ROUND 1

Dear Editors and Reviewers:

We would like to thank *World Journal of Gastroenterology* for giving us the opportunity to revise our manuscript entitled "*Machine-learning to predict portal vein thrombosis in patients with portal hypertension following splenectomy: A comparative analysis of three PPER-based practical models*" (Manuscript NO: 77119, Retrospective Study). We want to thank the Reviewers for constructive and insightful criticism and advice. We have carefully studied the comments and corrected them in the hope of approval. The modified part is marked in red on the paper (a marked version of the revised manuscript is provided in the supplementary material). We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the corrections will meet with approval. Below is our point-by-point response to the reviewer's comments. Thanks for all the help.

Sincerely,

Er-Lei Zhang

Responses to the Editorial Corrections:

To science editor:

Q1. The reviewers have raised a few major concerns that should be addressed: 1) The introduction section should be modified with advantages and justification of the proposed methods, comparison with other conventional methods, any statement should be correctly referenced.

Authors response: Thanks for your reminding. According to the suggestions of the reviewers, I have made appropriate modifications in the introduction section of the manuscript, clarified the advantages and rationality of machine learning compared with traditional methods, and the references involved are also listed later in accordance with journal requirements.

Q2. The reviewers have raised a few major concerns that should be addressed: 2) Authors

should clarify the effect of prophylactic anti-coagulation on their cohort and how it affected the results.

Authors response: Thanks for your suggestion. As mentioned by Reviewer #1, The authors wrote “Most scholars have recently advocated that the earlier the prophylactic anti-coagulant therapy is administered postoperatively, which will be more helpful in reducing the incidence of PVT” >> how they find that factor affecting the outcome in this cohort? And if it is affecting the model results? As a I see no mention in the table or the methodology regarding this therapeutic variable factor (prophylactic anti-coagulation)?

In fact, we mentioned “prophylactic anti-coagulant therapy” in the discussion part of the manuscript. The main purposes are as follows:

(1). The incidence of portal vein thrombosis (PVT) in patients with liver cirrhosis complicated with portal hypertension (PH) after splenectomy is 4.8%-51.5%[1-3], and it is highly likely to progress to acute liver failure endangering the patient’s life[4]. In the clinical settings, how to decrease the detrimental effect of PVT on cirrhotic patients with PH after splenectomy is a great challenge for surgeons.

(2). Unfortunately, so far, there is no standard prevention method for PVT after splenectomy in patients with liver cirrhosis complicated with PH[5]. In recent years, some studies have shown that early preventive anti-coagulant therapy can effectively reduce the incidence of PVT after splenectomy in patients with liver cirrhosis complicated with PH[6-8]. Ding *et al* conducted a network meta-analysis study with strong evidence that early administration of low-molecular-weight heparin combined with low-molecular-weight dextran appeared to be the most satisfactory treatment for preventing the development of PVT after splenectomy for cirrhotic patients with PH[9].

(3). Although postoperative prophylactic anti-coagulant therapy is a potentially effective method to reduce the incidence of PVT after splenectomy in patients with liver cirrhosis complicated with PH. However, as we mentioned in the discussion section of the manuscript, it still has several defects that can’t be ignored. First, even if a safe intervention regimen is selected, early postoperative anti-coagulation treatment can not completely avoid the risk of fatal bleeding, especially for patients with severe liver cirrhosis[9]. Second, the target individuals for selection of postoperative prophylactic anti-coagulation remains unclear. In the

context of the era of precision medicine, selecting targeted individuals and administering prophylactic anti-coagulation would both avoid excessive wastage of medical resources and reduce the occurrence of adverse events caused by postoperative prophylactic anti-coagulation.

(4). The clinical value of the present study is that the postoperative platelet elevation rate (PPER)-based model we constructed has an accuracy of up to 80% in predicting PVT after splenectomy, which could help clinicians to distinguish individuals at high risk of PVT early and efficiently after splenectomy and thereby choose individualized prophylactic anti-coagulation measures for patients.

