 0.05$) in the aggressive hydration group. Higher incidence of pancreatic necrosis (OR 2.34; 95% CI 1.60–3.42; $P < 0.05$) was major susceptible to observational studies, old patients and mild pancreatitis.
*Conclusions:* Compared to conservative hydration, aggressive hydration increases in-hospital mortality and the incidence of renal failure, pancreatic necrosis with relatively strong evidence. Further investigation should be designed with a definitive follow-up period and therapeutic goals to address reverse causation bias.


## 1. Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas that ranges from a mild self-limited disease to a severe life-threatening condition and is associated with a hospital mortality rate of 15% [1]. According to the updated Atlanta classification, there are two stages (early and late) that comprise three categories identified as mild, moderate, or severe [2]. Distant organs are commonly affected through a myriad of disturbances involving hyperinflammatory factors, injury to the vascular endothelium and redistribution of fluid as AP progresses [3].

Fluid administration for AP has gained worldwide attention among healthcare providers in the last 10 years. It is considered the cornerstone of early treatment of AP [4,5]. Despite efforts to investigate the advantages of aggressive hydration, which prior guidelines recommended [5,6], aggressive hydration remains controversial. Guidelines recommend aggressive hydration with an infusion rate of 250–500 ml/h or 5–10 ml/kg/h to maintain intravenous volume or stable hemodynamics [2,4]. Nevertheless, these strategies were mainly based on expert opinion [7,8], nonhuman studies [9,10] and limited clinical studies [11,12].

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Several studies comparing aggressive hydration and conservative hydration have been reported [12–20], and the advantages of aggressive hydration are difficult to discern due to limited sample sizes and conflicting results. Conversely, some trials [16,17,21–23] demonstrated that aggressive hydration may be associated with higher mortality or a greater incidence of adverse events. Recently, Gad et al. [24] performed a meta-analysis to investigate the efficiency and safety of aggressive hydration; however, some deficiencies due to duplicate studies and the inclusion of abstract data makes it difficult to assess the quality of the studies. They might overestimate the safety of aggressive hydration, even though the primary outcome is not statistically significant. Therefore, we performed this meta-analysis to pool the available data and evaluate the efficiency, safety and potential advantage of conservative hydration.

## 2. Methods

### 2.1. Search strategy and study selection

Studies were obtained from the electronic databases PubMed, Embase, and the Cochrane Library. Searches were restricted to human studies and English-language publications. The following MeSH terms and combinations were searched in "Title/Abstract": *lactate ringer's*, *pancreatitis*, and *fluid therapy* (detailed search strategy is shown in Supplementary Table S1). Additionally, the electronic search was supplemented with manual screening of the citation lists of all retrieved studies to broaden the search. When multiple studies reported duplicate data or the same population, the most recent or complete data were included. Before performing this meta-analysis, a priori analysis of the motivation and inclusion criteria of the identified studies was conducted; some studies that investigated the influence of fluid type, especially for lactated ringer's solution, were also appropriate for inclusion in the present study. Therefore, the MeSH term lactated ringer's solution and combinations of the individual words were added to our electronic search. The meta-analysis was performed identically with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for systematic reviews and meta-analyses [25]. The latest search was performed on February 1, 2021.

All comparative trials that compared aggressive hydration with conservative hydration had at least one of the following comparable outcomes and enrolled adult patients with AP. Aggressive hydration was defined as fluid administration at a rate greater than 10 ml/kg/h or 250 ml/h for the first 24 h. Alternatively, with significant variability in the medical record over time and difficulty with retrieving data on fluid volume (FV) every hour per kilogram from a case, patients receiving FV > 4,000 ml or more than 1/3 of the total 72 h FV within the first 24 h in observational studies were also considered to have fulfilled the definition of aggressive hydration. Fluid therapy at a lower rate or FV than aggressive hydration was defined as conservative hydration. Trials in which differentiation between aggressive and conservative fluid administration was not clearly predefined were excluded, as were trials relevant to patients undergoing fluid resuscitation for AP induced by endoscopic retrograde cholangiopancreatography or treated perioperatively. Editorials, letters, review articles, conference abstracts, case reports and animal experiments were not included.

### 2.2. Data extraction

Extractable data from the included trials were summarized individually by two of the authors (Zhan and Wu). Any discrepancies were resolved by the adjudicative senior authors (Liao and Lai).

The following data were extracted from the included studies: first author, year of publication, study design, characteristics of patients, inclusion and exclusion criteria, matching criteria, severity of AP, and number of enrolled cases for aggressive hydration and conservative hydration. Severity of AP was classified as mild or severe according to the Atlanta classification, research demonstration or the proportion of severe pancreatitis. If more than 50% of the enrolled patients had severe pancreatitis or two organs failure in the early phase of AP, the study was classified as predicting severe pancreatitis. Mortality (In-hospital mortality) was regarded as the primary safety outcome. Secondary outcomes comprised the posttreatment incidence of persistent systemic inflammatory response syndrome (SIRS), pancreatic necrosis, persistent organ failure (OF), renal failure, respiratory failure, and length of hospital stay (LOS). In addition to the primary endpoints, all eligible data were obtained within the first 24 h.

### 2.3. Quality assessment and statistical analysis

Trials were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to rate the level of evidence [26] with the GRADE profiler (GRADEpro, version 3.6). Regarding the quality of evidence, the included studies were classified separately as randomized control trials (RCTs) and observational studies into 4 categories as follows: very low, low, moderate, or high.

To assess the risk of bias, the Cochrane Collaboration tool was used to assess RCTs, and the Newcastle-Ottawa scale (NOS) was used to assess observational studies. The risk of bias in RCTs was rated according to six biases: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. To evaluate the dynamic change influenced by the complex intervention, blinding of patients and clinicians was extremely difficult and generally not feasible, we therefore determined that mortality was less susceptible to the absence of blinding. Trials were regarded as having a high risk of bias if at least one of the factors, other than blinding, was judged as high risk. The details of the quality assessment for the observational studies were summarized according to three factors: method of patient selection, comparability of study groups, and assessment of exposure. A score of 0–9 was allocated (as stars) to each observational study, and studies achieving seven or more stars were considered to be of high quality.

