ORIGINAL ARTICLE

Balanced Crystalloid Solution or Normal Saline in Fluid Resuscitation in Critically Ill Patients: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials

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Background: Both balanced crystalloid solution and normal saline are commonly used for fluid therapy in critically ill patients. However, the association between the types of crystalloid solution and patient outcomes remains inconclusive.

Materials and Methods: The authors performed a search using Pubmed, Embase, and Cochrane Central Register through January 2022. Randomized controlled trials (RCTs) comparing balanced crystalloids and normal saline in non-perioperative fluid resuscitation for critically ill adult patients were included. The primary outcome was 30-day mortality. A trial sequential analysis (TSA) was performed to assess the effect of each type of fluid on the outcomes. Secondary outcomes included the incidence of acute kidney injury (AKI), renal replacement therapy (RRT), and other pre-specified outcomes.

Results: Ten RCTs were identified and included 36,233 participants. Between the balanced crystalloids and the normal saline group, there were no significant differences in mortality at 30 days (relative risk [RR] 0.95, 95% confidence interval [CI] 0.89 to 1.02, I^2=0), the incidence of AKI (RR 0.95, 95% CI 0.90 to 1.01, I^2=0), and RRT (RR 0.93, 95% CI 0.86 to 1.01, I^2=13). However, patients receiving balanced crystalloids demonstrated a significantly lower serum chloride level than the patients receiving normal saline (MD –1.95, 95% CI –3.45 to –0.45, I^2=99). There was also no mortality difference in the sepsis and traumatic brain injury subgroups. The TSA confirmed the absence of an effect on mortality at 30 days and the incidence of AKI.

Conclusion: In critically ill patients, the use of balanced crystalloids does not decrease 30-day mortality or the incidence of AKI and RRT. However, data in specific subgroups of patients were underpowered and further studies are required. There were signals of benefit and risk of the balanced salt solution in the subgroups of sepsis and traumatic brain injury.

Trial registration: The present study was registered in the PROSPERO database, CRD42021275796.

Keywords: Balanced crystalloid; Normal saline; Critically ill patients; Mortality; Acute kidney injury

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Intravenous fluid therapy is a fundamental step in the management of critically ill patients, used for resuscitation and restoration of hemodynamics. Over decades, trials comparing different types of resuscitation fluid have been published. However, there is no robust evidence showing decreased mortality with any specific fluid types[1]. Clinical trials and meta-analyses comparing albumin and crystalloid solution also show no survival benefit, although the post hoc analysis of one study showed a reduction in mortality from albumin use in patients with septic shock[2-5].

Crystalloid is the type of fluid recommended for initial treatment in most patients requiring fluid therapy[6]. However, whether any specific type of crystalloids affects the outcomes remains inconclusive. Isotonic saline, the most commonly used crystalloid, may be associated with hyperchloremia, metabolic acidosis, acute kidney injury (AKI), and increased risk of death in some cohorts[7-9]. This raised concerns about the potential adverse effects of isotonic saline, leading to increased use of balanced crystalloids, the electrolyte compositions of which are

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more comparable to plasma[10]. Recently, randomized controlled trials (RCTs) have been published that compare isotonic saline and balanced solutions, with conflicting results. A single-center open-label trial conducted in the United States compared isotonic saline with lactated Ringer solution or Plasma-Lyte A and showed promising results with a lower composite outcome of death, new renal replacement therapy (RRT), or persistent renal dysfunction in the balanced crystalloid group[11]. Meanwhile, the results of meta-analyses including smaller trials and observational studies are still varied[12-14]. Recently, two large RCTs have been published, providing more information on this topic[12,13]. To update the evidence, the authors conducted this meta-analysis to assess the effects of balanced crystalloid versus normal saline on mortality and renal outcomes in non-perioperative critically ill adults.

Materials and Methods

The prespecified protocol was registered in the International Prospective Register of Systematic Reviews, Prospero (CRD42021275796) before data collection and analyses. The present study was conducted following the statement of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 202017. The protocol was also reviewed by Siriraj Hospital Institutional Review Board (IRB) and received the certificate of exemption in January 2022, protocol number 1045/2564.

