Reviewer 1

Dear Reviewer,

We appreciate the feedback and the time spent in the analysis of our study. Your evaluations and comments are of great importance to address previously possible questions that may arise in readers and to raise the quality of work.

We also have the help of one of the authors, Mr. Ethan Dwane Maahs, Native English Speaker, in the writing of this manuscript.

Regarding the considerations given, we will answer below and highlighted (green) the modifications on the manuscript.

The article is aimed to compare the diagnostic accuracy of capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) in cases of obscure gastrointestinal bleeding of vascular origin. The title is "Video capsule endoscope versus Double-balloon enteroscopy in the diagnosis of small bowel bleeding by vascular source: A systematic review and meta-analysis".

1. Several factors influence the outcome of the study. Please discuss these issues.

A greater sensitivity of DBE in small bowel OGIB after using the VCE as the initial examination was found. Considering the high sensibility of VCE in relation to DBE (93% x 84%), we suggest this use in suspicion of vascular lesions. Despite the low specificity found when using VCE after DBE, its post-test result is double than DBE (85% x 41.6%) which would make us suggest to use this feature after DBE with a negative finding. In this meta-analysis, we included studies in which VCE was performed before enteroscopy, and the route was chosen according to the possible location of the finding in the VCE. This leads to a higher probability of finding in DBE. On the other hand, this also means that some enteroscopies were not completed since they only used one of the insertion pathways.

In one study, that attempted complete small bowel examination, all patients underwent both an antegrade and retrograde DBE procedure whereas in the other studies the DBE strategy varied. In two studies, the antegrade or retrograde approach of DBE was chosen based on the VCE findings. One study

chose the route of DBE based on the medical history. One study chose the antegrade route of DBE in all cases, followed by an alternate approach if considered necessary. In many studies, the decision to perform an additional DBE using the alternate route was made after considering several factors, including the results of the initial procedure, clinical indication, and patient consents. Two studies had a single-blinded design.

The mean age of our study was 57.2 years. Angiectasias accounts for 20% to 30% of small bowel bleeding and are more commonly seen in older patients. Also, bleeding in those who use nonsteroidal anti-inflammatory drugs and proper intestinal preparation [41] facilitates the identification of lesions. The analyzed studies did not stratify the findings in the examinations regarding age, use of medications (nonsteroidal anti-inflammatory drugs), urgency/emergency indications, and bowel preparation, which prevents us from analyzing more data that would bring valuable information.

Although studies have assessed the diagnostic yield of VCE, push enteroscopy, and device-assisted enteroscopy in OGIB, the precise significance of lesions identified and the impact on clinical outcome has not been consistently evaluated for those modalities. In the case of OGIB, a positive patient outcome should be either cessation of bleeding or resolution of anemia. Several studies have demonstrated a change in patient management and improved outcomes following VCE and device-assisted enteroscopy [40].

Of the included manuscripts, seven included patients follow-up. The mean duration of follow-up varied from 5 to 12 months. Patients remained bleeding in most of these studies, ranging from 65 to 81% including those whose findings were external of the small bowel.

References:

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2. Please add more details of the discussion section.

We made modifications in the text and increased the details as suggested. We believe that the manuscript is interesting and more abundant in detail now. Thanks for your suggestion!!!

3. Please also add more details of the limitations of the study.

I apologize if we were quite brief on the limitations of our study. We modified the text and added more clear information. Thanks again for your valuable suggestion!!!

4. What are the new knowledges from this study? 5. Please recommend the readers "How to apply this knowledge for routine clinical practice?".

The study is helpful in the choice of the best initial diagnostic procedure in patients in whom vascular bleeding is suspected, such as in cases of vascular syndromes, elderly patients, and patients using anticoagulants. In many places, these procedures are associated with high costs and are not always available at the same center. Although there are suggestions for using DBE as the first choice in obscure bleeding, we have shown that, regardless of the severity of

the case, VCE would be the best and safest choice, including a 7% increase in diagnostic yield of DBE.