Data were combined for meta-analysis using Review Manager version 5.3, and the statistical tests were two-sided. The odds ratios (ORs) for dichotomous variables or weighted mean differences (WMDs) for continuous variables were calculated using the chi-square test with significance set at $P < 0.05$. Pooled data were estimated with 95% confidence intervals (CIs). Statistical heterogeneity was quantified using the $I^2$ statistic, with the level of significance set at $I^2 > 40\%$. If the heterogeneity was considered to be substantial, we performed the analysis with a random-effects model; otherwise, a fixed-effects model was used. Additionally, continuous data were presented as median and range values, and standard deviations were calculated using the technique described by Hozo et al. [27]. Prespecified subgroup analyses were performed to determine the source of heterogeneity regarding the average age, severity of pancreatitis and study type. To test the robustness of the outcomes, sensitivity analysis was performed by omitting one trial at a time and analyzing the remaining trials. Trials with events in both arms were included. Funnel plots were used to screen for potential publication bias.

## 3. Results

Thirteen included studies [12–20,28–31] published from 2009 to 2020 that enrolled 3127 patients fulfilled the selection criteria

(Fig. 1). An expanded search of the reference lists of the included studies and reviews did not yield any additional studies to evaluate. Some overlap in patients was potentially present in two trials [15,17]; however, a discrepancy between the study period and endpoints was displayed as well, and both studies were included in the final analysis.

### 3.1. Characteristics and quality assessment of the included studies

The study characteristics are shown in Table 1. Among the 5 included RCTs [12,13,15,17,28], 3 studies [12,13,28] were judged to be of high quality (Supplementary Figs. S1) and 2 studies [15,17] were judged to be of low quality with a high risk of bias in terms of selective reporting and other bias. These 2 studies presented a high risk of bias because of absence of declaration of conflict of interest and the lack of a clear definition of primary-secondary outcomes. One of the RCTs [15] that was published early used a clear definition of fluid rate (FR) similar to that of prior high-quality RCTs; another RCT [17] used a different method of assignment that was identical for investigating the influence of aggressive hydration. Among the 8 included observational studies [14,16,18–20,29–31], 5 studies [14,18,19,29,31] were assessed as high quality using the modified NOS, another 3 studies [16,20,30] were assessed as low quality (Supplementary Table S2). In terms of the therapeutic protocol for the observational studies, 6 studies [14,18,20,29–31] directly defined aggressive hydration with a clear FV, but in 2 studies [16,19], aggressive hydration was defined as the use of a percentage of the cumulative 72-h FR within the initial 24 h. However, all the included observational studies fulfilled the predefined criteria for aggressive hydration with an FV of at least 4,000 ml, except for one trial [19]. Patients in 6 studies [13,17,28–31] enrolled young patients (average age ≤50 years old), and the remaining 7 studies [12,14–16,18–20] enrolled old patients (average age >50 years old). Based on the description of the included studies or the proportion of severe pancreatitis, mild pancreatitis was reported in 7 studies [12–14,18,19,28,30], and 6 studies [15–17,20,29,31] enrolled patients with severe pancreatitis. Categorization of fluid type seems to be impossible due to the differences in protocols, but most of them selected a crystal solution as the main resuscitation fluid.

### 3.2. Primary outcome

Pooled data on mortality from 12 studies [12,14–20,28–31] showed a significant difference between the aggressive hydration and conservative hydration groups (9.8% and 7.6%; OR 1.66; 95% CI 1.28–2.16; $P = 0.0001$; $I^2 = 26\%$; Fig. 2). Subgroup analysis indicated that increased mortality was observed with aggressive hydration in both young patients (OR 2.26; 95% CI 1.38–3.68; $P = 0.001$) and old patients (OR 1.46; 95% CI 1.07–2.00; $P = 0.02$). Similarly, study type did not affect significant outcomes with respect to whether they were RCTs (OR 3.20; 95% CI 1.54–6.63; $P = 0.002$) or observational studies (OR 1.50; 95% CI 1.13–1.99; $P = 0.005$). Pooled estimate in patients with severe pancreatitis was statistically significant (OR 1.75; 95% CI 1.32–2.33; $P = 0.0001$), which may have been

