

We would like to thank the reviewers for their valuable work. We did our best to modify the paper according to their indications to increase the general quality of the paper and to reduce the risk of bias. In particular we deeply analyzed and discussed the role of different scopes used (standard and high-definition) as wisely suggested by both the reviewers.

We have also performed a new linguistic revision, added "core tip" and "article highlights", modified the references according to the journal style and uploaded original figures in Power Point and the original copy of a signed informed consent (with patient's information obfuscated) as requested by the editor.

1 Peer-review report

Reviewer #1: The authors of this large prospective single-center study support the use of the 4 L PEG for bowel preparation before colonoscopy (especially due to a significantly higher rate detection of polyp and adenoma). This is a controversial issue nowadays, since many recent articles show similar efficacy and tolerability of high-versus low-volumes. Generally, in the whole manuscript, the authors paid attention to details and data are easily to be followed.

Major issue: The authors presented four limitations of their study (which I agree with), but the main one – the use of two types of colonoscopes -lacks (both standard and high-definition colonoscopes).

We thank the reviewer for this relevant comment. We have indicated the number of procedures performed with high-definition (HD) and standard definition colonoscopes. There was no difference in the use of HD scopes in the two groups. Overall, the use of HD scopes was linked to higher adenoma detection rates compared to SD instruments. We have analyzed the impact of different imaging modalities on lesions detection rates in the two study groups. Performance of low-volume preparation seems strongly influenced by image resolution of colonoscopes, with fewer lesions detected compared to high-volume when using SD colonoscopes. We have largely discussed this results in the discussion section.

Other comments: • Please insert ORCID Numbers of the Authors

We have added the ORCID Numbers of all the authors as requested.

• Key words: Please correct "Glycole" to "Glycol"

The manuscripts has been revised accordingly.

• ABSTRACT: 1. Lesion detection rates are not presented among the aims, but mentioned in background and in methods (maybe you could use the same wording as in the aim: efficacy - both in terms of bowel cleansing and clinically relevant colonoscopy outcomes). 2. Please mention the period the study was carried out. 3. Please also mention that cancer detection and sessile/serrated lesion detection rates were compared (in Methods). 4. Results should mention that there were no differences in cancer detection and sessile/serrated lesion detection rates, between the two methods of bowel preparation. 5. Please correct: "≥75% dose intake was more frequent with LV (92.1% vs 94.6%, $p=0.003$)", by switching the percentages (LV – 94.6% vs HV – 92.1%), otherwise it is wrong.

We thank the reviewer for the comment. We have modified the abstract according to the suggestions provided.

• Please insert Core Tip in the whole manuscript.

We inserted Core Tip in the manuscript.

• BACKGROUND: Please insert references for "direct comparison of clinical outcomes such as ADR is available only in a minority of trials", as well as for "real-life data is both scarce and conflicting".

We have modified the second sentence to avoid repetition in the discussion; we have inserted references as requested.

• **METHODS: 1. Study design and subjects:** Please mention what follow-up did you perform – since the study was carried out between 2014 and 2016 and sent to be published only in 2021.

The study ended in December 2016, no further follow-up was performed. The reason for this significant delay is related to the fact that many investigators changed institution after the end of the enrollment phase of the study. Therefore, the analysis of data and the manuscript drafting were completed only in the last year.

We recognize that this delay is a weakness of our study, even so we believe that our data are currently valid and could be of interest, considering the increasing attention to bowel preparation observed in the last years.

2. Please explain why you decided to describe only polyp, adenoma, advanced adenoma, cancer, sessile/serrated lesions, and no other lesions (especially given that some patients were diagnosed with IBD).

The impact of bowel preparation on the diagnostic yield of colonoscopy for neoplastic or preneoplastic lesions detection has been well described. As we discussed in the paper, however, few studies have compared clinical performances of HV and LV preparations, for this reason we decided to focus on this topic.

We also included patients with IBD in order to give as much as possible information about the efficacy of the two preparations and patients' preferences and tolerability. However, the diagnostic yield of inflammatory lesions/diseases was outside the aims of our study.