It must be acknowledged that the above concern raised by Reviewer #1 is valuable and worthy of careful consideration. As mentioned above, recent studies have shown that anti-coagulant therapy can reduce the incidence of PVT after splenectomy. Therefore, in order to eliminate the possible impact of anti-coagulant therapy on the actual incidence of PVT after splenectomy, we exclude those with a previous history of anti-coagulant therapy and/or those received prophylactic anti-coagulant therapy after splenectomy (as shown in **Figure 1A** in the manuscript). The risk of postoperative PVT maybe underestimated if patients receiving anti-coagulant therapy, which will directly affect the accuracy of the PPER-based model in identifying individuals at high risk of PVT after splenectomy.

We think that the above concern proposed by Reviewer #1 is understandable. Prophylactic anti-coagulant therapy indeed did have an impact on the incidence of PVT after splenectomy in PH patients in this study cohort, and further underestimated the value of the prediction model for the risk of PVT after splenectomy. And we excluded patients who received prophylactic anti-coagulant therapy after splenectomy when designed this study. Therefore, the therapeutic variable factor (prophylactic anti-coagulation) will not be included in the table or the methodology in our study.

To company editor-in-chief:

Q1. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in

which all components are movable and editable), organize them into a single PowerPoint file.

Authors response: Thanks for your kind suggestion. I have adjusted all figures and figure legends to a unified format that meets the journal's publication requirements. In addition, I also provide decomposable figures (where all components are movable and editable) and organize them into a single PowerPoint file.

Q2. Please 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.

Authors response: Thanks for your suggestion. I have revised and adjusted all tables according to your suggestions and requirements.

Q3. 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.

Authors response: Thanks for your suggestion. The pictures provided in this study are original, so I have signed the pictures in the PowerPoint (PPT) according to your requirements.

Q4. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Authors response: Thanks for your suggestion. I have provided an English language certificate issued by a professional English language editing company as required.

Q5. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Authors response: Thanks for your suggestion. I have revised the title of the manuscript as "*Machine-learning predicts portal vein thrombosis after splenectomy in patients with portal*

hypertension: A comparative analysis of PPER-based models" upon the requirement of the journal (Title: The title should be no more than 18 words).

Responses to the Reviewer comments:

To the reviewer #1 comments:

Q1: Aim of the study the authors used the term "excavate", I think it is not appropriate here. Please modify to examine or assess or other more popular scientific term.

Authors response: Thanks for your suggestion. We agree with your opinion that the term "excavate" is really not commonly used, so I have replaced it with "evaluate" in the manuscript as you suggested.

Q2: Why the authors chose to use a machine learning programming to assess this issue instead of multivariate analysis, and are there any previous studies using the statistical methods per se to assess this issue in question?

Authors response: Thanks for your question. In the present study, we employed two methods (novel machine learning algorithms and conventional multivariate logistic regression analysis) to construct the PPER-based prediction model of PVT after splenectomy in cirrhotic patients with PH. The novel machine learning algorithms included the least absolute shrinkage and selection operator (LASSO) and the random forest (RF). We adopted novel machine learning algorithms to build predictive models due to the following considerations:

(1). In recent years, with the rapid development of artificial intelligence knowledge, novel machine learning algorithms based on clinical features have shown great potential in various aspects of medical research, especially in the construction of predictive models, and the features screened for model construction are clinically interpretable[10]. Gao *et al* [11] constructed four machine learning models based on COVID-19 patients' clinical data to distinguish individuals with the high-risk of mortality, with the areas under the curve (AUC) of 0.9760. Kawakami *et al* [12] developed several machine learning models based on clinical features, among which the RF model showed the best performance in distinguishing epithelial ovarian cancer from benign ovarian tumors with an AUC of 0.968.

(2). Currently, the wide range of applications of various machine learning methods has

surpassed conventional statistical analysis due to their higher accuracy, which might become increasingly applicable in the field of medical research[13, 14]. Churpek *et al* [15] conducted a multicenter study and concluded that several machine learning methods can predict clinical outcome variables more accurately than conventional logistic regression.

(3). Although compared with traditional multivariate analysis methods, machine learning algorithm has an overwhelming advantage in constructing clinical prediction model. However, to the best of our knowledge, so far, only Wang *et al* [16] tried to construct a prediction model of PVT after splenectomy in cirrhotic patients with PH using machine learning algorithms.

Given the above reasons, we finally applied this novel approach in the comparison with conventional methods in this retrospective study. Our results also illustrated that the novel machine learning method was slightly superior to conventional methods in the accuracy of predicting PVT after splenectomy.