Dear reviewer, we hope that we have answered all your questions and hope that your new analysis is positive. We look forward to your response and are available for any further questions.

Reviewer 2

Dear Reviewer,

We appreciate the feedback and the time spent in the analysis of our study. Your evaluations and comments are of great importance to address previously possible questions that may arise in readers and to raise the quality of work.

We also have the help of one of the authors, Mr. Ethan Dwane Maahs, Native English Speaker, in the writing of this manuscript.

Regarding the considerations given, we will answer below and highlighted (yellow) the modifications on the manuscript.

1) "from a vascular source" is superfluous and can be omitted given the title is already quite long and that really all bleeding stems from a vascular source."

We agree! We made the modification. Thank you for your valuable suggestion!

2) Abstract: - It would be helpful if the authors could mention what types of studies were included. E.g. only randomized, only prospective, prospective and retrospective, etc.

We apologize if we were not clear on this information. We used prospective and retrospective studies, including observational, Cohort, single-blinded, and multicenter studies.

We did the modification in the text, and we believe that it is clear now. Thank you for this valuable suggestion.

3) Introduction: -it is unclear why the authors chose to include only double balloon enteroscopy (DBE). -a stronger case needs to be made why a meta-analysis needs to be performed specifically on cases with bleeding from a vascular source. What percentage of bleeding is NOT from a vascular source??

Of the assisted enteroscopy techniques the studies have demonstrated a higher index of findings and complete exams with the use of DBE. Due to the limited amount of studies on this subject as well as the low level of evidence of

the available literature, we chose the DBE technique for the systematic review and meta-analysis to contribute to a high-quality evidence study.

For this meta-analysis, the data referring only to the sources of vascular bleeding in the studies were collected, excluding any non-vascular sources. Thus, 100% of the data presented are of vascular origin.

We modified the text and made this information clear in order to demonstrate the importance of this meta-analysis for the literature. Thanks for your comment!

4) Methods: -See comment in abstract section above. -It should be clarified if the study included both overt as well as occult bleeding or only one or the other. If both were included, they should have separate/stratified analyses, as these may be very different entities.

That is a great comment. We agree with your comments, but I can explain to you why we could not separate these entities.

For this analysis, both conditions, whether visible or not, were included in obscure bleeding. Unfortunately, the articles did not stratify the findings according to the type of bleeding (overt or occult) but according to the findings of the tests.

We have modified the text and made this information clearer. Thanks for the comment!

5) Results: -Overall, the Results section seems suboptimally composed, possibly due to the sequence in which results are presented or because organization is not great -The following sentence is difficult to understand, likely due to punctuation issues: "The lesions were identified 3150 exams (1722 VCE and 1428 DBE) in 2043 patients and of 2248 sources of bleeding 1467 were found to be vascular lesions."

You are right. We believe that the sentence would be better understood as follows: "In 3150 exams (1722 VCE and 1428 DBE) performed in 2043 patients, were identified 2248 sources of bleeding of which 1467 were found to be vascular lesions."

We corrected this sentence in the Results section. Thank you very much for this valuable suggestion.

6) Also, how could the number of lesions be lower than the number of patients? Perhaps the authors are trying to convey that in some patients, despite documented bleed, the source lesion was not found?

Regarding the number of patients x number of lesions, the number of patients reported is the total present in the studies, including those that do not have a vascular source of bleeding. The only stratification that the studies did

was according to the findings of the exams (tumor, angiectasia, mass, etc.). Thus, in some of these patients, no source was found that could be considered vascular by the inclusion criteria of this review. We did the analysis only taking into account the findings and not the number of patients.

7) What are DBEF and BDE?

We apologize for our typing. We wanted to say DBE. We already corrected it in the manuscript. Thanks again!!

8) What is a vascular lesion detection index?