3. Colonoscopy: I suggest an in-depth analysis be performed regarding the ADR, PDR, AADR, SDR and cancer rate detection, given the fact that both standard and high-definition colonoscopes were used. This could introduce an important bias. Please provide a table, separate for the two types of endoscopes used and aims of the study. Please also discuss and, if relevant, include as a limitation of your study.

We thank the reviewer for this important comment. We have completed the analysis as requested and we have resumed the results of separate analysis of lesions detection rates according to imaging modalities (HD or SD) in two new tables (table 4 and table 5, respectively). Discussion and limitations of the study were updated accordingly to these new findings.

4. Please provide what type of polyps were detected, as you mention PDR separately, ADR, AADR, SDR and cancer.

We introduced a more detailed description of the lesions detected in the results section. We did not collect morphology or exact size of polyps. We only considered the 1 cm cut-off for adenomas in order to categorize them as non-advanced or advanced based on previous relevant experiences in literature.

5. Aims of the study: This should be inserted by the end of Background, not in METHODS. Please insert the aims, by deleting the last sentence of the Background (Therefore, we have performed a real-life study...), as it shows almost the same aspects.

We have changed the paper accordingly to this indication.

• **RESULTS: Table 1 – significant difference for indications – please discuss more in detail.**

We have briefly described the differences in the results section and we have more extensively analyzed this aspect in the discussion section.

• **DISCUSSION: 1.** Please revise the following "This comparison is short of the newer LV preparations...", as it does not make any sense.

We have largely revised the discussion section, including this sentence.

2. When the low-volume of 1L PEG plus ascorbate was discussed, the authors did not mention a recent study published in the WJG: "Maida M, et al. Effectiveness of very low-volume preparation for colonoscopy: A prospective, multicenter observational study. World J Gastroenterol 2020; 26(16): 1950-1961". The authors assessed the effectiveness and tolerability of the 1 L preparation compared to 4 L and 2 L- PEG solutions in a real-life setting (therefore, since 1L PEG plus ascorbate was also compared with 4 L PEG, please correct your sentence - "the latter has been compared only with other low-volume preparations", as it is wrong).

We thank the reviewer for this important observation.

We intended to say that no RCTs have compared lesions detection rate of 2L PEG plus citrate and 1L PEG plus ascorbate versus high-volume preparations. We have modified the discussion for clarity, and we have mentioned the recent real-life study indicated and another recent abstract published in 2020.

- References: nothing from 2020 and 2021. Please insert recent studies (besides the one I mentioned).

We have inserted 3 references from the last two years, including the suggested study by Maida et al.

- Format of the style requested by the journal, including references is not adequate. Please correct.

We have revised the format of the paper and of the references.

- Minor revision of the English language is required (grammar, syntax and overall style).

We have performed a new linguistic revision.

- There are no « Conflict-of-Interest Disclosure Form » and « Copyright License Agreement ». Please add.

We have added the requested documents.

Reviewer #2: this topic is interesting and it is an issue of much debate. I have comments as regards this manuscript:

1- the clinical part of this work was completed the year 2016, so why the results were delayed till 2021.

The study ended in December 2016, no further follow-up was performed. The reason for this significant delay is related to the fact that many investigators changed institution after the end of the enrollment phase of the study. Therefore, the analysis of data and the manuscript drafting were completed only in the last year. We recognize that this delay is a weakness of our study, even so we believe that our data are currently valid and could be of interest, considering the increasing attention to bowel preparation observed in the last years.

2- why the endoscopists used 2 tps of endoscopies (standard and high definition), it will surely affect the results.

Thank you for this important observation. We have deeply revised the analysis according to this observation and discussed the novel results in the discussion section.

as regards the tables, three line tables are preferred. also add degree of freedom for every p value.

We have modified the layout of the tables and added p-value degrees of freedom as indicated.

3- language needs polishing

A new linguistic revision has been done.