Search strategy

The authors systematically searched Pubmed, Embase, and Cochrane Central Register from inception through January 2022, using the search terms listed in the Supplementary Table 1. The authors limited the search to human studies, including adult patients, and limited the language to English. The authors of the interesting abstracts were also contacted asking for more detailed data on the study.

Eligibility criteria

The authors included RCTs that recruited critically ill adult patients who required fluid resuscitation with study arms that compare isotonic saline versus balanced crystalloids such as Plasma-Lyte, Sterofundin, Ringer's lactate, or Ringer's acetate. Included trials must report at least one of the following outcomes, 30-day or 28-day mortality, 90-day mortality, or the incidence of AKI. Studies of perioperative fluid resuscitation, nonrandomized trials, trials that included patients who were not critically ill, trials that included only fluid therapy for maintenance rather than resuscitation, and trials in patients younger than 18 years were excluded.

Study selection

For study selection, two reviewers independently screened article titles and abstracts for inclusion, then the studies selected at initial screening were subjected to full text article review. Disagreements between the two investigators were resolved by a third reviewer. The reasons for exclusion were recorded.

Data extraction

The data were extracted from full text article documents and recorded in Excel spreadsheets, including study design and methodology, participant demographic data, baseline characteristics, fluid types, fluid volume, and all of the outcomes. One reviewer extracted the data, while another reviewer checked the extracted data. The disagreement between individual judgments was resolved by the third investigator. For the study data from Ratanarat et al.[14], reviewers found the abstract of the study during study selection, which matched the inclusion criteria, but the reviewers could not find a full paper published online, so the reviewers managed to reach the unpublished data. The missing data from publication studies was omitted and did not impute missing data.

Risk of bias assessment

The Cochrane tool to assess the risk of bias in a randomized trial, the RoB2 tool, was used to assess the quality of the included trials by two independent reviewers. The disagreements between the reviewers' judgments were resolved by the third reviewer.

Outcomes

The primary outcome was 30-day or 28-day mortality. Other additional outcomes were 90-day mortality, mortality at the longest time point, intensive care unit (ICU) mortality, hospital mortality, incidence of AKI and RRT, ventilator-free days, ICU stay duration, hospital stay duration, serum potassium, serum chloride, and serum bicarbonate. The authors also evaluated outcomes in different subgroups, including patients with sepsis, trauma, surgical, and traumatic brain injury.

Statistical analysis

Dichotomous outcomes were shown as relative

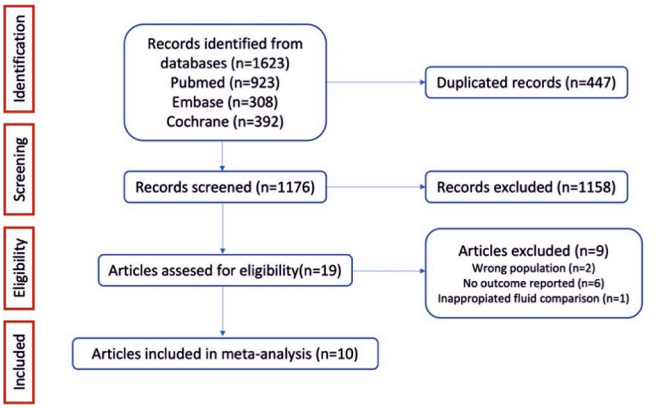

Figure 1. PRISMA flow diagram of the search results and excluded studies reasons.

risks (RR) and odds ratio (OR) with 95% confidence intervals (CI), and continuous results were shown as mean difference (MD) with 95% CI. The statistics x^2 and I^2 were used to assess the heterogeneity of the included studies, with a p-value of less than 0.1 or I^2 greater than 50% considered significant for heterogeneity. A random-effects model was used in the analysis. A funnel plot was used to assess publication bias.

The authors also performed a trial sequential analysis (TSA), using the TSA software version 0.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark[15], to obtain a conclusive result on the use of balanced crystalloids versus normal saline on mortality at 30-days. TSA is a methodology used to control random errors and estimate the required information size for meta-analysis[15,16]. The authors calculated the required information size based on a RR reduction of 10%, a power value of 0.9, and a type I error of 5%. All analyses were performed in R v3.6.3 (R foundation) and a p-value less than 0.05 was considered significant[17].

Quality of evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[18] with the GRADEpro Guideline Development Tool[19].