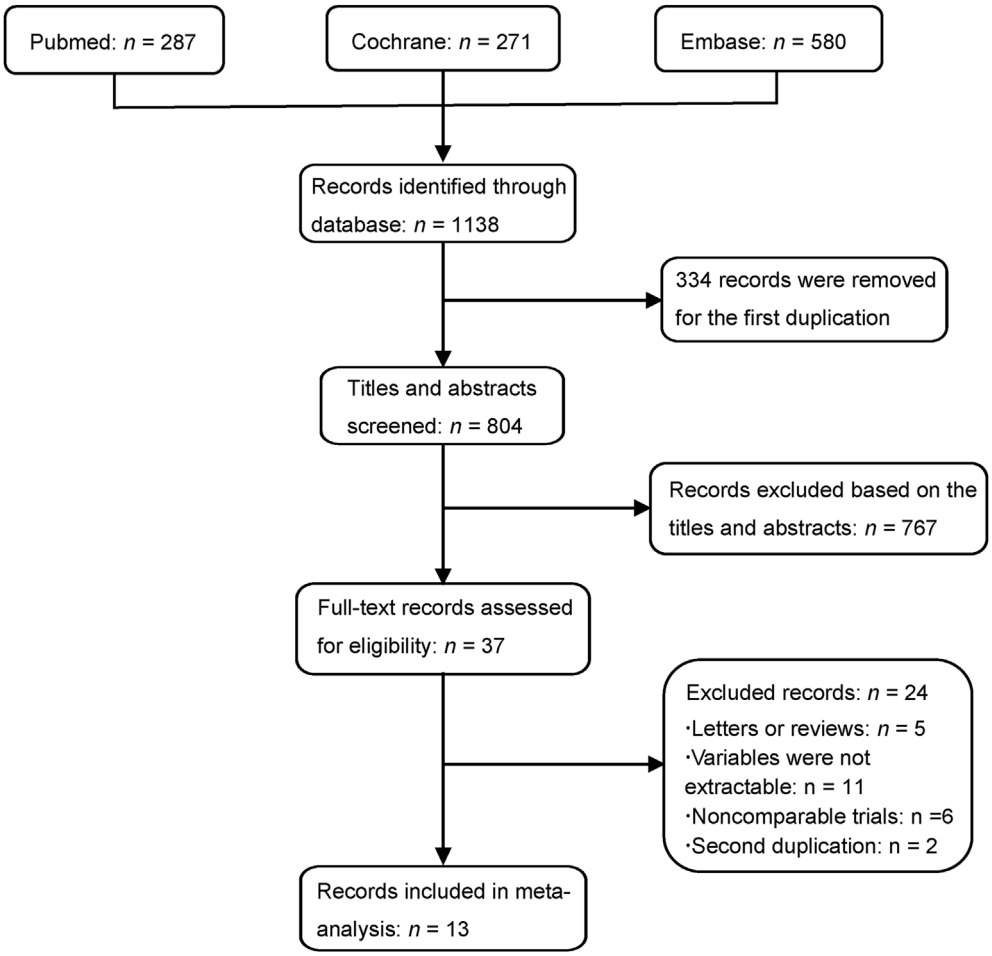


**Fig. 1.** PRISMA flow diagram showing inclusion and exclusion of studies.

**Table 1**
Characteristics of included studies.

| Study | Type | Patients | | FR and/or FV (first 24 h) | | Mean/median age (years) | | Severity of pancreatitis | Included outcomes | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | aggressive | conservative | aggressive | conservative | aggressive | conservative | | | |
| Buxbaum et al. [13] | RCT | 27 | 33 | 20 ml/kg bolus follow by 3 ml/kg/h; 5.6 L | 10 ml/kg bolus follow by 3 ml/kg/h; 3.9 L | 44.4 | 45.3 | mild | Persistent SIRS | High |
| Cuéllar et al. [28] | RCT | 43 | 45 | 20 ml/kg follow by 3 ml/kg/h; 4.3 L | 1.5 ml/kg/h; 2.6 L | 36.69 | 38.6 | mild | Mortality; OF; LOS; RF; persistent SIRS; PN; Re.F | High |
| De-Madaria et al.[#] [14] | RP | 61 | 63 | FV > 4.1 L | FV < 3.1 L | 57 | 73 | mild | Mortality; OF; PN; Re.F | High |
| Gardner et al. [16] | R | 17 | 28 | FV ≥ 1/3 of 72 h total FV; 4.9 L | FV < 1/3 of 72 h total FV; 1.7 L | 53 | 57 | severe | Mortality; OF; LOS; persistent SIRS; PN | Low |
| Li et al. [&] [29] | RP | 70 | 78 | FR ≥ 3 ml/kg/h; 4.5 L | FR < 3 ml/kg/h; 3.8 L | 46 | 46 | severe | Mortality; RF; Re.F | High |
| Mao et al. * [15] | RCT | 36 | 40 | 10–15 ml/kg/h; 4.2 L | 5–10 ml/kg/h; 4.8 L | 51.3 | 50.2 | severe | Mortality; RF; persistent SIRS | Low |
| Mao et al. * [17] | RCT | 56 | 59 | Rapid hemodilution; 5.8 L | Slow hemodilution; 4.8 L | 49.8 | 48.8 | severe | Mortality; persistent SIRS | Low |
| Messallam et al. [30] | R | 103 | 102 | FV ≥ 4.475 L; 5.9 L | FV ≤ 2.8 L; 1.6 L | 43.7 | 48.3 | mild | Mortality; OF; LOS | Low |
| Singh et al.[#] [18] | R | 256 | 260 | FV > 4.3 L | FV < 3.2 L | 55.4 | 49.5 | mild | Mortality; OF; PN | High |
| Warndorf et al. [19] | R | 340 | 94 | FV ≥ 1/3 of 72 h total FV; 3.5 L | FV < 1/3 of 72 h total FV; 2.4 L | 54 | 49 | mild | Mortality; OF; LOS; persistent SIRS | High |
| Wu et al. [12] | RCT | 19 | 21 | 20 ml/kg follow by 3 ml/kg/h; 4.3 L | 1.5 ml/kg/h; 4.6 L | 51 | 51 | mild | Mortality; OF; LOS; RF; persistent SIRS; PN; Re.F | High |
| Yamashita et al. [20] | R | 389 | 708 | FV ≥ 6 L; 8.7 L | FV < 6 L; 3.9 L | 55.5 | 60.4 | severe | Mortality; RF; Re.F | Low |
| Ye et al. [31] | R | 55 | 124 | FV ≥ 4 L; 5.1 L | FV < 4 L; 2.9 L | 44.63 | 47.31 | severe | Mortality; OF; LOS; RF; PN; Re.F | High |

*FV* fluid volume, *FR* fluid rate, *RCT* randomized control trial, *R* retrospective, *RP* retrospective design, prospective data collection. *SIRS* systemic inflammatory response syndrome; *OF* organ failure; *LOS* length of hospital stayed; *RF* respiratory failure; *PN* pancreatic necrosis; *Re.F* renal failure.
*Overlapping patients were potentially presented in these studies, but different outcomes were displayed as well.
[#]Fluid volume was not display directly, but the cumulative total fluid volume in aggressive hydration group was higher than 4 L.
[&]Fluid rate was lower than 5 ml/kg/h, but the cumulative total fluid volume in first 24 h was higher than 4 L.
[¶]Severity of pancreatitis of each study was evaluated by the proportion of severe pancreatitis or recorded through the description of author.

influenced by the inclusion of studies enrolling patients with severe pancreatitis and observational studies enrolling young patients (Supplementary Tables S3 and S4). When the data were split into prespecified subgroups, the test for subgroup differences provided no evidence that the higher mortality of aggressive hydration differed by study type, average age or the severity of pancreatitis ($P = 0.26$).

