Dear Word Journal of Gastroenterology Editorial Office,

Thank you for giving me the opportunity to submit a revised draft of my manuscript titled [*One in Four Patients with Gastrointestinal Bleeding Develops Shock or Hemodynamic Instability: A Systematic Review and Meta-analysis*] to the [*World Journal of Gastroenterology*]. We appreciate the time and effort you and the reviewers have dedicated to providing valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. Please let us know if any further changes are required.

Here is a point-by-point response to the reviewers' comments and concerns.

Again, thank you for your valuable time and expertise invested in our manuscript.
Sincerely,

Bálint Erőss, Mahmoud Obeidat

Dear Reviewers,

Thank you for your review. We greatly appreciate your comments which have significantly improved our manuscript. Please find our point-by-point response to your comments below. We hope our revised manuscript will meet your expectations and you will find it suitable for publication. Please let us know if any further changes are required.

Again, thank you for your valuable time invested in our manuscript.

Kindest regards,

Comments from Reviewer 1

Comment 1: *Abstract: Please, the study aim was described following the PICO statement.*

Response 1: Thank you for this comment. Since our study is a proportional meta-analysis, we used the CoCoPop framework (condition, context, population). Our aim in the abstract was [*We aimed to meta-analyze the available data to determine these proportions in different bleeding sources*]. We changed it to a more straightforward sentence [*To determine the pooled event rates in the available literature and specify them based on the bleeding source*]. The PICO framework is mainly used for interventional clinical questions. However, that was not the case in our study. For why we used the CoCoPop framework, please see this paper by Munn Zachary *et al.* 2018 (DOI: 10.1186/s12874-017-0468-4), Table 1.

Action 1: Following the journal guideline, our aim in the abstract is changed into [*To determine the pooled event rates in the available literature and specify them based on the bleeding source*]; this section should not be more than 20 words.

Comment 2*: Please, include the I2 in your findings.*

Response 2: Thank you for pointing this out. We agree with this comment. Therefore, we have added the heterogeneity I^2 into our findings. We have incorporated your suggestion throughout the manuscript (abstract and main text).

Action 2: I^2 is added to all our results. For example, 0.25 (CI: 0.17–0.36, I^2 = 100%).

Comment 3: *Introduction: As described above. The study aim was described following the PICO statement.*

Response 3: Thank you for this comment. In the introduction, we highlighted why hemodynamic instability and shock are essential factors in gastrointestinal bleeding and mentioned that they are associated with unfavorable outcomes such as mortality and rebleeding. Then, we highlighted the gaps in the most recent update of the ESGE guideline regarding hemodynamic resuscitation. At the end of our introduction, we clearly stated our aim: [*Therefore, we aimed to highlight the importance of recognizing those patients by quantifying the pooled event rates based on the bleeding source*].

Action 3: None.

Comment 4: *Methods: The authors could explicate because they applied the CoCoPop framework instead PICO statement to establish the eligibility criteria.*

Response 4: Thank you for this comment. Since our study is a proportional meta-analysis, the CoCoPop framework is the most suitable framework for establishing the eligibility criteria as we wrote in the methods part [*The condition was hemodynamic instability and/or shock, gastrointestinal bleeding as a context, and our population was adult patients*]. The PICO framework is mainly used for interventional clinical questions. However, that was not the case in our study. Please see the study by Munn Zachary et al. 2018 (DOI: 10.1186/s12874-017-0468-4), Table 1, for different frameworks.

Action 4: None.

Comment 5: *The screening and selection were performed by two authors (M.O. and E.T.) and Data extraction by another author (M.O. and A.R). Usually, the authors who performed the screening also performed data extraction. The authors could explain to me this difference.*

Response 5: Thank you for pointing this out. We agree with your comment. We divided the tasks among the researchers since we had a vast pool of more than 11,000 studies. However, at the beginning of our study, we established a transparent selection and data extraction protocols that all authors agreed on. The independent reviewers used these protocols during the selection and data extraction process. M.O. was included in all phases of selection and extraction since he is the paper's first author. A.R. participated in the selection, and E.T. in the data extraction. In the methods

part of the main text, we highlighted that any disagreement in the selection and extraction was resolved by involving the corresponding author (B.E.).

Action 5: None.