It would be the diagnostic yield of the examination for vascular lesions. We modified this expression to avoid misunderstanding. Thanks for the alert.

9) Discussion: -What is meant by: "Our review shows DBE is reasonably sensitive and has high specificity, however it performs worse VCE performance." ?

When using the VCE as the initial examination, a greater sensitivity than DBE in small bowel OGIB were found. Considering the high sensibility of VCE in relation to DBE (93% x 84%), we suggest its initial use in the suspicion of vascular lesions. Despite the low specificity found when using VCE after DBE, its post-test result is double that of DBE (85% x 41.6%), which would make us suggest to use this feature after DBE with a negative finding. In this meta-analysis, we included studies in which VCE was performed before enteroscopy without the enteroscopy anterograde or retrograde route, chosen according to the possible location of the finding in the VCE.

10) The limitations paragraph is quite brief; would encourage the authors to reflect on and include other limitations.

You are right. We report more data referring to the limitations of the study.

11) The real take-home message is unclear. Are the authors suggesting that DBE not be performed as an initial test? I.e. that capsule be performed so as to improve the yield? Or should DBE be performed as an initial test only when the bleeding is overt?

The study is helpful in the choice of the best initial diagnostic procedure in patients in whom vascular bleeding is suspected, such as in cases of vascular syndromes, elderly patients, and patients using anticoagulants. In many places, these procedures are associated with high costs and are not always available at

the same center. Although there are suggestions for using DBE as the first choice in obscure bleeding, we have shown that, regardless of the severity of the case, VCE would be the best and safest choice, including a 7% increase in diagnostic yield of DBE.

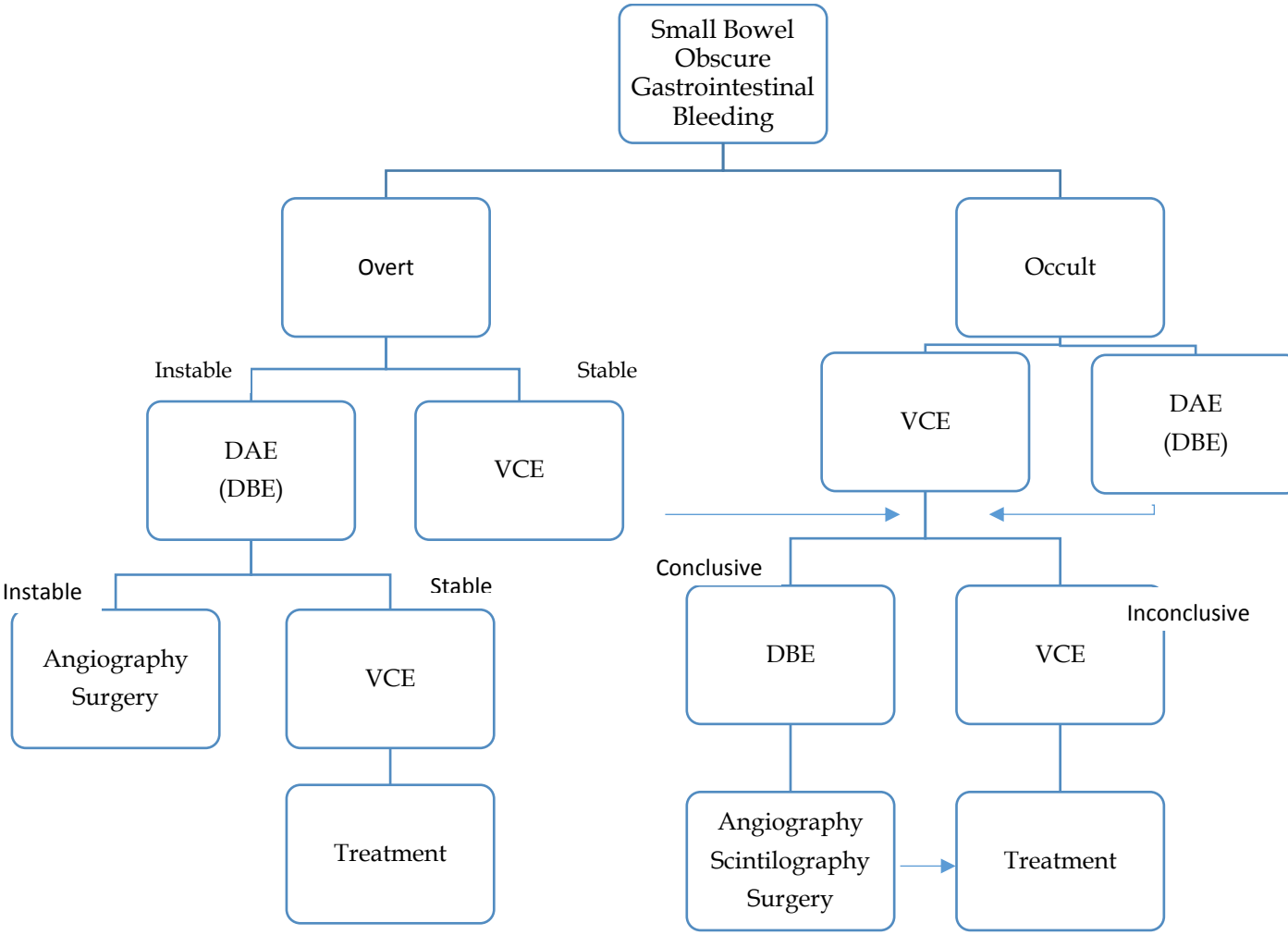
We have modified the text to make this message clearer. Thanks for your valuable comment!!