Ethical approval

The protocol for the present study was approved by the Human Research Protection Unit, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (protocol number 1045/2564) and was carried out according to the principles of the Declaration of Helsinki.

Results

One thousand six hundred twenty-three articles were retrieved from the systematic search. After removing duplications, 1,176 articles were included in the study. After screening, 19 full-text articles were assessed for eligibility, and 10 studies met the inclusion criteria, consisting of 36,233 participants (Figure 1). The included studies were published between 2013 and 2022. The characteristics of the included RCTs are summarized in Supplementary Table 2.

Primary outcome

Seven studies reported the outcome of 30-day or 28-day mortality. The pooled data analysis did not show significant differences in 30-day mortality between the balanced crystalloid group and the normal saline group (RR 0.95, 95% CI 0.89 to 1.02, I^2=0) (Figure 2). TSA confirmed that balanced crystalloids would not be considered better than normal saline on 30-day mortality as the futility boundary had been crossed (Figure 3). There was no evidence of publication bias on visual inspection of the funnel plot (Supplementary Figure 11).

Secondary outcomes

The mean serum chloride in the balanced crystalloids group was significantly lower than that in the normal saline group (MD –1.95, 95% CI –3.45 to –0.45, I^2=99) (Supplementary Figure 1). However, there were no significant differences in the incidence of AKI or RRT between the two groups, with a RR of 0.95 (95% CI 0.90 to 1.01, I^2=0) (Figure 4) and 0.93 (95% CI 0.86 to 1.01, I^2=13) (Figure 5), respectively. Using TSA, the results also confirmed the non-difference in the incidence of AKI between both groups (Figure 6).

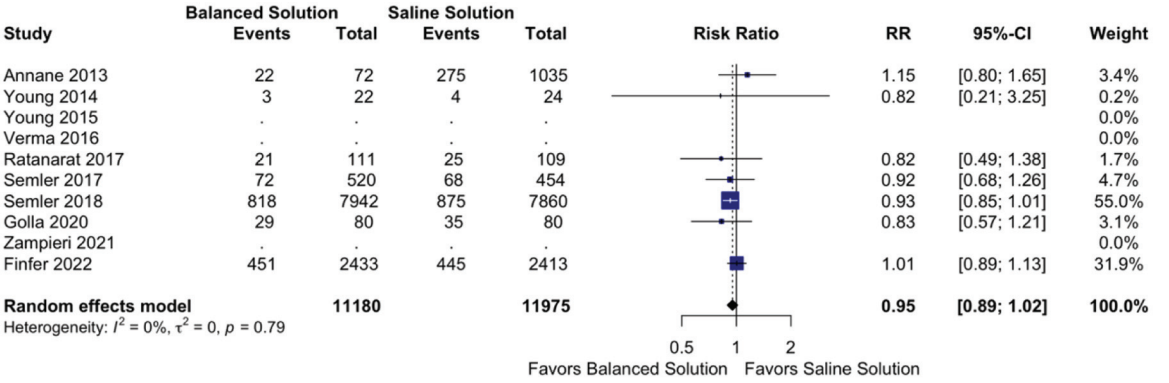

Figure 2. Forest plot for 30-day mortality.

