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**Manuscript #: 80974**

**Title: The global epidemiology of upper and lower gastrointestinal bleeding in the general population: A systematic review**

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To the Editorial office,

*World Journal of Gastrointestinal Surgery*

Thank you for considering our manuscript (no. 80974) and giving us the opportunity to submit a revision. Please find enclosed our response to each of the reviewers' and editors' comments with corresponding edits made in our revised manuscript.

We hope that we have satisfactorily addressed the comments and that you will find our revised manuscript suitable for publication in World Journal of Gastroenterology Surgery.

Kind regards,

Pareen Vora (corresponding author)

## Responses to Company Editor-in-Chief's comments

**Comment 1:** I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

**Authors' response:** Thank you for the suggestion – the tool seems to be very useful to identify latest articles. We have performed keyword searches using this tool as requested, and some of the articles we found are already included in the review and discussion; however, we did not find any additional articles to reference.

## Responses to Reviewer's comments

### Reviewer #1

**Comment 1:** The term inception is not sufficient the exact date used for extracting articles from databases has to be mentioned in the abstract and materials and methods section.

**Authors' response:** We have change 'inception' to the actual date, which is 01 January 1965.

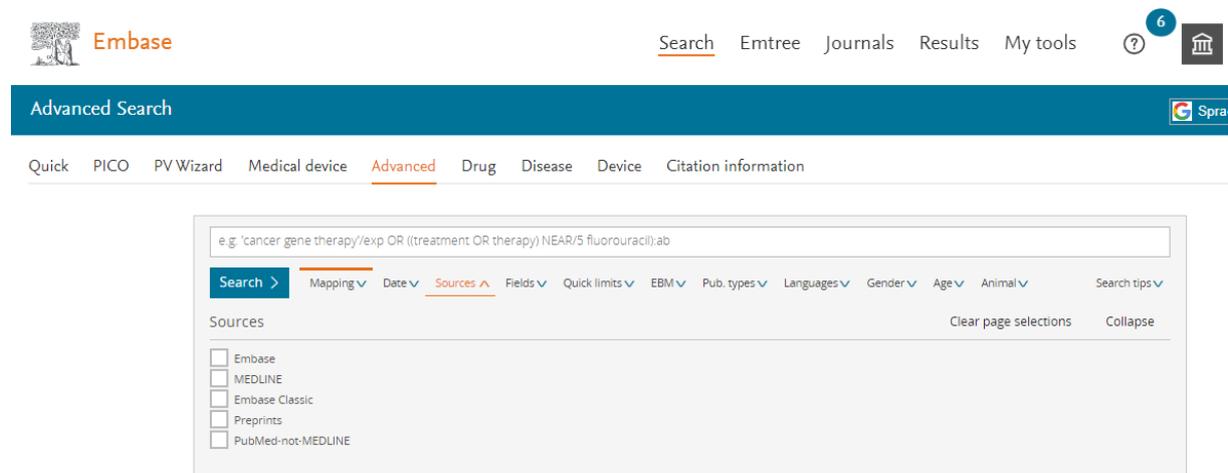
**Comment 2:** The title of this paper should mention systematic review and meta-analysis.

**Authors' response:** The title is now changed to "The global epidemiology of upper and lower gastrointestinal bleeding in the general population: A systematic review".

Please note that we did not perform a meta-analysis and, therefore, have not included this in the title.

**Comment 3.** Two major databases were missed out was not searched google scholars and Pubmed and the main aim is to present the long term global epidemiological data on GIB

**Authors' response:** PubMed is not a database *per se* but is an interface that researchers use to access and to search Medline database, which contains journal citations and abstracts for biomedical literature from around the world. Hence, we mention Medline as one of the data sources for our literature search and not PubMed.(1) Instead of using PubMed interface to access Medline, we accessed both Medline and Embase databases through the EMBASE interface (screenshot below), which prevents against mistakes in the search algorithm applied to the two sources and efficiently removes any duplicates.



We chose not to search Google Scholar as previous research has shown that it is inappropriate as a principal search system.(1) Furthermore, while Google Scholar can complement Medline and EMBASE in that it has greater coverage of the Gray literature, theses, and abstracts etc, we were concerned only with published research that had undergone peer review. Furthermore, the topic we are investigating includes common terms and topics which would lead to a huge number of hits on Google Scholar most of which is already covered by Medline and Embase.

**Comment 4:** The term ‘variceal bleeding’ was not used to search the databases which is not correct because variceal bleeding is an status of active bleeding when the patients were hospitalized and if we miss out this specific term in search string this article will miss all the serious patients

**Authors’ response:** Our search criteria included the terms ‘Gastrointestinal bleeding’ in title/abstract, which includes all subtypes of GI bleeding. When talking about publications on variceal GI bleeding, we strongly believe that authors would not use the term ‘variceal bleeding’ without also using the words ‘gastrointestinal’ and ‘bleeding’ in the same sentence or paragraph (i.e. in the title/abstract of an article). There would therefore be no need to use the specific term ‘variceal bleeding’ as a keyword because any articles including this term would have been picked up by the broad keywords used in any case.