Q3. In the exclusion criteria the authors stated that they excluded “platelet count on the first and third day after the operation (PLT1, PLT3) were not elevated compared to the preoperative values”, could they elaborate why they didn’t add to the model this group? Either as a control group or as a prediction to the reverse of not having a postoperative effect on the platelet count?

Authors response: Thanks for your valuable question. Actually, we conducted this retrospective study for the following reasons:

(1). To investigate the predictive value of the amplitude of postoperative elevated platelet count for the development of PVT after splenectomy.

(2). Based on the PPER and other clinical features, novel machine learning was applied to construct the prediction models for PVT after splenectomy.

The main purpose of this study was to evaluate the effect of the ratio of elevated postoperative platelet counts on PVT after splenectomy. Thus, we excluded patients with no elevated platelet count on day 1 and 3 after operation when we designed this study.

Actually, your question is of great value and guidance. That’s what we’re going to do next. We are preparing a prospective study to stratify the risk of developing PVT after splenectomy in cirrhotic patients with PH into low- and high-risk statuses using the PPER-based model

constructed in this study. We will enroll patients whose platelet count didn't increase on the first or third day after splenectomy as the control group, and then compare the incidence of PVT with low-risk PVT group and high-risk PVT group, which is the further verification and promotion of the prediction models constructed in this retrospective study.

Q4. The authors stated "We diagnosed PVT by color Doppler ultrasound examination and enhanced CT would be applied as an auxiliary examination when its diagnosis was questioned" does they mean CT angiography on the abdomen with contrast? Or triphasic CT or contrasted CT? please clarify.

Authors response: Thanks for your question, we discussed this issue with the professional radiologist in our hospital. Finally, we replace the "enhanced CT" in the manuscript with "contrast-enhanced CT"[17]. This expression may be more accurate.

Q5. The thrombophilia as a cause of thrombosis, are there any attributed clinical problem causing it, rather than the splenectomy, for example reactionary. This is consistent with the results of the study, where the authors stated "In most cases, platelet, erythrocyte, and leukocyte counts rose dramatically over a short time after splenectomy in patients with PH, and the blood was hypercoagulable [8]. Therefore, previous studies suggested that preoperative low platelet and leukocyte count were founders for the formation of PVT postoperatively [38]. This study revealed that the preoperative lymphocyte count was an influential factor in PVT postoperatively, which coincided with the above view.">>>This will lead to bias caused by confounding factors, could the authors clarify how they dealt with that issue? Or they stated them as a direct and independent cause for the PVT?

Authors response: Thanks for your question. The pathogenesis of thrombus is extremely complex and its occurrence is usually the result of multi-factors working together. Studies indicated that thrombus occurrence mainly depends on the interrelationship between three physiological factors of Virchow's triad: hypercoagulable state of blood, stasis of blood flow and intravascular vessel wall injury[18, 19]. However, due to the unique anatomical structure of portal vein system, the mechanism of PVT formation has not been fully clarified so far[17].

PVT is a relatively rare disease in the general population[20]. However, patients with liver cirrhosis, especially those complicated with PH, have a rising risk of developing PVT to

3.7%-24.4% due to the increase of portal vein pressure, slow portal vein blood flow, blood stasis and hypercoagulability[21-25]. In a recent review, Senzolo *et al* [26] emphasized that in addition to the classic Virchow's triad is the key factor of PVT in patients with liver cirrhosis, other factors also play an important role. Among other risk factors for PVT in cirrhosis, splenectomy and portosystemic-shunt surgery have been reported as being determinants of PVT due to venous injury and/or by altering portal venous flow[27]. Endoscopic therapy for esophageal varices (with sclerotherapy or variceal band ligation), endothelial injury or endotoxemia after endoscopic sclerotherapy have been shown to play an important role in PVT development[28, 29]. In addition, it has been suggested that cryptogenic and NASH cirrhosis are associated with a higher risk of PVT compared to other etiologies of cirrhosis[30-32]. In this study, our aim was to explore the independent risk factors of PVT after splenectomy in cirrhotic patients with PH, and to construct practical models for predicting PVT based on these factors. Considering the influencing factors of PVT formation in patients with liver cirrhosis mentioned above, in order to avoid the possible impact of confounding factors on the final results of this study, in fact, we carefully considered these problems when designing this regression study, and we mainly took the following measures:

(1). In the above we mentioned that there may be differences in the risk of developing PVT in cirrhosis caused by different etiologies. Therefore, only HBV-related cirrhosis was included in this study, while cirrhosis due to other etiologies was excluded.