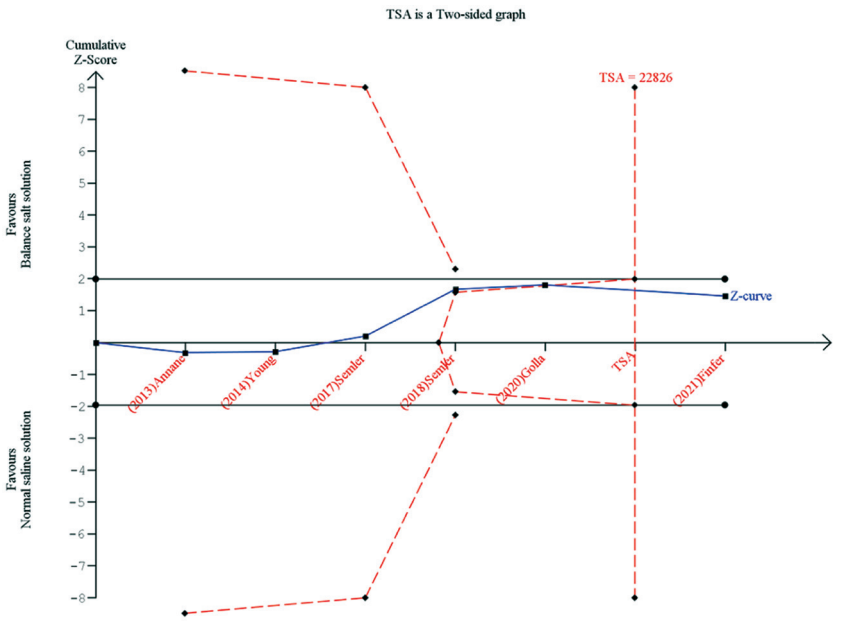

Figure 3. Trial sequential analysis assesses the effect of balanced crystalloids vs. normal saline on 30-day mortality. The cumulative meta-analysis (blue line) did not cross the conventional or the alpha-spending efficacy boundary. However, it crossed the futility boundary, confirming the absence of an effect on 30-day mortality.

There was no significant difference in mortality in the longest follow-up period (RR 0.96, 95% CI 0.92 to 1.00, I^2=0) (Supplementary Figure 2), ICU mortality (RR 0.98, 95% CI 0.92 to 1.04, I^2=0) (Supplementary Figure 3), and hospital mortality (RR 0.96, 95% CI 0.92 to 1.00, I^2=0) (Supplementary Figure 4). Although there were significantly more ventilator-free days (MD 0.6, 95% CI 0.09 to 1.11, I^2=83) (Supplementary Figure 5) in the balanced crystalloid group, no significant differences were found in the ICU length of stay (MD 0.07, 95% CI –0.34 to 0.48, I^2=5) (Supplementary Figure 6) and the hospital length of stay (MD –0.35, 95% CI –0.71 to 0.02, I^2=0) (Supplementary Figure 7).

Subgroup analysis

The primary outcome of 30-day mortality was evaluated in subgroups of patients with sepsis, trauma, surgical patients, and patients with traumatic brain injury (Supplementary Figure 8). There was no significant difference between the two study fluids in all subgroups. The pooled estimate for RR of 30-day mortality in the subgroup of patients with sepsis, trauma, surgical patients, and patients with traumatic brain injury was 0.93 (95% CI 0.87 to 1.00, I^2=0), 0.99 (95% CI 0.80 to 1.22, I^2=0), 0.95 (95% CI 0.86 to 1.04, I^2=0), and 1.26 (95% CI 0.97 to 1.64, I^2=7), respectively.

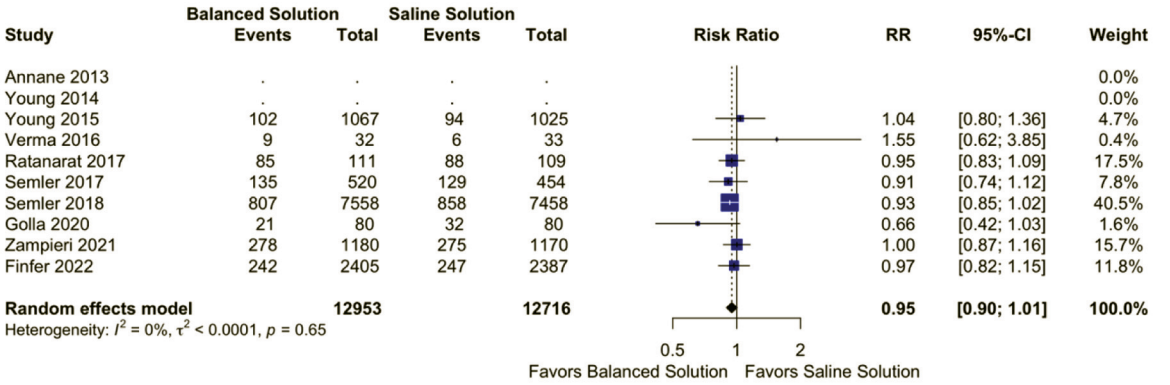

Figure 4. Forest plot for acute kidney injury.

