

Athens, 27th April
2021

To the Editor-in-Chief of *World Journal of Gastrointestinal Endoscopy*

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript with ID: Manuscript NO.: 64871, entitled "COVID-19 in the endoscopy unit: How likely is transmission of infection? Results from an international, multicenter study". We submit the revised manuscript version, having answered all comments raised by the editors and the reviewers. Detailed point-to-point responses are listed below, and edits are in track-changes and highlighted mode throughout the document to assist the reviewers. We hope that our amended paper fulfils the requirements for publication in your prestigious journal.

Sincerely,

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Reviewer #1:

Specific Comments to Authors: *The paper by Papanikolaou et al. presents the results of an observational study aimed to assess the risk of COVID19 contagion in the endoscopy unit under current clinical practice recommendations. It is a multicenter international study involving 1267 endoscopies. The authors found a very low infection rate and conclude that the risk is rather low. This is a valuable initiative in the current context, in principle, although it has important limitations. Some are acknowledged by the authors already. My comments are given below.*

MAJOR COMMENTS

1. *Abstract: Methods should include the multicenter design (now in Aim) and the testing protocol in patients and PEU. Also the exclusion of positive patients. It is said that 75% patients 'turned positive' – what does this mean exactly, as patients were not tested before endoscopy?*

Authors' reply: We are thankful to the reviewer for this insightful corrections. We have amended the Abstract section (please see page 4 of the revised manuscript) to correct or include all the missing information. Moreover, we corrected the phrase “turned positive”, to clearly indicate that the majority of patients (n=6/8, 75%) who were eventually found to be positive for COVID-19 post-endoscopy had undergone an esophagogastroduodenoscopy procedure.

2. *The interpretation of the probable contagion route is not explained. In principle this would mean that a likely alternative route of transmission has been identified, but this requires case by case details.*

Authors' reply: We are thankful to the reviewer for giving us the opportunity to clarify this matter. We deliberately avoided to provide any interpretation of the probable contagion route, since this would be based only on random speculations rather than actual evidence. Additionally, the extremely small number of positive cases and the design of the study are also factors preventing a definitive causal relationship to be established. In any case, we would like to underline that principal aim of this study was not to address

issues related to potential route of infection transmission, rather than investigate the actual possibility of COVID-19 transmission in endoscopic units, when established guidelines are implemented. However, we added a paragraph commenting this in *Discussion* (please see page 15, lines 14-19 of the revised manuscript).

3. *The main problem of the study in my eyes is that, given an estimated very low infection rate, little can be drawn from the positive cases detected. In other words, for some 3% of positive patients (of which we do not know whether they were infected prior to endoscopy) we get 3% positive PEU. Is this a low risk? What is the background risk in a comparable population? There are no data (or comment) about the possible contact between positive PEU and patients. Also in P10 L7 it says 22.4% of patients were 'retested', this is confusing.*

Authors' reply: We are thankful to the reviewer for this comment. We agree with the reviewer that very little solid conclusions can be drawn from the eight positive cases and this is also beyond the scope of this study. Contrariwise, we aimed to evaluate incidence and outcome of infection among patients undergoing endoscopy and PEU, when the ESGE/ESGENA recommendations (Gralnek IM *et al.* - Reference No 3) are followed. In this regard, our retrospective study showed that risk of COVID-19 infection for patients undergoing GI endoscopy is indeed very low. As already presented in the Discussion section (page 12, lines 13-25), the background risk in a comparable European population (Repici A *et al.* - Reference No 6) was found similarly low to ours (1 in 802 patients - infection rate of 0.12%), with international data being consistent to ours (Rodrigues-Pinto E, *et al.* - Reference No 10, Miyake S *et al.* - Reference No 11), as well. Patients' re-testing with PCR in case of new symptoms onset was available at the physician's discretion on a case-by-case basis, across all participating centers. This percentage refers to those who were re-tested by their doctors, because they presented symptoms potentially due to COVID-19 infection. In any case, we amended the *Methods* (please see page 8 and lines 5-7) and *Results*

sections (please see page 10 and lines 5-7) of the revised manuscript, to prevent misleading the reader.

4. Positive patients are excluded from analysis and results are given for 1135 patients out of 1222. This is stated clearly only in Results. These are probably symptomatic patients warranting a PCR test, but we get no information about percents here. Only in the Discussion it is said that about a fourth of patients underwent pretesting. If these patients did undergo endoscopy, why were they excluded? Also under what circumstances were patients tested a posteriori? Same for PEU. PCR is used in both cases but there is little else in the way of information. Further, according to the abstract data from 163 PEU were recorded – what percent is this?

Authors' reply: We are thankful to the reviewer for this comment. Please let us provide some clarifications on this issue. Positive patients were indeed those symptomatic and eventually found positive for COVID-19 infection after pre-endoscopic PCR-testing. There is no reason to include these patients in the analysis or provide additional information, since the position statement by ESGE/ESGENA for risk stratification applies only to potentially COVID-19 infected patients requiring endoscopy. PCR-testing *a posteriori* was performed at each physician's discretion on a case-by-case basis, taking into account each patient's clinical status; with the same principal applying also for the PEU. 163 was the total (100%) number of PEU included in the study. This is a different population of subjects studied and not part of the patients undergoing endoscopy; thus, no percent is available. However, we amended the **Abstract** and Methods section (please see page 4-5 and page 8, lines 5-7 of the revised manuscript, respectively) to better state this and avoid confusion.

