

Reply to reviewers comments:

Reviewer 1	
<p>1) In the introduction the authors state that TEG and ROTEM provide 'a global assessment of the coagulation system'. Whilst these tests are likely more accurately representing hemostatic status than PT and platelet count, also these tests are far from perfect, and I would like the authors to give this statement a little more nuance (J Clin Gastroenterol. 2020 Apr;54(4):389-391).</p>	<p>We thank the reviewer for their comments. The stated lines have been revised as follows on page 5 lines 128-136</p> <p>“The conventional tests of coagulation, namely prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) and platelet counts assess only specific components of the coagulation system (intrinsic or extrinsic pathway) and therefore do not provide a complete overview of the hemostatic derangements in cirrhotics.</p> <p>Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are widely touted to provide a more accurate “global assessment” of the coagulation system but have important caveats of not being able to assess levels of Protein C and von Willebrand Factor, which play important roles in the coagulation pathway in cirrhotics”</p> <p>The article mentioned by the reviewer has been cited in this paragraph (citation number 3)</p>
<p>2) Also in the introduction it is stated that 'severe thrombocytopenia is believed to increase the risk of procedural bleeding in cirrhotics'. Also this statement needs to be toned down as there are also studies showing a lack of predictive value of platelet count for procedural bleeding (see statements on this in the recently published EASL guidance document: https://pubmed.ncbi.nlm.nih.gov/35300861/).</p>	<p>We thank the reviewer for their comments. The statement mentioned by the reviewer has been modified on Page 4 lines 139-142 to read as follows:</p> <p>‘while severe thrombocytopenia may be associated with increased risk of procedural bleeding, several studies have demonstrated a lack of predictive value of platelet count for procedure related bleeding in cirrhotics. The impact of thrombocytopenia on severity of AVB is unclear.</p> <p>The EASL clinical practice guidelines have been cited in the discussion section (citation</p>

	number 27)
3) The statement in the beginning of the introduction on 'a procoagulant state in several cirrhotic patients' is vague. There is evidence for hypercoagulable features in all patients with cirrhosis, even those who are critically ill.	<p>We thank the reviewer for their comments. The line mentioned by the reviewer has been removed and the discussion rephrased as</p> <p>“Clinically, some patients demonstrate increased bleeding rates with invasive procedures, while others may develop spontaneous thrombosis of the main portal vein or its tributaries, indicating that the coagulation system in cirrhotics behaves differently in individual patients, demonstrating both pro- and anticoagulant tendencies”</p> <p>On Page 12, lines 341-345</p>
4) Pag 13, top - please also cite the 2022 EASL guideline.	We thank the reviewer for the comments. The citation has been added in line 359 as citation 27.
5) page 13 middle - the discussion of the Mohanty and Blasi studies is vague - don't all 3 studies basically conclude the same (lab values do not predict outcome, transfusion is bad)? Also, the Blasi study doesn't deal with active bleeding, but with post-prophylactic band ligation, so the comparison is somewhat confusing.	<p>We thank the reviewer for their comments. The paragraph mentioned by the reviewer has been changed as follows on Page 13, lines 370-375</p> <p>“There is also a lot of scepticism associated with FFP transfusion in these patients based on the results of the retrospective study of 244 patients by Mohanty et al. which reported more severe episodes of bleeding along with higher rebleed rates at day 5, longer hospital stay and higher mortality at 42 days among 100 patients with AVB who received FFP.¹² Even for patients undergoing prophylactic EVL of varices, higher rates of post EVL bleed to be associated with advanced liver disease and not baseline INR or platelets in a study by Blasi et al.³³ Thus baseline deranged platelets or INR do not lead to higher post EVL bleeding rates in a prophylactic or emergent setting and attempting to correct it with transfusions may lead to more harm than good.”</p>
6) The discussion can be considerably shortened as it reiterates results.	<p>We thank the reviewer for the comments.</p> <p>We have reviewed the entire discussion</p>

	<p>segment and cut down on repetitive/redundant statements as advised.</p> <p>The changes at various parts of the discussion have been highlighted as follows</p> <ol style="list-style-type: none"> 1. Page 12: Lines 341-346, 351-352, 355-356 2. Page 13: Lines 365-368, 370-371, 376-378, 382-385. 3. Page 14: Lines 389-390, 400-401, 414 4. Page 15: Line 417 5. Minor grammatical errors corrected as suggested by the reviewer <p>The current word count of the discussion is 1357 words as compared to 1657 words in the initial manuscript</p>
<p>7) Why aren't details on the multivariable analyses shown?</p>	<p>We thank the reviewer for the comments.</p> <p>We have now provided propensity score matched data with univariate and multivariate hazard ratios.</p>
<p>Reviewer 2</p>	
<p>1. Key words. Do the key words reflect the focus of the manuscript? It is recommended to use MeSH headings as the keywords. Please correct, if possible.</p>	<p>We thank the reviewer for the comments. We have used the MeSH browser provided by the national library of medicine to use appropriate keywords. The following keywords have been added on Page 3, lines 95 and 96-</p> <p>“Gastrointestinal hemorrhage” and “mortality”</p>
<p>2. Background. Does the manuscript adequately describe the background, present status and significance of the study?</p> <p>The background of the manuscript has tried to provide the background and information relevant to the study but it needs more clarification and rephrasing of the sentence.</p>	<p>We thank the reviewer for the comments.</p> <p>The Background/Introduction section has been revised on Page 5, lines 128-136 and 139-142, to provide more clarity and information as relevant to our study</p>
<p>3. Discussion. Does the manuscript interpret the findings adequately and appropriately,</p>	<p>We thank the reviewer for the comments. The discussion portion has been reviewed and the</p>