### 3.3. Secondary outcomes

Six studies [12,14,20,28,30,31] assessed the incidence of renal failure. Patients in the aggressive hydration group experienced renal failure more frequently than those in the conservative hydration group (19.2% and 9.3%; OR 2.38; 95% CI 1.78–3.18; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. S2). The test for subgroup differences was not significant ($P = 0.40$). Subgroup analysis on young patients (OR 2.35; 95% CI 1.26–4.40; $P = 0.008$) and old patients (OR 2.39; 95% CI 1.72–3.31; $P < 0.00001$) also revealed the disadvantage of aggressive hydration. However, in subgroup analysis based on the severity of pancreatitis, unclear evidence was obtained for an effect in patients with mild pancreatitis (OR 1.18; 95% CI 0.46–3.01; $P = 0.73$), whereas patients with severe pancreatitis (OR 2.58; 95% CI 1.90–3.50; $P \leq 0.00001$) showed clear evidence of requiring conservative hydration in the included observational studies (Supplementary Table S4). After separating RCTs from observational studies for further subgroup analysis, nonsignificant differences were found for the included RCTs (Supplementary Table S3).

Regarding pancreatic necrosis, the available data extracted from 6 studies [12,14,16,18,28,31] showed a significant difference (OR 2.34; 95% CI 1.60–3.42; $P < 0.0001$; $I^2 = 0\%$; Supplementary Fig. S3). The test for subgroup differences was not significant ($P = 1.00$). However, limited data assessing pancreatic necrosis for the subgroup analysis of young patients (OR 2.34; 95% CI 0.70–7.82), RCTs (OR 1.73; 95% CI 0.43–6.92) and severe pancreatitis (OR 2.02; 95% CI 0.73–5.54) showed no significant differences ($P > 0.05$), while the remaining of the studies with subgroups of old patients (OR 2.34; 95% CI 1.57–3.49), observational studies (OR 2.40; 95% CI 1.62–3.56) and mild pancreatitis (OR 2.40; 95% CI 1.60–3.62) showed significant differences ($P \leq 0.00001$).

Eight studies [12,14,16,18,19,28,30,31] reporting the incidence of persistent OF were analyzed (Supplementary Fig. S4) and the pooled data did not show a significant difference (OR 1.56; 95% CI 0.93–2.61; $P = 0.09$; $I^2 = 52\%$). The test for subgroup differences was not statistically significant after splitting the studies by study type, average age or severity of pancreatitis ($P = 0.95$).

Pooled data from 6 studies [12,16,19,28,30,31] that assessed LOS are shown in Supplementary Fig. S5, and the results showed no significant differences in the subgroup analyses of study type and average age ($P > 0.05$). However, when analyzing the subgroup data according to the severity of pancreatitis, which were derived from the observational studies, pooled estimates indicated that the aggressive hydration group had a longer LOS than the conservative hydration group among patients with severe pancreatitis (WMD, 7.61; 95% CI 5.51–9.71; $P < 0.00001$; $I^2 = 0\%$), whereas no evidence of a difference was shown among patients with mild pancreatitis (WMD, 0.11; 95% CI -0.86-1.08; $P = 0.82$; $I^2 = 77\%$), and the test for subgroup differences provided evidence that the LOS of the aggressive hydration group was affected by the severity of pancreatitis ($P < 0.00001$).

