Reviewer A

Comment: The manuscript entitled "Shenfu Injection as Treatment for Critical Illness: A Narrative Review of Clinical Trials" is a concise and well-written narrative review of Shenfu injection outcomes in clinical trials during the past decades. Authors clearly identified the inclusion and exclusion criteria, separated the studies according to the disease/illness and discussed the limitations of the manuscript. As an observation, I would suggest the authors to indicate, whenever possible, the preparation of the Shenfu injection (the content of main compounds, dilution, from where it was obtained...). I believe such details would be important for next studies.

Reply: We thank Reviewer A for their kind words. In terms of how the preparation was described, we list the volumetric dose of Shenfu Injection that was given. While we agree that knowing the exact formulation in each study would be helpful, unfortunately most studies do not report this information.

Reviewer B

Comment: It is interesting to know the findings of the study. This study showed the therapeutic benefits of Shenfu injection in the treatment of Critical Illness including cariogenic shock, heart failure and cardiac arrest. However, multi center randomized double blind trials are needed to confirm the findings of this study.

Reply: We agree that further multicenter randomized double-blind trials are needed. Our conclusion highlights this need. We thank Reviewer B for their consideration of our manuscript.

Reviewer C

Comment: This paper reviewed SFI's efficacy in various illness and was well written. I have no comments.

Reply: We are very grateful to Reviewer C for their kind words and for their consideration of our work.

Reviewer D

Comment: In the paper titled "Shenfu Injection as Treatment for Critical Illness: A Narrative Review of Clinical Trials", the authors intended to explore the results of clinical trials that have tested Shenfu injection (SFI)'s efficacy in various critical illnesses(including heart failure, cardiac arrest, and septic shock). This manuscript does not bring any new knowledge or data. One reason is that the paper is a narrative review which has its own limits, on the other hand, the manuscript is not well arranged and the logic is not clear. What the authors want to tell is just "new research

is needed to evaluate whether SFI is a useful addition to existing treatments for these conditions." Such results and conclusion may not be much more to read.

Reply: While we agree that a narrative review does not publish any new data, we respectfully feel there is a need in the literature for a narrative review that summarizes some clinical trials that have explored the use of Shenfu Injection for critical illness. We chose to organize the results of our review based on specific illness types; for instance, there are sections that each specifically discuss trials involving heart failure, cardiac arrest, sepsis, and pulmonary disease. We respectfully feel this is the best way to categorize the various trials we review. We are appreciative of Reviewer D's feedback and review of our work.

Reviewer E

Comment 1: In the key content and findings of an abstract section, the author stated, "The design, methodology, and key findings of each trial or meta-analysis were summarized and discussed. Key limitations were highlighted and discussed." There seems to be quite a general explanation. Please express some highlights of the result of this study in this section.

Reply: We have added additional language to the abstract that better summarizes the findings of our narrative review.

Comment 2: In the "3.1 Shenfu Injection for Heart Failure" section, the author stated that "Among the 144 patients who completed the protocol and underwent full analysis, those who received SFI in addition to standard therapy had significantly better clinical outcomes compared to patients in the control group: the NYHA classification improved in 78.38% of patients following SFI administration vs. only 61.43% in patients receiving placebo (relative risk [RR]=1.28, 95% confidence interval [95%CI]: 1.02–1.59, p=0.003)." Referring to the cited article: "Wang X et al. 2019 (DOI: 10.1155/2019/9297163)," there was revealed in the text as "SFI treatment significantly improved the NYHA classification by 78.38% compared to the 61.43% increase observed in the placebo group (P=0.0026, relative risk [RR] = 1.2759, 95% confidence interval [CI]: 1.0231-1.5913; Table 2)." In Table 2, entitled "Comparison of NYHA classification between SFI and placebo group" of Wang X et al.'s article, the p-value of this comparison was "0.026." There was a p-value difference between reporting in the text (p=0.0026) and Table 2 (p=0.026) of Wang X et al.'s article. Therefore, I recheck the statistical analysis of that Wang X et al.'s Table 2 with Stata version 18 (using the chi-squared test or Fisher's exact test, same as Wang X et al.'s article did): SFI group (n=74) with excellent + valid = 18+40 = 58 cases, and Placebo group (n=70) with excellent + valid = 8+35 = 43 cases. I combine the excellent + valid and the invalid + worsened according to the Table 2 footnote of Wang X et al.'s article as "Effective rate was defined as proportion of all patients who experienced an excellent or valid outcome. Similarly, the effective rate was defined as the proportion of all patients who experienced an invalid and worsened outcome." Eventually, my rechecking shows the same risk ratio = 1.2759 (95% CI 1.0231 - 1.5913); however, there is a difference in p-value = 0.026 (from the chi-squared test) (p-value = 0.030 from 2-sided Fisher's exact). Thus, I suggest using the p-value in this manuscript as p=0.03 rather than 0.003.

Reply: This is an extremely important observation noted by Reviewer E. In revisiting Wang et. al. (2019), we agree that there appears to be a discrepancy when comparing the p value reported in the main text and Table 2. Specifically, the main text states p=0.0026, while the table states p=0.026. Reviewer E performed a statistical analysis of Wang et al.'s data and arrived at a p value of p=0.03. We also calculated the RR ourselves and similarly got a p-value of 0.03, so we have made this correction in the text.

Comment 3: In the "3.2 Shenfu Injection in Cardiac Arrest" section, the author stated that "There was no statistically significant difference in survival to discharge (6.7% [40/599] in the SFI group vs 5.6% [34/599] in the control group, p=0.53)." Referring to the cited article: "Shao et al. 2020 (DOI: 10.1016/j.resuscitation.2019.11.010)." There was reported in Shao et al.'s Table 2 (entitled "Outcome of study participants") as "Survival to admission: SFI group = 40/599 (6.7%), control group = 34/602 (5.6%), p=0.53," and "Survival to discharge: SFI group = 17/596 (2.9%), control group = 7/597 (1.2%), p=0.06." Therefore, please correct these results in the manuscript.

Reply: This is another important observation. We have added language to our discussion of Shao et al. (2020) that clarifies this. We now report both survival to admission and survival to discharge. We are extremely grateful and appreciative of the comments and suggestions provided by Reviewer E.