

Dear Editor-in-chief of World Journal of World Journal of Gastroenterology,

The authors send a revised version of the manuscript entitled "Appropriateness of the study of iron deficiency anemia prior to referral for small bowel evaluation at a tertiary center" (ESPS manuscript NO: 33025) to be considered by your Journal.

In order to take into consideration the comments of the editor and reviewers, the authors submit a revised manuscript with all amendments highlighted. Moreover, a point-by-point response is provided to all the comments of the editor and the reviewers:

Editor:

As requested by the Editor, a new version of the revised manuscript in a word document is provided to simplify the edition of the article.

Reviewer No 02953753:

"Anemia work up is a globally time and source consuming issue for gastroenterologists. The text and the given percentages are perhaps useful to create awareness on this issue."

Answer to Reviewer:

In fact, anemia is a common cause of referral to gastroenterologists. Taking into account our results and in order to achieve appropriate use of resources, the pre-referral study of anemia should be optimized. A better communication between the different specialties is required to enable prompt and correct management of patients.

Reviewer No 02953209:

"Thank you for the opportunity to revise this interesting manuscript. It picks up a subject relevant for many specialties, mostly for gastroenterologists. There are some minor spelling mistakes and 1 or 2 sentences that are not quite clear in their meaning due to syntax errors, for example the following sentence: "On the other hand, this work has also important merits, namely it is real life study so, contrarily to previous data on this important topic, data here presented reflects real life practice." Another

example: “patients performed EGD”. It was certainly the physicians that performed the investigation. I think the otherwise well written paper will be easily adjusted accordingly.”

Answer to Reviewer:

As requested by the reviewer, grammar and syntax errors were corrected. Pertinent references were also added.

“Please define the term “pre-referral study” better. Throughout the text, it seems to refer to all investigations including blood tests and Endoscopies. However, in table 5 it seems to exclude Endoscopies and CD- testing. Please clarify.”

Answer to Reviewer:

All studies performed before tertiary center referral in the context of anemia work-up, including blood tests, endoscopic and imagological studies, were retrospectively collected. However, an appropriate pre-referral study, our composite endpoint, was simply considered the execution of esophagogastroduodenoscopy (EGD) with *Helicobacter Pylori* (Hp) investigation, colonoscopy with quality standards and Celiac Disease (CD) screening. In Table 5, we present the association of several demographic and clinical data with small bowel evaluation, whether they are included in the composite endpoint or not.

“I think that there is a fundamental question that needs to be discussed in the manuscript. For example, if the emergency department refers an IDE patient explicitly for small bowel evaluation, it is up to the gastroenterology department to make sure that adequate studies are performed beforehand. Furthermore, the performing gastroenterologist should be addressed when Colonoscopy is performed without quality standards or EGD without CD and Hp testing. This cannot be up to the referring cardiology department, the general practitioner or the emergency department. Are the referrals from other departments without proper EGD/ Colonoscopy etc. incorrect because they don't perform it themselves and might just have phrased the question/the consult to your department wrongly!? EGD/Colonoscopy is an outsourced action performed by a specialist, namely the

gastroenterologist. Without the performing physician thinking about indications and consequences, e.g. omitting to take specimens for Hp and CD testing, the actual problem lies within the non-existence of guidelines or a lack of adherence to these guidelines by the gastroenterologists. Thus, for example the sentence in the “Core Tip”: “Better communication and definition of referral protocols between the different specialties are required to enable patients to be promptly and correctly managed.” would then be wrong and should be something like: “Better communication and standards for the definition and workup of IDE are required to enable patients to be promptly and correctly managed by the different gastroenterologists.” What I am trying to say is that the problem does not lie within the referring department, but with the gastroenterologists who have performed the previous tests/endoscopies.”

Answer to Reviewer:

In fact, and taking into account our data, the adherence to IDA management guidelines by gastroenterologists can also be enhanced, a factor that could somewhat optimize the referral of IDA patients to tertiary centers. As discussed by the reviewer, endoscopists performing outsourced EGDs and colonoscopies may have a role in improving pre-referral studies. Endoscopists and facilities performing outsourced endoscopies should be encouraged to perform biopsies for Hp and celiac disease screening in the setting of IDA and ensure that the bowel preparation meets quality standards. In the case of an inadequate bowel preparation, the colonoscopy report should mention the need of a second colonoscopy with an adequate bowel preparation. This was added to the manuscript.

However, taking into consideration that both EGD and colonoscopy are outsourced, open-access procedures, and also the crescent waiting list both for appointments and procedures at tertiary centers, we consider the focus must also be on the adequate referral of patients, with the performance of a minimum initial IDA work-up before referral. This will ensure appropriate use of resources, increase patient convenience, reduce costs and perhaps improve patient outcomes.

“According to Table 5, the previous study/EGD/CD testing etc. only had a significant p-value for Colonoscopy. As a result, the others tests had no significant influence on whether or not the SB Appropriate Preparation was not significantly connected to subsequent SB evaluation. Please comment on these points.”

Answer to Reviewer:

In fact, only colonoscopy presented a significant association with subsequent SB evaluation. However, we see a trend towards a more frequent SB evaluation in patients with an ample pre-referral study, both in terms of our global composite endpoint and in its individual components. Indeed, besides colonoscopy, this associations did not reach statistical significance (a fact that could be hampered by a somewhat limited number of patients included in the study), but p values almost reached the 0.05 threshold: $p = 0.07$ for EGD and $p = 0.06$ for Celiac Disease screening. These data make us conclude that patients with an adequate pre-referral study are the ones in which SB studies have the greatest utility and the ones who should be referred, ensuring appropriate use of resources.

“Table 1 Is “internal medicine” a general department compared to cardiology, nephrology, gastroenterology etc.? This should be commented on.”

Answer to Reviewer:

Yes, in our center as well as in our whole country, Internal Medicine is structured as an independent department as well as Cardiology, Gastreenterology, etc.

Otherwise, I think that the manuscript would be suitable for publication after the mentioned revisions.”

After consideration of the reviewer comments, the authors send a revised version of the manuscript to be considered by your Journal.

Kind regards,

Jaime Pereira Rodrigues