Comment 6*: The authors must describe how Hemodynamic instability and Shock on admission were defined.*

Response 6: Thank you for pointing this out. We totally agree with your comment. We have collected all definitions of hemodynamic instability and shock among the included study in tables 13 and 14 in the supplementary material, respectively.

Action 6: Definitions of hemodynamic instability and shock were added in Supplementary Table 13 and Table 14, as suggested. We referred to that in the discussion part of the main text [*All definitions of HI and shock can be found in Supplementary Table 13 and Table 14, respectively*].

Comment 7: *Was a sensitivity analysis performed based on the risk of bias assessment?*

Response 7: Thank you for your comment. As our study is a proportional meta-analysis, the risk of bias tool was 'Joanna Briggs Institute Prevalence Critical Appraisal Tool'. This tool includes nine questions, and a final score out of 9 was given for each study, as shown in Supplementary Table 5. However, we have done a leave-one-out influential sensitivity analysis, as shown in Supplementary Figures 10-16, where omitting a high risk of bias studies did not change the proportion of shock or hemodynamic instability.

Action 7: None.

Comment 8: *Results: Table S2 and S1 could be deleted.*

Response 8: Thank you for your suggestion. As these two tables are part of the supplementary material, we can definitely delete them. However, we suggest keeping them for transparency as it is reported in the PRISMA checklist. Table S1 [*Now it is called Supplementary Table 1*] is our search key in the three main databases and Table S2 [*Now it is called Supplementary Table 2*] shows all the excluded studies after full text selection and the reason for exclusion. For the PRISMA checklist, please check the following link, Search strategy (item 7) and Study selection (item 16a).

Action 8: None.

Comment 9: *Each study in table S5 must include a reference.*

Response 9: Thank you for pointing this out. We have incorporated your suggestion in Table S5. [*Now it is called Supplementary Table 5*].

Action 9: We included a reference for each study in Table S5 [*Now it is called Supplementary Table 5*].

Comments from Reviewer 2

Comment 1: *It is recommended that the aim of the study in the abstract be made a stand-alone sentence rather than an extension of BACKGROUND. In its current form, the aim is not very clear. The aim in the article itself and the abstract are different; it is recommended that it be corrected.*

Response 1: Thank you for pointing this out. We totally agree with your suggestion. Considering the journal's guidelines, the aim section should not exceed 20 words.

Actions 1: We changed the aim of our study in the abstract to a more precise sentence [*To determine the pooled event rates in the available literature and specify them based on the bleeding source*].

Comment 2: *The materials and methods do not describe the criteria for hemodynamic instability and shock that were considered in the current analysis. It is necessary to detail these data. There is some discussion, but the criteria that were considered in the current study should be clearer.*

Response 2: Thank you for raising this point. We totally agree with you. We accepted all definitions of hemodynamic instability and shock reported in the included studies. We have collected all the definitions and included them in supplementary Tables 13 and 14.

Actions 2: We have added a sentence in the method part [*All definitions of hemodynamic instability and shock were accepted*]. In addition, we included Supplementary Table 13 and Table 14 with all the definitions of hemodynamic instability and shock, as reported in the included studies.

Comment 3: *Have any other relationships of hemodynamic instability been analyzed, e.g., age, disease, prognosis, etc.? It would be helpful to increase the understanding of the clinical relevance of the current study.*

Response 3: Thank you for this suggestion. It would have been interesting to explore this aspect. However, in the case of our study, we consulted with our bio-statistical team, who advised us that due to the considerable overlap in the mean ages and standard deviations, it is impossible to draw any statistical conclusion regarding the effect of age on our investigated outcomes. However, we realized that some studies focused on the elderly population; for example, in the discussion part, we wrote [*We observed some outliers in different sources of bleeding; in variceal bleeding,*

intensive care unit admission, elderly population, and severe uncontrolled bleeding were possible predictors for higher rates of shock and HI. In non-variceal bleeding, elderly patients > 60 years and those who underwent embolization accounted for the highest rate of HI on admission and during hospitalization, respectively]. Due to the lack of homogenous studies, performing additional subgroup analyses was impossible. In addition, investigating other aspects was not reported in our PROSPERO, which was registered prior to the conduction of the study.

Actions 3: None.