(2). A history of previous endoscopic or surgical treatment as mentioned above would influence the incidence of PVT in cirrhotic patients, and therefore we excluded patients with previous endoscopic treatment, splenic embolism, or surgical intervention from the exclusion criteria.

(3). Of course, to allow uniformity of patients at baseline, all 483 of our enrolled participants were cirrhotic patients with PH, and we excluded patients who underwent splenectomy because of neoplastic or hematological factors.

(4). In the exclusion criteria, we excluded patients with a history of previous anti-coagulant treatment for thrombotic disease or those received prophylactic anti-coagulant treatment postoperatively, as this was also a confounding factor affecting our study.

Q6. The authors wrote “Most scholars have recently advocated that the earlier the prophylactic anti-coagulant therapy is administered postoperatively, which will be more helpful in reducing the incidence of PVT” >> how they find that factor affecting the outcome in this cohort? And if it is affecting the model results? As a I see no mention in the table or the methodology regarding this therapeutic variable factor (prophylactic anti-coagulation)?

Authors response: Thanks for your question. Recent studies have shown that anti-coagulant therapy can reduce the incidence of PVT after splenectomy[6-8]. Therefore, in order to eliminate the possible impact of anti-coagulant therapy on the actual incidence of PVT after splenectomy, we exclude those with a previous history of anti-coagulant therapy and/or those received prophylactic anti-coagulant therapy after splenectomy (as shown in **Figure 1A** in the manuscript). The risk of postoperative PVT maybe underestimated if patients receiving anti-coagulant therapy, which will directly affect the accuracy of the PPER-based model in identifying individuals at high risk of PVT after splenectomy.

We think that your concern is understandable. Prophylactic anti-coagulant therapy indeed did have an impact on the incidence of PVT after splenectomy in PH patients in this study cohort, and further underestimated the value of the prediction model for the risk of PVT after splenectomy. And we excluded patients who received prophylactic anti-coagulant therapy after splenectomy when designed this study. Therefore, the therapeutic variable factor (prophylactic anti-coagulation) will not be included in the table or the methodology in our study.

Q7. The authors stated in the limitation of their study “Second, the uncommon preoperative factors that may influence the formation of PVT, such as splenic vein diameter, spleen volume, and portal vein flow velocity [8, 19], were not routinely measured in our institution and thus failed to be included in the present study. “>> But some of these parameters for example splenic vein diameter could be assessed through the CT scan angiography films or abdominal ultrasound, so why they were not assessed?

Authors response: Thanks for your question. Due to the nature of retrospective research, this study does have some unavoidable defects. In fact, 483 eligible participants in this study underwent routine preoperative examinations of abdominal ultrasound and contrast-enhanced CT within 7 days before operation, but the imaging report in our institution didn’t routinely

describe the characteristic information of splenic vein diameter, spleen volume, and portal vein flow velocity, unless there were special requirements. Therefore, we were unable to obtain this information from the electronic medical record system in our institution.

Thank you again for your question. Your concern has important guidance for our prospective research to be carried out in the later stage. We will communicate with our specialized imaging physicians to ensure that each enrolled patient has characteristic information on splenic vein diameter, spleen volume, and portal vein flow rate in their diagnostic electronic imaging reports.

To the reviewer #2 comments:

1. In the Introduction section, the drawbacks of each conventional technique should be described clearly.

Authors response: Thanks for your suggestion. According to your suggestion, I have made appropriate modifications in the introduction section of the manuscript, clarified the drawbacks of traditional methods compared with machine learning.

2. You should emphasize the difference between other methods to clarify the position of this work further.

Authors response: Thanks for your kind suggestion. We have emphasized the uniqueness of our prediction model for PVT after splenectomy in comparison with other methods in the introduction section of the manuscript, which has now been reasonably modified according to your recommendations. Please find it in our revised marked manuscript.

Q3. The Wide ranges of applications need to be addressed in the Introduction.