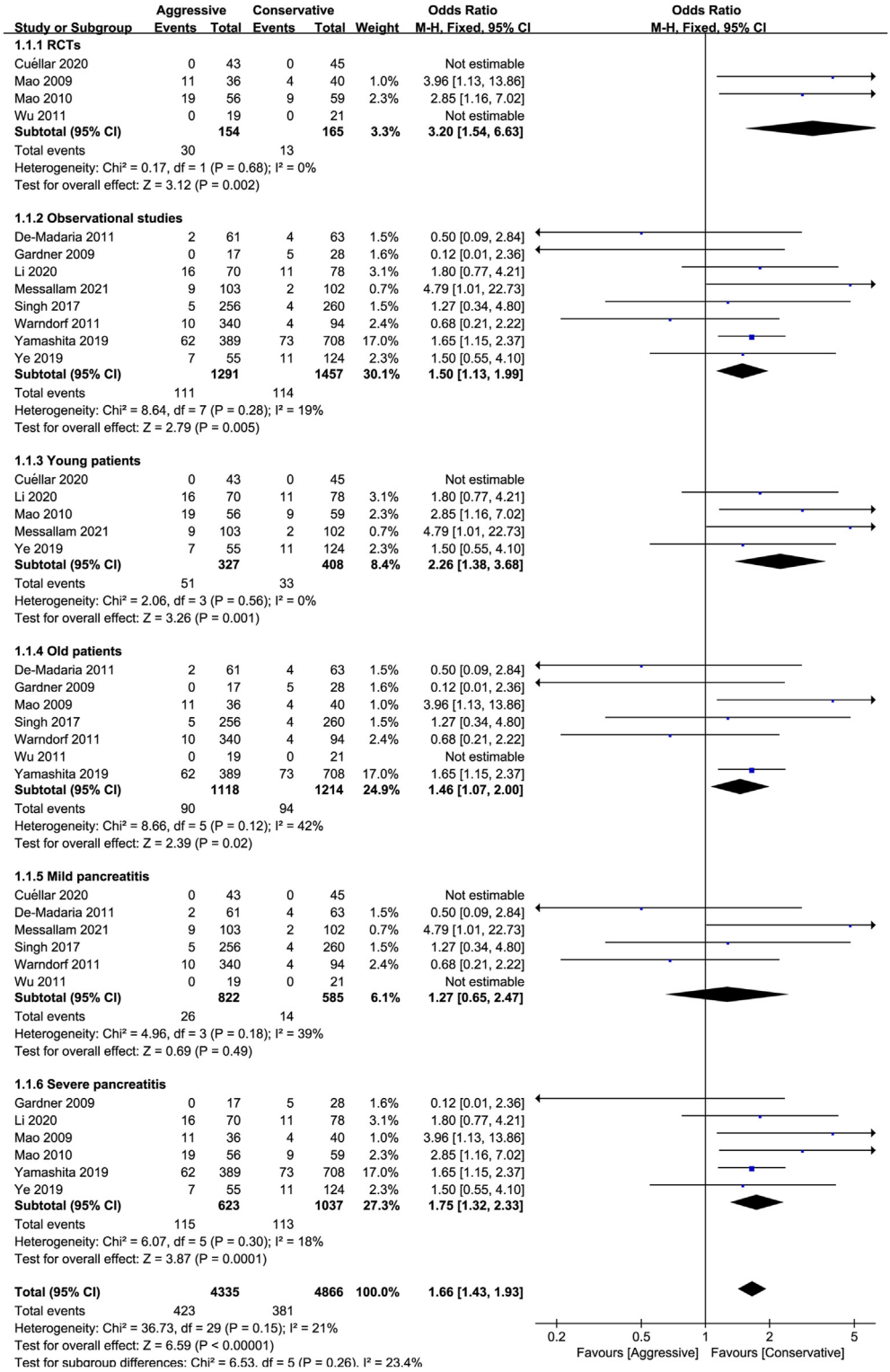


**Fig. 2.** Forest plot displays meta-analysis of in-hospital mortality with odds ratio and corresponding 95%CI with relevant to the overall random effects model; *CI* confidence interval, *M-H* Mantel-Haenszel.

Similarly, a nonsignificant difference (OR 1.16; 95% CI 0.49–2.74; $P = 0.74$; $I^2 = 78\%$; Supplementary Fig. S6) was observed when the incidence of persistent SIRS within 24 h was analyzed independently in 7 studies [12,13,15–17,19,28]. Neither studies grouped by study type nor those grouped by average age showed any statistical significance ($P > 0.05$). However, subgroup analysis showed that aggressive hydration seemed to be beneficial for preventing SIRS aggravation in patients with mild pancreatitis (OR 0.52; 95% CI 0.27–0.97; $P = 0.04$), while conservative hydration in patients with severe pancreatitis seemed to be beneficial (OR 2.83; 95% CI 1.58–5.04; $P = 0.0004$). These two diametrically opposed results inevitably provide evidence that the results were affected by the

severity of pancreatitis (test for subgroup differences, $P = 0.0001$). Further subgroup analysis separating RCTs and observational studies showed that the benefit of aggressive hydration was only derived from an observational study [19], while the benefit of conservative hydration was derived from 2 RCTs [15,17] (Supplementary Tables S3 and S4).

Pooled data from 6 trials [12,15,20,28,29,31] confirmed a significant disadvantage in the aggressive hydration group in terms of the incidence of respiratory failure (OR 3.67; 95% CI 2.62–5.14; $P < 0.00001$; $I^2 = 64\%$; Supplementary Fig. S7). The test for subgroup differences was not significant ($P = 0.23$) There were insufficient data to separately subclassify patients based on their utilization of mechanical ventilation and respiratory failure. Subgroup analysis for old patients showed a significant difference between hydration groups (OR 4.88; 95% CI 3.72–6.40; $P < 0.00001$), while no significant difference was found in the subgroup analysis for young patients ($P > 0.05$). When these studies were subdivided by the severity of pancreatitis, patients with severe pancreatitis had a higher incidence of respiratory failure in the aggressive hydration group (OR 5.08; 95% CI 2.31–11.15; $P < 0.00001$), but no similar significant difference was found in the subgroup analysis of patients with mild pancreatitis ($P > 0.05$). Further subgroup analysis was performed after separating RCTs from observational studies (Supplementary Tables S3 and S4), and the results intuitively revealed that significant differences among the studies including old patients and patients with severe pancreatitis.

### 3.4. Sensitivity analysis and publication bias

The sensitivity analysis results are shown in Table 2. The minimum and maximum values of WMD or OR for every outcome are shown. With respect to the results for mortality, renal failure, pancreatic necrosis, respiratory failure and persistent SIRS within 24 h, omitting 1 study did not change the overall conclusion of this meta-analysis. However, the overall estimates for persistent OF (OR 1.81; 95% CI 1.08–3.02; $P = 0.02$; $I^2 = 41\%$) and LOS (WMD 2.29; 95% CI 0.52–4.07; $P = 0.01$; $I^2 = 92\%$) were changed after omitting the study published by Warndorf et al. [19]. Additionally, omitting the same trial in the subgroup analysis of old patients for persistent SIRS yielded a significant change (OR 2.37; 95% CI 1.12–5.02; $P = 0.02$) and led to a nonsignificant difference in the subgroup analysis of patients with mild pancreatitis (OR 0.78; 95% CI 0.34–1.79; $P = 0.56$).

The publication bias for reporting in-hospital morality in this meta-analysis is shown in Fig. 3. There was no obvious publication bias, with a homogeneous distribution around the vertical direction, and the 95% CI included all of the included trials.

