REPLY POINT BY POINT

The authors wish to thank the reviewers for their insightful comments which helped to improve the quality of our manuscript. Each criticism has been addressed below in a point-by-point fashion:

Answers to reviewer 00503571:

1) Review is too long and should be better structured and shortened.

Manuscript has been modified according to reviewer's remarks.

2) Authors stated that thrombocytosis in IBD could be related both to iron deficiency and being as surrogate marker of inflammation. However, the significance of iron deficiency as the cause of thrombocytosis in IBD seems to be overestimated. There are no publications (or observations from clinical practice) that iron supplementation could normalize elevated platelets in IBD. Contrarily, anti-inflammatory treatment is very effective in normalization of number of platelets.

This is an interesting remark and we would like to be more analytical on the subject. It has long been acknowledged that thrombocytosis is a frequent manifestation of IBD related to disease activity, as it is presented in our manuscript. Nevertheless, there are studies pointing out that iron deficiency can also be PLT count regulator in anemic patients, even otherwise healthy (ref 57, 58), with reactive thrombocytosis presented more frequently in literature.
In IBD over the last years, two studies from Kulnigg-Dabsch et al (ref 55, 56) and one from our center (ref 46) revealed a significant correlation between iron scarcity and PLT parameters. In the first Kulnigg-Dabsch's study (ref 55) it was demonstrated that iron supplementation, did normalize PLT count in IBD patients with low inflammatory indices, revealing a possible regulatory effect of iron in PLT production. In the second Kulnigg-Dabsch's study (ref 56) iron replacement was not only associated to PLT count decrease, but also to a significant decrease in PLT activation markers suggesting that iron management may express even anti-thromboembolic properties in IBD patients. Moreover, in a study from our center (ref 46), PLT number revealed strong relationship with both inflammatory and iron deficiency parameters in a series of consecutive IBD patients. Taking into account the increased number of anemic patients in the study, the increased iron deficiency markers and the low inflammatory indices of our patients we assume that iron scarcity consist a dominant cause of thrombocytosis in IBD.
Until now, no study was designed in a way to discriminate to what extent iron deficiency and inflammation account for the elevated PLT count

observed in some in IBD patients, but it is certain that iron capacity is a major governor in PLT production in all humans and especially in iron deficient subjects like many IBD patients.

Answers to reviewer 00069475:

All remarks have been accepted and incorporated in the manuscript

Answers to reviewer 00068103:

1) The paragraph titled "Platelets as active inflammatory components" needs intensively describing, especially the interaction and bilateral function regulation between PLT and immune cells, and the possible mechanism. A schematic illustration is encouraged and required about the interaction between PLT and immune cells.

We thank the reviewer for this valuable remark. A number articles and reviews, even in previous issues of this journal, have been devoted to PLT role as inflammatory components in disorders like IBD and their decisive interplay with immune system. Since a clinical approach emphasizing on the clinical aspects of PLT in IBD is lacking, we decided not to scrutinize in pathophysiological paths and interaction mechanisms between PLT and other cells in inflammatory diseases, but make a rather more clinical approach (as it is stressed in the title of our manuscript) addressing chiefly to clinical physicians colleagues. Believing that we presented a general outline of the most important articles implicating PLT and IBD immune reactions, we avoided to further analyze the interplay between PLT and immune system cells in inflammation, as this could destruct the attention of the reader from IBD.

2) Minor concerns: The language needs to be revised, as well as word spelling. For example, in page 3, line 11 "week", etc

Language and word spelling was revised.

Answers to reviewer 00189171:

1) This paper summarizes all the relevant knowledge regarding the role of platelets in the pathogenesis of inflammatory bowel diseases. It also review the complications of which may connected to abnormal platelet count or dysfunction. Major concerns: Cause of elevated platelet count may be related to many causes. Inflammation and iron deficiency are the main relevant ones in inflammatory bowel disease. Authors reviewed the pro- and cons – as it is

stated in the manuscript. Despite the conflicting results in the literature, the authors should unfold they own ideas regarding their own opinion about the cause of elevated platelet count (iron deficiency or inflammation), predictive value of morphological changes of platelets, etc. As authors of this review has an experimental experience on this field, the readers may interested in their opinion on these conflicting data. I feel the conclusion section to be too short.

Reviewer's comment is valuable. We added a paragraph in the conclusion that stands for our opinion on the subject of PLT and iron deficiency.

2) Minor concerns: Use of the abbreviations should be revised, because the high number of them makes the manuscript a bit hard to read. Those which are not used further on the manuscript should be eliminated from the text. Some of them are positioned on a wrong place, eg. IBD in the first sentence are used as a duplication, and there is no displayed the resolution of the PLT in the first paragraph. Some other abbreviations are also not cleared further on (C-Mpl, SCCAI, CDAI, PLA, MPs, etc.)

According to reviewer's remark, abbreviations were reduced in number, positioned in the right place and further cleared if needed. Nevertheless, C-Mpl receptor for thrombopoietin is the full name and not the abbreviation and remained as it was.

3) First sentence of the second chapter of the second part of the manuscript ("Thrombopoesis is the biological function of PLT…") I a bit confusing for me, it should be cleared.

Reviewer's comment has been revised in the manuscript.

4) Manuscript would be more convenient to read if one or two well-designed figure would illustrate the text. Figure(s) might sign the factors which influence the count and function of the platelets and which are produced by the platelets itself, also.

We thank the reviewer for the remark. Two figures have been incorporated in the manuscript.

5) 12th page, 2nd chapter: soluble fraction of P-selectin instead of sP-selection

Reviewer's comment has been accepted and incorporated in the manuscript.

6) There is a section in the "quantitative and qualitative platelet changes" regarding the thromboembolism, and another one later (page 14). These parts should be harmonized.

We thank the reviewer for the remark. It wasn't our aim in ''quantitative and qualitative platelet changes'' section to analyze the subject of thromboembolism and IBD, but rather make a comment about the lack of association between PLT count and thrombosis in IBD, as it is observed in patients with cancer. We felt this was the proper place to do, because this is the part that we thoroughly refer to PLT count in IBD. On the other hand, in page 14 is the main section analyzing the subject of thromboembolism and IBD in detail and citing all the well known studies.