<p>highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? The discussion part looks relevant but there are various spelling and grammatical errors.</p>	<p>following changes have been made to improve readability</p> <ol style="list-style-type: none"> 1. Removal of redundant or repetitive statements 2. Correction of inadvertent spelling and grammatical errors
<p>4. Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? The tables so far are clear but if possible the significance of the findings should be mentioned where necessary</p>	<p>We thank the reviewer for the comments.</p> <p>We have mentioned the significance of the findings in the text along with the reference to the appropriate figure.</p>
<p>5. References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? The references of the manuscript has to follow the referencing style guidelines of the journal.</p>	<p>We thank the reviewer for the comments.</p> <p>We have edited the references to meet the referencing style guidelines of the journal in terms of</p> <ol style="list-style-type: none"> 1. All author names have been mentioned 2. PMID and doi have been added wherever available
<p>6. Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Some part of the discussion has grammatical errors and should be addressed.</p>	<p>We thank the reviewer for the comments. As mentioned in response to comment 3, we have made every effort to remove any inadvertent spelling and grammatical errors in the discussion segment.</p>
<p>7. Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4)</p>	<p>We thank the reviewer for the comments.</p> <p>We have provided a STROBE checklist with the relevant data as supplementary material</p>

<p>STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study.</p>	
<p>Reviewer 3</p>	
<p>1. In this report, the baseline characteristics of patients were collected. It is better if the authors can analyze the relationship between variables such as platelet count level and prothrombin time with rebleeding and mortality on days 5 and 42 in this population.</p>	<p>We thank the reviewer for the comments.</p> <p>We have now provided overall cohort data and propensity score matched for rebleed and mortality at 42-days. The univariate and multivariate hazard ratio are shown in tables. The hazard ratio for the 5-day rebleeding for platelet count was 0.998 (0.993-1.002), P=0.275 and INR was 1.376 (1.041-1818), P=0.025.</p> <p>We have added the following statement in the text.</p> <p>Platelet counts were not significantly associated with 5-day rebleeding, HR, 0.998 (0.993-1.002), P=0.275 whereas, INR was significantly associated with HR, 1.376 (1.041-1818), P=0.025.</p>
<p>2. The variable expression should be determined by normality test. If the continuous data were normally distributed, a mean±SD should be considered.</p>	<p>We thank the reviewer for the comments.</p> <p>We have checked the normality of the data with the Shapiro-Wilk test. All variables at baseline were not normally distributed, hence represented as median (IQR). After propensity score matching (PSM) only 2 variables were normally distributed. In order to maintain uniformity of data representation, we have provided all data as median (IQR)</p> <p>The following statement has been added in the statistical analysis section:</p> <p>The normality of the data was assessed using the Shapiro-Wilk test.</p>
<p>3. Since the sample number between platelets transfusion group and the control</p>	<p>We thank the reviewer for the comments.</p>

<p>group, a propensity score matching (PSM) model was suggested for balancing confounders between the two groups.</p>	<p>As suggested, we have provided a PSM analysis. We have matched for variables which were significantly different at baseline between the groups those who received platelets and those who did not. The variables matched were age, pulse rate, creatinine, sodium, ascites, hepatic encephalopathy, and transfusion of fresh frozen plasma. The PSM analysis has 89 patients in each group as demonstrated in table 3</p>
<p>4. The authors used odds ratio (OR) in table 4 and table 5. While in this prospective study, including mortality data, risk ratio (RR) and/or hazard ratio (HR) might be more properly.</p>	<p>We thank the reviewer for the comments. We have now provided the data of univariate and multivariate hazard ratio for mortality and rebleeding in the new tables 4,5.</p>
<p>5. In table 4 and table 5, the author summarized the parameters associated with 42-day rebleeding and 42-day mortality, respectively. The details of multivariate analysis should be presented in these two parts.</p>	<p>We thank the reviewer for the comments. We have now provided the details of multivariate analysis for 42-days rebleeding and mortality in the new tables 4,5.</p>

<p>Comments by Editor-in-Chief</p>	
<p>1. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”.</p>	<p>We thank the editor-in-chief for the comments. The figure legends have been modified as per the suggestions provided.</p>
<p>2. The author(s) must include the keyword “chronic liver disease” in the manuscript title.</p>	<p>We thank the editor-in-chief for the comments. We have effected the change in the title which now reads “Effect of Thrombocytopenia and Platelet transfusion on Outcomes of Acute Variceal Bleeding in Patients with Chronic Liver Disease: A real world experience”</p>
<p>3. Please provide the original figure documents.</p>	<p>We thank the editor-in-chief for the comments.</p>

	The original figure documents have been provided.
4. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.	We thank the editor-in-chief for the comments. The figures have been provided in PowerPoint format, in numerical order, as requested
5. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights.	We thank the editor-in-chief for the comments. All data provided in the manuscript is original and does not need any additional copyright.
6. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.	We thank the editor-in-chief for the comments. All figures are original.
7. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.	We thank the editor-in-chief for the comments. All the tables have been made in the format advised.