### 3.5. Quality of evidence

The GRADE system was used to rate the level of evidence by study type: RCTs and observational studies. All relevant reasons for downgrading and upgrading are displayed in Supplementary Tables S5 and S6. For the primary outcome, the quality of RCTs was rated as high, while that of observational studies was rated as low. Notably, before the dose response gradient was assessed, we tried to pool the primary outcome from 4 included studies [17,20,30,31] whose FV in the aggressive hydration group was higher than 5 L and the calculated value of mortality was 16.09%, higher than that in the conservative hydration group (the calculated value was 9.6%). In addition, when we subdivided studies with the FV threshold of 5 L, the mortality in aggressive hydration group for other studies, which FV is less than 5 L but higher than 4 L in aggressive hydration group, is merely 5.2%, while that of in conservative hydration group is 5.09%, both are significantly lower than aggressive hydration group which FV is higher than 5 L. On the other hand, there was one included study [19] might be a best proof of this section, the FV in two arms of this study is less than 4 L, and the mortality in aggressive hydration is only 2.9%. Therefore, a dose response gradient likely existed, and the quality of the primary outcome was upgraded. Additionally, when we assessed the large effect of mortality in RCTs, the risk ratio was calculated to be higher than 2 after we changed the effect measure in RevMan, and we upgraded the evidence according to the indication of software help. The evidence for each of the following outcomes was rated as moderate: incidence of renal failure, pancreatic necrosis, and respiratory failure. The remaining evidence of outcomes for persistent SIRS, OF and LOS was rated as low to very low. For the observational studies, two reports of renal failure and pancreatic necrosis was rated as moderate; the remaining evidence was rated as low to very low.

**Table 2**
Sensitivity analysis comparison of aggressive hydration and conservative hydration.

| Outcomes | Omitting study | Studies, no | aggressive | conservative | WMD/OR* | 95% CI | *P* value※ | Study heterogeneity | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Patients, no | Patients, no | | | | $\chi2$ | df | *P* | $I^2$ |
| *Primary outcome* | | | | | | | | | | | |
| In-hospital mortality | Mao et al. [17] | 9 | 1327 | 1497 | 1.58 | 1.20-2.08 | **0.001** | 10.77 | 8 | 0.21 | 26% |
| | Gardner et al. [16] | 9 | 1366 | 1528 | 1.74 | 1.33-2.27 | **< 0.0001** | 9.22 | 8 | 0.32 | 13% |
| | Warndorf et al. [19] | 9 | 1043 | 1462 | 1.74 | 1.33-2.27 | **< 0.0001** | 9.90 | 8 | 0.27 | 19% |
| *Secondary outcomes* | | | | | | | | | | | |
| Renal failure | Yamashita et al. [20] | 5 | 248 | 331 | 2.26 | 1.29-3.96 | **0.005** | 4.38 | 4 | 0.36 | 9% |
| | Cuéllar et al. [28] | 5 | 594 | 994 | 2.53 | 1.88-3.41 | **<0.00001** | 0.97 | 4 | 0.91 | 0% |
| Pancreatic necrosis | Singh et al. [18] | 5 | 195 | 281 | 1.93 | 1.02–3.64 | **0.04** | 1.11 | 4 | 0.89 | 0% |
| | Gardner et al. [16] | 5 | 434 | 513 | 2.48 | 1.66-3.70 | **<0.00001** | 1.02 | 4 | 0.91 | 0% |
| Persistent organ failure | Ye et al. [31] | 7 | 839 | 613 | 1.36 | 0.79-2.37 | 0.27 | 10.83 | 6 | 0.09 | 45% |
| | Warndorf et al.#[19] | 7 | 554 | 643 | 1.81 | 1.08-3.02 | **0.02** | 10.09 | 6 | 0.12 | 41% |
| LOS (days) | Ye et al. [31] | 5 | 376 | 143 | 0.12 | −0.82-1.05 | 0.81 | 13.17 | 4 | 0.01 | 70% |
| | Warndorf et al.# [19] | 5 | 237 | 320 | 2.29 | 0.52-4.07 | **0.01** | 51.97 | 4 | <0.00001 | 92% |
| Persistent SIRS | Mao et al. [17] | 6 | 482 | 261 | 0.97 | 0.39-2.44 | 0.95 | 19.44 | 5 | 0.002 | 74% |
| | Warndorf et al. [19] | 6 | 198 | 226 | 1.65 | 0.86-3.16 | 0.13 | 8.21 | 5 | 0.14 | 39% |
| Respiratory failure | Li et al.[29] | 5 | 542 | 938 | 3.02 | 1.45-6.29 | **0.003** | 11.62 | 4 | 0.02 | 66% |
| | Cuéllar et al. [28] | 5 | 569 | 971 | 4.87 | 2.38-9.98 | **< 0.0001** | 9.59 | 4 | 0.05 | 58% |

*WMD/OR* weight mean difference/odds ratio, *CI* confidence interval, *df* degrees of freedom, *LOS* length of hospital stayed, *SIRS* systemic inflammatory response syndrome.
*Minimum and maximum value of WMD or OR of every outcome are shown after the sensitivity analysis.
※Statistically significance results were shown in bold.
#Compared to the initial results for the organ failure and LOS, significant differences were changed after sensitivity analysis.