Authors response: Thanks for your valuable suggestion. Your proposal is extremely meaningful and we believe that it is beneficial to make this manuscript more acceptable. Therefore, we have made appropriate amendments in the introduction section of the manuscript according to your recommendation. Please find it in our revised manuscript.

Q4. Add the advantages of the proposed system in one quoted line for justifying the proposed

approach in the Introduction section.

Authors response: Thanks for your suggestion. We have made appropriate modifications in the introduction section of the manuscript according to your suggestion, which will make our work more perfect.

Q5. In the introduction, the findings of the present research work should be compared with the recent work of the same field towards claiming the contribution made. kindly provide several references to substantiate the claim made in the abstract (that is, provide references to other groups who do or have done research in this area).

Authors response: Thanks for your suggestion. In the introduction section of the manuscript, I have made appropriate modifications according to your proposal, and compared the results of our work with recent publised work in the same field, so as to show the contribution of this research. In addition, we also provide several references to confirm the claims made in the abstract.

Q6. Authors can refer to some latest related works from reputed journals like IEEE/ACM Transactions, Elsevier, Inderscience, Springer, Taylor & Francis, etc.

Authors response: Thanks for your suggestion. I have added the latest related works published in the reputed journals in our revised manuscript as new references according to your recommendation.

REFERENCES

1 Ikeda M, Sekimoto M, Takiguchi S, Kubota M, Ikenaga M, Yamamoto H, Fujiwara Y, Ohue M, Yasuda T, Imamura H, Tatsuta M, Yano M, Furukawa H, Monden M. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: a prospective study with contrast-enhanced CT scan. *Ann Surg* 2005; **241**(2): 208-216 [PMID: 15650628 PMCID: PMC1356904 DOI: 10.1097/01.sla.0000151794.28392.a6]

2 Krauth MT, Lechner K, Neugebauer EA, Pabinger I. The postoperative splenic/portal vein thrombosis after splenectomy and its prevention--an unresolved issue. *Haematologica* 2008; **93**(8): 1227-1232 [PMID: 18556406 DOI: 10.3324/haematol.12682]

3 Qi X, Bai M, Guo X, Fan D. Pharmacologic prophylaxis of portal venous system thrombosis after splenectomy: a meta-analysis. *Gastroenterol Res Pract* 2014; **2014**: 292689 [PMID: 25243008 PMCID:

PMC4163290 DOI: 10.1155/2014/292689]

4 Zhang Y, Xu BY, Wang XB, Zheng X, Huang Y, Chen J, Meng ZJ, Gao YH, Qian ZP, Liu F, Lu XB, Shi Y, Shang J, Li H, Wang SY, Yin S, Sun SN, Hou YX, Xiong Y, Chen J, Li BL, Lei Q, Gao N, Ji LJ, Li J, Jie FR, Zhao RH, Liu JP, Lin TF, Chen LY, Tan WT, Zhang Q, Zou CC, Huang ZB, Jiang XH, Luo S, Liu CY, Zhang YY, Li T, Ren HT, Wang SJ, Deng GH, Xiong SE, Liu XX, Wang C, Yuan W, Gu WY, Qiao L, Wang TY, Wu DD, Dong FC, Li H, Hua J. Prevalence and Clinical Significance of Portal Vein Thrombosis in Patients With Cirrhosis and Acute Decompensation. *Clin Gastroenterol Hepatol* 2020; **18**(11): 2564-2572 e2561 [PMID: 32109631 DOI: 10.1016/j.cgh.2020.02.037]

5 Kawanaka H, Akahoshi T, Kinjo N, Konishi K, Yoshida D, Anegawa G, Yamaguchi S, Uehara H, Hashimoto N, Tsutsumi N, Tomikawa M, Maehara Y. Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism. *Ann Surg* 2010; **251**(1): 76-83 [PMID: 19864937 DOI: 10.1097/SLA.0b013e3181bdf8ad]

6 Yao W, Feng Y, Liu T, Li W, Zhang M, Yao Y, Wu S. Rivaroxaban versus low-molecular weight heparin plus warfarin prevents portal vein system thrombosis after splenectomy and pericardial devascularization: A randomized clinical trial. *EXCLI J* 2021; **20**: 537-549 [PMID: 33883982 PMCID: PMC8056059 DOI: 10.17179/excli2020-3120]