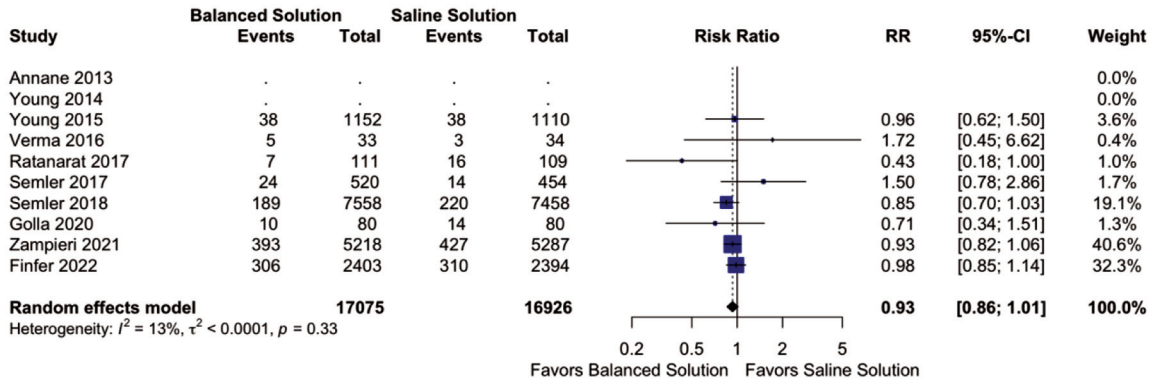

Figure 5. Forest plot for renal replacement therapy.

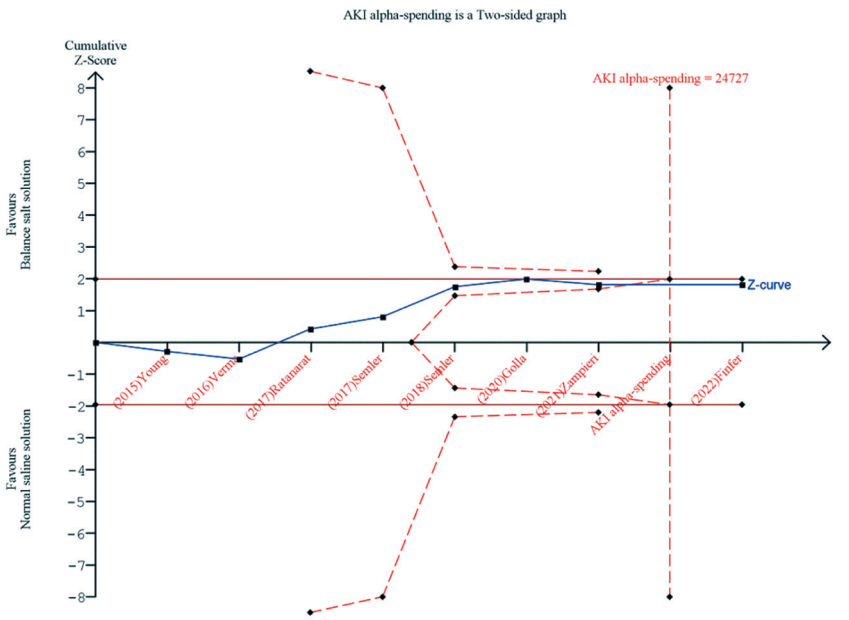

Figure 6. Trial sequential analysis assesses the effect of balanced crystalloids vs. normal saline on the incidence of acute kidney injury. The cumulative meta-analysis (blue line) did not cross the conventional or the alpha-spending efficacy boundary. However, it crossed the futility boundary, confirming the absence of an effect on the incidence of acute kidney injury.

Risk of bias and evidence grades

The risk of bias is summarized in Supplementary Figure 9. There were six studies considered to have low risk of bias and four studies considered unclear risk of bias. None of the studies with a high risk of bias was included in the present meta-analysis. The GRADE criteria for evidence quality were evaluated for mortality at 30 days, incidence of AKI, and days without ventilator, which showed high, moderate, and moderate certainty, respectively (Supplementary Figure 10).