5. In P12, last paragraph, the authors allude to the possible connection between upper endoscopy procedure and COVID19 contagion, this is confusing again because it there is increased risk it should be mostly patient to personnel, correct? Overall, the paper is difficult to interpret, despite the fact that it is a quite simple study. So this is one problem. Once this is solved, probably little can be known from it, which is a second problem although more understandable.

Authors' reply: We accept the reviewer's criticism on this issue. Indeed, the possible connection between an upper endoscopy procedure and COVID19 contagion would result in increased risk for infection transmission to personnel rather than the patients themselves. Therefore, we omitted the respective paragraph from the *Discussion* section (please see page 12, lines 29-30 and page 13 lines 1-4, as well as references no 12 and 13) to avoid giving misleading information. Aside that, in our opinion the current study adds to the existing literature by highlighting the fact that the risk for COVID-19 infection related to endoscopy is very low, when guidelines are followed.

MINOR COMMENTS 1. Page 6, line 10: please rephrase, perhaps something like 'Moreover, endoscopy involves also the assisting personnel...'

Authors' reply: Done

2. P8 L5: each patient

Authors' reply: Done

3. P9 L11: which author is the statician?

Authors' reply: Associate Professor of Gastroenterology and Internal Medicine I.S. Papanikolaou (IP) is the statistician.

4. P9 L15: reference?

Authors' reply: Done

5. Probably explain abbreviations in full in the tables as well.

Authors' reply: Done

Reviewer #2:

Specific Comments to Authors: Overall, the manuscript highlights an important aspect in the field of gastroenterology, a clinical dilemma of whether or not to perform endoscopic procedures (especially elective) during the pandemic. However, the manuscript can gain strength if the authors can also provide the indication for the procedures (i.e. elective versus emergency cases) and then compare the two groups. Also, as mentioned in the limitations section, prior testing for SARS-CoV-2 in patients on list for endoscopy would have further augmented the study results.

Correction in the results section: 1267 endoscopies (instead of 126) In the discussion section, authors are labelling this study as a TRIAL (it's a retrospective analysis)

Authors' reply: We are thankful to the reviewer for this interesting comment. However, we would like to clarify that patients' stratification as low- or high-risk for potential COVID-19 infection was conducted uniformly across all participating centres according to the position statement for GI-endoscopy during the COVID-19 pandemic by ESGE/ESGENA^[3], which clearly lists which endoscopic procedures should be definitely performed and which can be postponed, policy that was followed in our study. Thus, all the endoscopies performed in our series, if not emergency were nevertheless completely necessary and none were pure elective. This can be clearly seen in Figure 2, which shows the drastic reduction of endoscopies (i.e., elective ones) during the study period. A comment has been in the *Discussion* (please see page 14, lines 10-17 of the revised manuscript).

According to the reviewers suggestion, we have amended the Results (please see page 10, line 1) as well as the *Discussion* section (please see page 12, lines 2-3 of the revised manuscript) to clearly indicate that this was an analysis of retrospectively collected data within a prospectively built database.

Reviewer #3:

Specific Comments to Authors: *This study was planned to assess the impact of COVID-19 on endoscopy during the first European lockdown (March-May 2020) in multi-center study. In general, this plan is an interesting topic and a well-written manuscript. Therefore, I recommend the publication.*

Authors' reply: We are thankful to the reviewer for this kind comment.

Reviewer #4:

Specific Comments to Authors: *It's an original study. It can be accepted*

Authors' reply: We are thankful to the reviewer for this kind comment.

Re-review

It would be a lot better if changes were indicated in some way in the manuscript. I am not sure whether this is required by the journal but it is much easier to assess the edited manuscript this way. The lines given by the authors do not match, which does not help. 1. OK. 2. Right. Then wouldn't it be preferable to say nothing at all? See also below. 3. This comment by the authors sums up the problem with this paper, which is the presentation. I fully agree with the first part of this paragraph: this is the value of the study. But it is not clear enough, as the manuscript goes beyond that to hint at possible contagions and so forth. Regarding the second part, the design is simple, yet it is confusing to the reader. Let's see: out of 1135 patients not positive (untested or tested negative), 254 were found to be positive a posteriori, that's the 22.4%. But if you say they were retested you imply that only pre-tested patients were tested a posteriori. This makes no sense to me, although I reckon it is possible. According to this, there was no COVID19 test performed after endoscopy to any patients that were not tested prior to it. That is some coincidence! Thus I am guessing that it is either that or there is an error in the presentation. It could be that the percentage of untested patients was very low, but this is not the case according to the Discussion. Either way, this should be clearer. A diagram would help (I actually drew one myself so as not to get lost). 4. It makes sense to focus on nonpositive patients for those reasons, but actually the risk of infection would be best assessed in this population, would it not? As for PEU, simply say 'all 163 PEU'. Again, clarity. 5. I fully agree.

Science editor:

Specific Comments to Authors: (5) Self-cited references: There are 2 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Authors’ reply: (5): We have removed Ref no 18 (Karampekos *et al.*) and now there is only once self-citation; (1) we provide the original figure documents within a separate PowerPoint file uploaded with the revised version of our manuscript; (2) The “Article Highlights” section has been added (please see pages 16-17 of the revised manuscript)