12) Figure and Tables: -No major concerns or critiques.

Thanks!

13)A suggested management algorithm would be helpful.

Great idea!!! We did it! Thank you very much!



Suggested management approach to overt and occult small-bowel bleeding after upper endoscopy and colonoscopy did not identify the vascular bleeding origin. Positive test results should direct specific therapy. When VCE is contraindicated or unavailable, device-assisted endoscopy (DAE) may be the initial test for small-bowel evaluation.

Label: VCE, video capsule endoscopy; DBE, double balloon enteroscopy.

Dear reviewer, we hope that we have answered all your questions and hope that your new analysis is positive. We look forward to your response, and we are available for any further questions.

Reviewer 3

Dear Reviewer,

We appreciate the feedback and the time spent in the analysis of our study.

1.Dear Author, I read the article. You should publish this article (Video capsule endoscope versus Double-balloon enteroscopy in the diagnosis of small bowel bleeding by vascular source: A systematic review and meta-analysis). Sincerely yours. Prof. Dr. Vedat Goral Istanbul Medipol University. Istanbul. Turkey

We want to thank the reviewer for the time in evaluating our article and for his generous comment.

Reviewer's ID: 03726743

The manuscript is considerably improved from prior. My only two residual comments would be:

Thank you very much. Below you can check the answers for your comments.

-Please define "vascular lesion" in the methods section. All GI bleeding comes from a blood vessel, and thus a vascular source; thus, because the authors are using this term in a selective manner, it should be clear what exactly they are referring to up front and early.

Thank you. That's a great suggestion. We included the definition in the main text. We classified 'vascular lesions' as: angiodysplasias, varices, hemangiomas, red spots, and Dieulafoy lesions. Bleeding from tumor, ulcer, erosions, polyps and masses were not classified as vascular lesions, but were considered bleeding from alternative sources.

-In the proposed algorithm, do the authors mean to suggest that VCE or DBE are appropriate as first line diagnostic modalities for occult OGIB? For overt bleeding, they seem to suggest DBE if unstable and VCE if stable, thus it would be helpful for the reader to know if one should be favored over the other for occult bleeding cases.

Thank you. That's also a great question. We included this information in the algorithm.