7 Zhang N, Yao Y, Xue W, Wu S. Early prophylactic anti-coagulation for portal vein system thrombosis after splenectomy: A systematic review and meta-analysis. *Biomed Rep* 2016; **5**(4): 483-490 [PMID: 27699018 PMCID: PMC5038582 DOI: 10.3892/br.2016.755]

8 Yang S, He C, Fan X, Ding W, Wu X, Li J. Early prophylactic anti-coagulation via transjugular intrahepatic route for portal vein thrombosis after splenectomy in cirrhotic portal hypertension. *J Vasc Interv Radiol* 2015; **26**(7): 1009-1017 [PMID: 25921970 DOI: 10.1016/j.jvir.2015.03.008]

9 Ding H, Zhang Y, Zhao L, Wu S, Liu J, Wang C, Pei T, Su Y. What intervention regimen is most effective prevention for Portal venous system thrombosis after splenectomy in cirrhotics patients with Portal hypertension? Systematic review and network meta-analysis. *Pharmacol Res* 2020; **157**: 104825 [PMID: 32330553 DOI: 10.1016/j.phrs.2020.104825]

10 Dong Z, Lin Y, Lin F, Luo X, Lin Z, Zhang Y, Li L, Li ZP, Feng ST, Cai H, Peng Z. Prediction of Early Treatment Response to Initial Conventional Transarterial Chemoembolization Therapy for Hepatocellular Carcinoma by Machine-Learning Model Based on Computed Tomography. *J Hepatocell Carcinoma* 2021; **8**: 1473-1484 [PMID: 34877267 PMCID: PMC8643205 DOI: 10.2147/JHC.S334674]

11 Gao Y, Cai GY, Fang W, Li HY, Wang SY, Chen L, Yu Y, Liu D, Xu S, Cui PF, Zeng SQ, Feng XX, Yu RD, Wang Y, Yuan Y, Jiao XF, Chi JH, Liu JH, Li RY, Zheng X, Song CY, Jin N, Gong WJ, Liu XY, Huang L, Tian X, Li L, Xing H, Ma D, Li CR, Ye F, Gao QL. Machine learning based early warning system enables accurate mortality risk prediction for COVID-19. *Nat Commun* 2020; **11**(1): 5033 [PMID: 33024092 PMCID: PMC7538910 DOI: 10.1038/s41467-020-18684-2]

12 Kawakami E, Tabata J, Yanaihara N, Ishikawa T, Koseki K, Iida Y, Saito M, Komazaki H, Shapiro JS, Goto C, Akiyama Y, Saito R, Saito M, Takano H, Yamada K, Okamoto A. Application of Artificial Intelligence for Preoperative Diagnostic and Prognostic Prediction in Epithelial Ovarian Cancer Based on Blood Biomarkers. *Clin Cancer Res* 2019; **25**(10): 3006-3015 [PMID: 30979733 DOI: 10.1158/1078-0432.CCR-18-3378]

13 Ganggayah MD, Taib NA, Har YC, Lio P, Dhillon SK. Predicting factors for survival of breast cancer patients using machine learning techniques. *BMC Med Inform Decis Mak* 2019; **19**(1): 48 [PMID: 30902088 PMCID: PMC6431077 DOI: 10.1186/s12911-019-0801-4]

14 Heo J, Yoon JG, Park H, Kim YD, Nam HS, Heo JH. Machine Learning-Based Model for Prediction

of Outcomes in Acute Stroke. *Stroke* 2019; **50**(5): 1263-1265 [PMID: 30890116 DOI: 10.1161/STROKEAHA.118.024293]

15 Churpek MM, Yuen TC, Winslow C, Meltzer DO, Kattan MW, Edelson DP. Multicenter Comparison of Machine Learning Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards. *Crit Care Med* 2016; **44**(2): 368-374 [PMID: 26771782 PMCID: PMC4736499 DOI: 10.1097/CCM.0000000000001571]

16 Wang M, Ding L, Xu M, Xie J, Wu S, Xu S, Yao Y, Liu Q. A novel method detecting the key clinic factors of portal vein system thrombosis of splenectomy & cardia devascularization patients for cirrhosis & portal hypertension. *BMC Bioinformatics* 2019; **20**(Suppl 22): 720 [PMID: 31888439 PMCID: PMC6936084 DOI: 10.1186/s12859-019-3233-3]