Furthermore, the aim of this review was to provide representative and population-based estimates on GIB (which is mentioned in the inclusion criteria), the majority of which is non-variceal GI bleeding. While screening the references, we did encounter publications on variceal bleeding, but these were small single center or hospital-based studies, rather than population-based studies reported epidemiological measures. We have modified the statement in the manuscript results section that “No population-based study was identified that reported epidemiological variables of interest for variceal UGIB”. We also now acknowledge this in the discussion/limitations section.

**Comment 5:** The reason why RCTs and interventional studies were excluded please mention in short and it must be mentioned.

**Authors’ response:** This was a review of the global epidemiology of GI bleeding. RCTs and interventional studies are controlled experimental studies that are not designed to assess epidemiology of a disease or a condition. They are not population-based but rather based on selected groups of individuals, hence, epidemiological data cannot be gained from RCTs or interventional studies. We have now added a sentence in the Material and Methods (‘Inclusion and exclusion criteria’ section) – “We excluded randomized controlled trials and interventional studies as they are not

designed to assess epidemiology of a disease and based on selected group of individuals.”

**Comment 6:** Since this article can be used as a reference by many readers because of this study question please register the article in PROSPERO and before that perform the searches in PUBMED and Google scholars. Please take extra time but provide accurate data to readers.

**Authors’ response:** Please refer to our response to Comment 3 regarding PubMed and Google scholar. We tried to register our review on PROSPERO; however, we were unable to register as we have already completed the review. As you can see in the screenshot below, their policy has changed since October 2019, where they say that they “will only accept reviews provided that data extraction has not yet started.”(2)

**Full searches**

Exhaustive searches to identify all publications eligible for inclusion in the review.

Not started Started **Completed**

**Full screening of search results against eligibility criteria**

Not started Started **Completed**

**Data extraction**

Extracting or obtaining data from included studies or other sources.

Not started Started **Completed**

Reviews that have started or completed data extraction are not eligible for inclusion in PROSPERO. The aim of the register is to capture information at the design stage.

Go back to My PROSPERO

**Comment 7:** Please don’t forget to present the systematic review flowchart in revised manuscript.

**Authors’ response:** Please note that the PRISMA flowchart can be found as Supplementary Figure 1, which we have also referenced in the first paragraph of the results section. We were unable to include the PRISMA flowchart in the main body

as we reached the limit with other figures and tables, which we regard as more important and informative, in the main body.

**Comment 8:** Please perform the literature review in such a way that the incidence rate of variceal rebleeding could be estimated in this article

**Authors' response:** Please see our response to comment 3. Articles on variceal rebleeding will have been captured by our search; however, none were found that presented population-based epidemiological data. All studies we found on variceal bleeding were small and not population-based, where we would overestimate the rates, hence they were excluded from the review.

**Reviewer #2:**

**Comment 1:** What is the difference between LGIB case-fatality and LGIB-related mortality? Could they be mutually substituted?

**Authors' response:** Case-fatality and mortality are different types of epidemiological rates and cannot be mutually substituted. Case-fatality is simply the number of cases who die as a percentage of all cases; for example, the number of LGIB-related deaths divided by the total number of LGIB cases and presented as a percentage. In contrast, mortality rates are expressed as deaths per person-years (i.e. the denominator takes both the number of people and the time they were observed for into account). Please note that both terms are already defined in the manuscript in the 'Data analysis' section in the Methods.

**Comment 2:** The content of majority of the manuscript is mainly associated the GIB epidemiology, which is not commensurate with the title of the article "The global burden of upper and lower gastrointestinal bleeding in the general population". It is might be better if the economic burden caused by disease of GIB were also appropriately analysed.

**Authors' response:** We have changed the title to be more commensurate with the content of the manuscript. The title is now changed to "The global epidemiology of upper and lower gastrointestinal bleeding in the general population: A systematic

review". The word 'burden' is now not included in the title, and we appreciate that this may have been misleading because the study was only on GIB epidemiology. Economic burden of GIB was out-of-scope of this review.

**Comment 3:** The conclusion of manuscript should be reasonably modified, so as to make it more commensurate with content of analysis.

**Authors' response:** We have modified the conclusion in both the main body of text and in the abstract to be more commensurate with the content of analysis, without directly repeating the data for each epidemiological outcome evaluated as this is discussed further up in the Discussion.

## Reference

- (1) Gusenbauer M, Haddaway NR. Which academic search systems are suitable for systematic reviews or meta-analyses? Evaluating retrieval qualities of Google Scholar, PubMed, and 26 other resources. *Res Synth Methods*. 2020 Mar;11(2):181-217. doi: 10.1002/jrsm.1378. Epub 2020 Jan 28. PMID: 31614060; PMCID: PMC7079055.
- (2) National Library of Medicine. About MEDLINE® and PubMed®: The Resources Guide.  
<https://www.nlm.nih.gov/bsd/pmresources.html#:~:text=MEDLINE%C2%AE%20contains%20journal%20citations,full%20text%20articles%20when%20possible.&text=The%20following%20resources%20provide%20detailed%20information%20about%20MEDLINE%20data%20and%20searching%20PubMed>
- (3) National Institute for Health Research. PROSPERA. International prospective register of systematic reviews.  
<https://www.crd.york.ac.uk/prospero/#aboutregpage>