

Dear Editor,

We are pleased to submit for publication our systematic review titled: "Platelet rich plasma effectiveness in bowel anastomoses: A systematic review"

We are grateful to the editors and reviewers for providing insightful feedback on our study. We have carefully reviewed the recommendations and have revised our manuscript accordingly. Addressing each of their comments has certainly improved our manuscript. Detailed point-by-point responses to the editor's and reviewer's comments are provided below.

Comment 1.

As the authors state, it is still unclear what is actually effect of PRP on anastomosis site healing. According to the previous reports, evaluating factors were anastomotic burst pressure, tissue hydroxyproline, collagen deposition, and inflammatory cells deposition. If possible, please show the figure which factors in the healing process PRP may act on. It can make it easier for the reader to understand the effect of PRP.

We appreciate the reviewer's comment and we agree that illustrating the PRP associated factors that affect the healing process would be of utmost importance for our study. To this end, we included a figure that depicts the multimodal effects of PRP and related factors that are involved in the healing process. The figure is cited in the discussion part of the manuscript. The figure has also been included in the end of the response to reviewers file for your convenience.

Comment 2.

Aydin et al (2020) reported the effect of PRP, and they focused on its concentration. Low level PRP was effective, on the contrary, high level PRP is more likely to inhibit healing. It is very important factors about this research, so please mention about it in the discussion.

We would like to thank the reviewer for this valuable comment. We have modified our discussion section (including the appropriate references) to stress the importance of different PRP concentrations on bowel anastomosis.

Nevertheless, the platelet concentration of PRP applied to the anastomotic area may also affect the healing outcomes. To that extend, Aydin et al. showed that low platelet concentration results in superior outcomes in terms of anastomotic bursting pressure and collagen concentration at the anastomotic site compared to high platelet concentration PRP [17].

We believe that future studies should focus on the effect of different PRP concentrations in bowel anastomosis.

Comment 3.

As the authors pointed out, further research is needed to confirm the safety and effectiveness of PRP on human bowel anastomoses, and to transfer the human clinical study. How much blood sample is needed to obtain the required PRP?

We appreciate the reviewer's comment. In general, a small quantity of peripheral blood is required for PRP preparation in human subjects. The current data are mainly derived from aesthetic and orthopedic surgery. We have modified our discussion section (including the appropriate references) accordingly.

Currently, most studies report that a sample of 5-20 ml of peripheral blood is required to extract 2-5 ml of PRP. The amount of peripheral blood required for PRP preparation depends on the technique or commercial kit that are used during the isolation process [58,59].

Comment 4.

Although platelets aggregation occur early in the healing process of bowel anastomosis in inflammation period, thrombocytopenia becomes a risk factor for anastomosis leak? Reference 1. Aydin MA, Guler EM, Demiroz AS, et al. Comparison of Platelet-Rich Plasma-Impregnated Suture Material with Low and High Platelet Concentration to Improve Colonic Anastomotic Wound Healing in Rats. *Gastroenterol Res Pract.* 2020; 2020: 7386285.

We would like to thank the reviewer for this observation. Both thrombocytopenia and thrombocytosis have been associated with bowel anastomosis leak. Again, we have modified our discussion and added the relevant references.

Dysregulation of circulating platelets, the main component of PRP, has been associated with anastomotic leak. Both thrombocytosis and thrombocytopenia have been described as factors associated with anastomotic leak. However, these results should be interpreted with caution as the dysregulation of circulating platelets could be attributed to malnutrition (thrombocytopenia) or sepsis (thrombocytosis), which are well established risk factors associated with anastomotic leak [53,54].

Sincerely,

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Figure 2. Platelet rich plasma effect on the healing process of bowel anastomosis. (Created with BioRender.com)