17 Anton A, Camprecios G, Perez-Campuzano V, Orts L, Garcia-Pagan JC, Hernandez-Gea V. The Pathophysiology of Portal Vein Thrombosis in Cirrhosis: Getting Deeper into Virchow's Triad. *J Clin Med* 2022; **11**(3) [PMID: 35160251 PMCID: PMC8837039 DOI: 10.3390/jcm11030800]

18 Kumar DR, Hanlin E, Glurich I, Mazza JJ, Yale SH. Virchow's contribution to the understanding of thrombosis and cellular biology. *Clin Med Res* 2010; **8**(3-4): 168-172 [PMID: 20739582 PMCID: PMC3006583 DOI: 10.3121/cmr.2009.866]

19 Wolberg AS, Aleman MM, Leiderman K, Machlus KR. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg* 2012; **114**(2): 275-285 [PMID: 22104070 PMCID: PMC3264782 DOI: 10.1213/ANE.0b013e31823a088c]

20 Rajani R, Bjornsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, Melin T, Sangfelt P, Wallerstedt S, Almer S. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. *Aliment Pharmacol Ther* 2010; **32**(9): 1154-1162 [PMID: 21039677 DOI: 10.1111/j.1365-2036.2010.04454.x]

21 Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, Riccardi L, Lancellotti S, Santoliquido A, Flore R, Pompili M, Rapaccini GL, Tondi P, Gasbarrini GB, Landolfi R, Gasbarrini A. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol* 2009; **51**(4): 682-689 [PMID: 19464747 DOI: 10.1016/j.jhep.2009.03.013]

22 Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: risk factors and correlation with the Model for End-stage Liver Disease scoring system. *Eur J Gastroenterol Hepatol* 2015; **27**(5): 585-592 [PMID: 25769098 DOI: 10.1097/MEG.0000000000000325]

23 Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC, Groupe d'Etude et de Traitement du Carcinome H. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology* 2015; **61**(2): 660-667 [PMID: 25284616 DOI: 10.1002/hep.27546]

24 Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turola E, Fornaciari G, Schianchi S, Ferrari A, Valla D. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012; **143**(5): 1253-1260 e1254 [PMID: 22819864 DOI: 10.1053/j.gastro.2012.07.018]

25 Noronha Ferreira C, Marinho RT, Cortez-Pinto H, Ferreira P, Dias MS, Vasconcelos M, Alexandrino P, Serejo F, Pedro AJ, Goncalves A, Palma S, Leite I, Reis D, Damiao F, Valente A, Xavier Brito L, Baldaia C, Fatela N, Ramalho F, Velosa J. Incidence, predictive factors and clinical significance of development of portal vein thrombosis in cirrhosis: A prospective study. *Liver Int* 2019; **39**(8): 1459-1467

[PMID: 31021512 DOI: 10.1111/liv.14121]
26 Senzolo M, Garcia-Tsao G, Garcia-Pagan JC. Current knowledge and management of portal vein thrombosis in cirrhosis. *J Hepatol* 2021; **75**(2): 442-453 [PMID: 33930474 DOI: 10.1016/j.jhep.2021.04.029]
27 Gong C, Qin X, Yang J, Guo T. The Best anti-coagulation Strategy for Cirrhotic Patients who Underwent Splenectomy: A Network Meta-Analysis. *Gastroenterol Res Pract* 2017; **2017**: 9216172 [PMID: 28676822 PMCID: PMC5476877 DOI: 10.1155/2017/9216172]
28 Rodriguez-Castro KI, Porte RJ, Nadal E, Germani G, Burra P, Senzolo M. Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. *Transplantation* 2012; **94**(11): 1145-1153 [PMID: 23128996 DOI: 10.1097/TP.0b013e31826e8e53]
29 Amitrano L, Brancaccio V, Guardascione MA, Margaglione M, Iannaccone L, D'Andrea G, Marmo R, Ames PR, Balzano A. Inherited coagulation disorders in cirrhotic patients with portal vein thrombosis. *Hepatology* 2000; **31**(2): 345-348 [PMID: 10655256 DOI: 10.1002/hep.510310213]
30 Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo P, Tector AJ. Portal Vein Thrombosis Is a Risk Factor for Poor Early Outcomes After Liver Transplantation: Analysis of Risk Factors and Outcomes for Portal Vein Thrombosis in Waitlisted Patients. *Transplantation* 2016; **100**(1): 126-133 [PMID: 26050013 DOI: 10.1097/TP.0000000000000785]
31 Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. *Liver Transpl* 2015; **21**(8): 1016-1021 [PMID: 25845711 PMCID: PMC6615024 DOI: 10.1002/lt.24134]
32 Tripodi A, Fracanzani AL, Chantarangkul V, Primignani M, Fargion S. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. *J Hepatol* 2017; **66**(1): 248-250 [PMID: 27769731 DOI: 10.1016/j.jhep.2016.09.025]