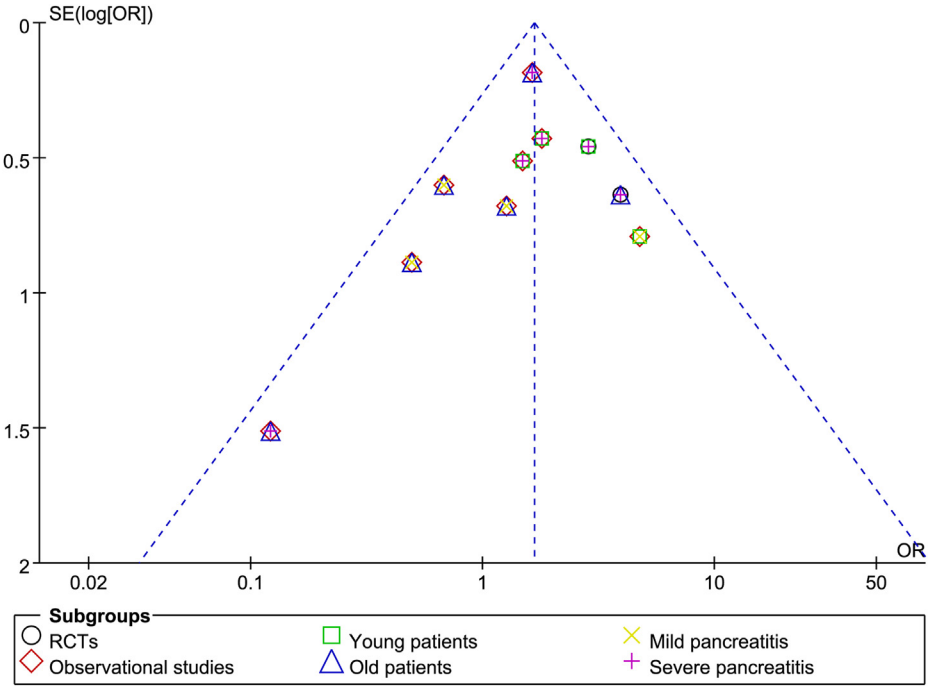


**Fig. 3.** Funnel plot illustrating analysis of in-hospital mortality; *SE* standard error, *OR* odds ratio, *RCT* randomized control trial.

## 4. Discussion

In this meta-analysis of 13 trials incorporating 3127 patients, treatment with aggressive hydration compared with conservative hydration indicated a significant disadvantage in terms of mortality, renal failure and pancreatic necrosis with relatively strong evidence. According to the comprehensive data analysis, the mortality basically indicates the adverse aspects of aggressive hydration treatment, which is not affected by the prespecified subgroup analysis, such as study type and average age. However, when the patients were subdivided according to the severity of pancreatitis, the results suggested the disadvantageous treatment of the aggressive hydration group compared with that of the conservative hydration group in patients with severe pancreatitis. Similarly, subgroup analysis for renal failure also found a disadvantage among patients with severe pancreatitis in the aggressive hydration group, in addition to subgroup analysis for respiratory failure and persistent SIRS after 24 h also yielded similar results. Conversely, the pooled data of patients with mild pancreatitis suggested that the aggressive hydration treatment group was disadvantageous with regard to pancreatic necrosis. Although the same subgroup analysis of persistent SIRS after 24 h suggested the benefits of aggressive hydration, the result showed no statistical significance after omitting one controversial study [19] in the sensitivity analysis. Additionally, there was a trend towards longer LOS in patients with severe pancreatitis in the aggressive hydration group. Therefore, implementation of aggressive hydration treatment in patients with severe pancreatitis must be performed with caution.

RCTs and observational studies were separated for further subgroup analysis according to average age and the severity of pancreatitis. The pooled data of RCTs were similar to those of observational studies in terms of the mortality and incidence of respiratory failure, which were mainly derived from the studies enrolling patients with severe pancreatitis and old patients. In fact, pooling limited data from RCTs to perform subgroup analysis is difficult, and the overall data analysis of secondary outcomes with significant differences was similar to the results of subgroup analysis, which were mainly derived from the included observational studies. Regarding the incidence of renal failure, the subgroup analysis showed the disadvantage of aggressive hydration in observational studies; however, it should be indicated that nearly 75% of the patients included had severe pancreatitis. Conversely, when a higher proportion of patients with mild pancreatitis were included, an adverse effect of aggressive hydration was observed in the data analysis of the incidence of pancreatic necrosis.

However, pooled estimates from the sensitivity analysis were changed after excluding the study conducted by Warndorf et al. [19]. Although this study fulfilled the inclusion criteria and the risk of bias assessment indicated that the study was high quality, there were several potential factors relevant to the statistical alteration. Such as the FV less than 4,000 ml, unbalanced sample sizes in both study arms and finally, the number of included patients with mild pancreatitis in this study accounts for a large proportion of the total sample size. As a result, if the factors were indeed shown, a significant difference in estimates for OF and persistent SIRS could be found, and aggressive hydration was potentially related to the increased incidence of and persistent SIRS in the subgroup of old patients. In addition, the calculated standard deviation of LOS in this study may not be normally distributed, but the result remained inconclusive, possibly due to the nonnormal distribution published by two other studies [16,30].

In the evolution of AP, there are multiple factors, including vomiting, fluid loss in the third space et al. that could induce hypovolemia. Following the progression of hypovolemia, pancreatic microcirculation could be disturbed, resulting in the release of multiple inflammatory cytokines, pancreatic ischemia and multisystem OF. Therefore, improved splanchnic hypovolemia and inhibition of the early inflammatory cascade are the fundamental goals of aggressive hydration.

However, aggressive hydration is commonly accompanied by visceral edema [32] and excessive chloride [33], which may contribute to intra-abdominal hypertension and impaired renal function, and both of these results can affect each other simultaneously [34,35]. In addition, some studies concluded that the

impairment of pancreatic circulation is another main cause of pancreatic necrosis and that fluid resuscitation could rapidly restore the function of the pancreatic microcirculation [7,36]. However, previous studies [10,37–39] have shown that aggressive hydration can improve neither pancreatic ischemia nor the disturbance of oxygen delivery caused by microcirculatory disorders. This type of pathological event may be caused by the hemodilution-induced decrease in hematocrit, which is a risk factor for the development of and pancreatic necrosis [40]. Therefore, accumulating evidence in recent studies [14–17,28,30,31] has indicated the aggressive hydration accompanied by more severe complications, and these consistencies strongly support our findings. Furthermore, some studies [14,22,41] showed that an intravenous FV > 4 L during the first 24 h in AP was related to an increased incidence of acute fluid collection, renal failure and respiratory failure. However, these studies included patients with mild pancreatitis, limiting their findings from further expansion in clinical practice. Six studies [15–17,20,29,31] in this meta-analysis enrolled patients with severe pancreatitis, and the total FV in the first 24 h of each aggressive hydration group was more than 4 L, while that of the conservative hydration group was less than 4 L. Corresponding to the complication of aggressive hydration, almost all the studies provided evidence of its disadvantages regarding renal failure, respiratory failure and mortality.