Discussion

The present study was a systematic review and meta-analysis that included ten RCTs comparing balanced crystalloids versus normal saline for fluid resuscitation in critically ill adult patients. It did not demonstrate significant differences in 30-day mortality or incidence of AKI and RRT. Moreover, the TSA also confirmed the present results because the futility border has been crossed. The present study results are consistent with a prior meta-analysis by Liu et al. that included nine RCTs that showed no difference in mortality, AKI morbidity, and RRT use. However, the result of that study was unable to be conclusive, according to the TSA result[20]. From the addition of the two most recent RCTs[12,13] in the present study, which increased the total number of participants, resulting in sufficient data to confirm the primary outcome by using TSA. Another recently published meta-analysis by Hammond et al.[21], which also included the two recently published RCTs[12,13], demonstrated results with similar conclusions when using the frequentist approach. However, using Bayesian analysis, it indicated a high probability that using balanced crystalloids reduces 90-day mortality. Still, the primary outcome of the study by Hammond et al. might have been confounded by other factors that occurred during the long 90-day period rather than the type of crystalloid itself.

Hyperchloremia-associated AKI has been hypothesized from the belief that a chloride-rich fluid may induce renal afferent arteriole vasoconstriction, leading to renal hypoperfusion. Although the present study meta-analysis demonstrated a significantly lower mean serum chloride in the balanced crystalloids group, the relatively small difference in mean chloride serum chloride level and the low incidence of hyperchloremia in both groups could be an explanation for the non-significant difference in clinical outcomes, including the incidence of AKI, RRT, and the mean serum creatinine difference.

The authors estimated the effect between the two types of crystalloids on mortality, in the subgroup of patients with sepsis. It was consistent with a reduction in RR of 13% to 0% risk of death. There is a non-significant trend of lower mortality towards the balanced crystalloid group, which is consistent with the results of a secondary analysis of the SMART clinical trial that showed significantly lower mortality at 30 days in hospital compared to saline use in patients with sepsis[22]. On the contrary, the estimates in the subgroup of patients with traumatic brain injury are consistent with a reduction in RR of 3% to a relative increase of mortality of 64%, similar to the result of the analysis of subgroups in the BaSICS trial, which showed a significant increase in mortality in 90 days in the same population[13]. This should raise concern for using balanced crystalloids in patients with traumatic brain injury. The possible physiological explanation was the lower osmolarity in the balanced salt solution compared to normal saline solution. However, data for each subgroup was not available in all RCTs included in the present study, resulting in an inadequate sample size. More studies are required in these subgroups before a conclusion can be made.

Although the present review provides updated evidence, it still has the following potential limitations. First, the studies included in this meta-analysis are quite heterogeneous, including patients with different etiology and severity of illness, different definitions of the outcome, and different times of follow-up. Nonetheless, this meta-analysis consists of the most up-to-date data and the authors also provided TSA to confirm the results. Second, the information of the subgroups, and the number of patients included, is limited for evaluation, and to make a conclusion about the effect of the balanced crystalloid versus normal saline in specific subgroups. However, there were signals of benefit and risk of a balanced salt solution in the subgroups of sepsis and traumatic brain injury. These will open the door to conducting further research on a more specific group of patients. Third, different types of balanced crystalloid fluid were used in different studies, in which the fluid compositions could be comparable but still not identical. Therefore, whether the type of balanced crystalloid might have different effects on critically ill adults still needs more study data. Lastly, most critically ill patients received fluid resuscitation before randomization, but fluid volume was not provided in all studies and the volume of fluid resuscitation can affect the outcome.

Conclusion

Balanced crystalloids used in the resuscitation of critically ill adult patients were not associated with a reduction in mortality at 30 days and the incidence of AKI and RRT. Furthermore, TSA also provided the same conclusion with an adequate sample size. However, the data in specific subgroups are underpowered to answer this question, thus, further studies are needed.

What is already known on this topic?

The better resuscitation fluid in critically ill patients is still debated.

What does this study add?

In critically ill patients, the use of balanced crystalloids does not decrease the 30-day mortality or the incidence of AKI and RRT. However, data in specific subgroups of patients were underpowered, and further studies are needed.

Data availability

The Supplementary Tables and Figures of the present study are available at https://docs.google.com/document/d/14Er5Xu8SdsC4joR7s9qOopjBbf_gnSQ5/edit?usp=drive_link&ouid=104272010897485891795&rtpof=true&sd=true.

Conflicts of interest

None of the authors has a conflict of interest. All authors agree with the content of this manuscript.

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