Since the first meta-analysis on aggressive hydration for AP by Gad et al. [24], additional evidence to support the benefit of fluid therapy has not been reported, even though the report indicated potential inferiority of aggressive hydration without exact statistical significance. Although we agree with the standpoints from the study, some deficiencies remain noteworthy. Firstly, a lower FR threshold of 3–5 ml/kg/h in the first 24 h was defined as aggressive fluid resuscitation, which was inconsistent and not specific to prior guidelines [5]. More than two-thirds of the included studies were observational studies, indicating that refining an immutable FV to an exact FR per hour per kilogram is impossible. Secondly, the included studies enrolled two potentially overlapping trials published by Buxbaum et al. [13,42] and Mao et al. [15,17] without definite reason. Exaggerative outcomes were possibly generated due to this deficiency. Thirdly, for the meta-analysis of SIRS, data were extracted without differentiation of the stage prior to and posttreatment. The study tried to analyze the influence of fluid therapy, however, data [14,31] extracted from the stage prior to treatment should not be regarded as the therapeutic effect. Consequently, our group was motivated to further investigate the benefit of fluid therapy.

Consistent with our study, the initiation of fluid therapy is primarily due to individual pathologic changes, which also arise as a concerning issue of reverse causation bias. A standard method to address this issue is excluding the initial outcomes in the early follow-up period to avoid the impact of these premature outcomes on subsequent intervention. However, only Buxbaum et al. [13] mentioned the complete follow-up period and performed survival analysis among the included literature. The remaining studies reported neither an explicit follow-up time nor the results after 24 h of intervention. Pooled insufficient data are not valid approaches to analyze reverse causation bias. The major issue initially explored by this meta-analysis is determining whether aggressive hydration is advantageous compared with conservative hydration. Therefore, the core problem related to reverse causation bias is that an infused FV would be altered based on the severity of pancreatitis by clinical judgment; for example, patients with severe pancreatitis have higher chances of receiving more fluid, which subsequently might be blamed for poor outcomes, a concern highlighted by de-Madaria et al. [14] and Singh et al. [18]. Nevertheless, each patient in aggressive hydration group almost had equal chance to receive fluid more than 4 L, while that of less than 4 L in conservative hydration group, there is no case of receiving different doses of fluid in the same group of patients because of different severity of pancreatitis. This also indirectly provides evidence that reverse causation bias is relatively reduced, because the grouping method of included studies have a relatively uniform boundary to distinguish whether fluid therapy is aggressive or conservative.

Therefore, clinical advocacy for conservative hydration has received increased attention because of the non-neglectful improvements in pulmonary/renal failure, pancreatic necrosis, and mortality [15,17,18,29,31,43,44]. Adverse events, which decreased as described above, are potentially related to prior underlying pathology, and the study reported by Warndorf et al. [19] might be the best proof of this. Overall, given the estimated homogeneity and significance of the results, our findings strengthen the hypothesis that conservative hydration is not inferior to aggressive hydration.

The following limitations of our meta-analysis should be taken into account. The main limitation is that more than half of the included trials were observational studies, and the remaining 5 RCTs were conducted with small sample sizes. Although in-hospital mortality is unlikely to be influenced by a lack of blinding [45] due to the complex dynamic evaluation, this evidence should be interpreted with caution due to the small-study effect [46]. Secondly, the subgroup analysis yielded significant outcomes compared with the original analysis, indicating unstable endpoints because of a specific study. Additionally, our research protocol had not applied for registration on the PROSPERO website, and this deficiency may cause our plan to overlap with that of other researchers. Finally, the issue of reverse causation bias could not be addressed in the present meta-analysis, and this limitation might be the primary challenge of most studies evaluating the benefit or harm of fluid therapy associated with aggressive hydration in patients with AP.

Overall, this meta-analysis is the first report of the disadvantage of aggressive hydration and found a timely, conclusive outcome as data have accumulated and become available for inspection by meta-analytical theory. A broad strategy was used to identify eligible studies to increase the sensitivity of the study. Detailed sensitivity and subgroup analysis were performed to minimize the heterogeneity of every outcome. Therefore, up-to-date information was provided in our study.

## 5. Conclusion

In adults with AP, compared with conservative hydration, aggressive hydration is associated with increased in-hospital mortality and an increased incidence of renal failure and pancreatic necrosis. In old patients and/or severe pancreatitis, aggressive hydration is potentially related to an increased incidence of respiratory failure and persistent SIRS and a prolonged hospital stay. Meanwhile, the increase in persistent OF and SIRS within 24 h is potentially influenced by controversial practices. Nevertheless, several limitations presented above prevent us from drawing definitive conclusions. Further well-designed, properly powered trials with definite follow-up time will be required to confirm and update the findings of this meta-analysis.

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## Authors' contributions

Jiyang Liao, Yang Zhan and Jianbo Lai contributed to the study conception and design. Literature search, data collection and

analysis were performed by Yang Zhan, Huachu Wu and Xian Peng. The first draft and review of the manuscript was prepared by Jiyang Liao and Yang Zhan. Supervision, material support and project administration were performed by Jianbo Lai and Zhijun Yao. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declaration of competing interest

The authors declare that they have no competing interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.01.001.

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