ROUND 2

Dear Editors and Reviewer:

Thank you for your letter and the reviewer's valuable comments concerning our manuscript entitled "*Machine-learning predicts portal vein thrombosis after splenectomy in patients with portal hypertension: A comparative analysis of PPER-based models*" (Manuscript NO: 77119, Manuscript Type: ORIGINAL ARTICLE). These comments have important guiding significance for our research. We have carefully studied the comments and corrected them in the hope of approval. The modified part is marked in red on the paper (77119_ revised manuscript marked version). We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewer's warm work earnestly, and hope that the correction will meet with approval. Below is our point-by-point response to the reviewer's comments.

Sincerely,

Er-Lei Zhang

Responses to the Editors' comments

Q1: There are some specific comments to be modified in the second-round review. Please revise the manuscript according to its comments and make a point-to-point response to the review comments. Note that it is not my opinion, but the reviewer's opinion. Please see the attachment for the reviewer's opinion (77119_RevisionReviewReport).

Authors response: Thanks for your suggestion. I have carefully studied the constructive comments put forward by the reviewer and made appropriate modifications in the manuscript

according to these opinions, which will make the manuscript more perfect. I also made a point-to-point response to the comments made by the reviewer (77119_Reply).

Q2: Corresponding authors are requested to sign the attached Conflict-of-interest-statement.

Authors response: Thanks for your reminding. The corresponding author (Er-Lei Zhang) has signed the Conflict-of-interest-statement (77119_ Conflict-of-interest-statement).

Q3: Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. please don't include any *, #, †, §, ‡, ¥, @….in your Figures; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01.

Authors response: Thanks for your valuable comments, I have modified the Figures according to your suggestions (77119_Figures).

Q4: For S1 in Supplementary material, please provide the table in Word, not Excel.

Authors response: Thanks for your suggestions, I have adapted the table (S1 in the supplemental material) to word format (77119_S1).

Q5: Abbreviations other than COVID-19 and SARS-CoV-2 are not allowed in the title of the article., and no more than 18 words are allowed. The title cannot start with "the, a, an".

Authors response: Thanks for your suggestion, I have revised the title as "*Machine-learning predicts portal vein thrombosis after splenectomy in patients with portal hypertension: Comparative analysis of three practical models*" with your comments.

Responses to the Reviewer's comments:

Q1: The authors mentioned in their answer to reviewers that ". And we excluded patients who received prophylactic anti-coagulant therapy after splenectomy when designed this study. Therefore, the therapeutic variable factor (prophylactic anti-coagulation) will not be included in the table or the methodology in our study." >> I recommend that this exclusion criterion be mentioned clearly in the methodology to avoid reader's confusion.

Authors response: Thanks for your precious suggestions. According to your opinions, I have changed the "postoperative prophylactic anticoagulation" to "received prophylactic anti-coagulant therapy after splenectomy" in the materials and methods section of the manuscript (article 8 exclusion criteria). I strongly agree that such a description is more understandable to readers.

Q2: To the authors: please add your explanation in Q2 to reviewer #1, of why choosing a machine learning program instead of the most common statistical method for analysis, in introduction or methodology to explain the benefit of the new technique.

Authors response: Thanks for your suggestion. I have added the explanation in Q2 to reviewer #1 to the fifth paragraph of the introduction section of the manuscript.

Q3: Could the authors add their explanation in Q3 to reviewer #1 to the discussion?

Authors response: Thanks for your suggestion. Your valuable comments are attached great importance by our team. Indeed, we greatly favor to add the explanation in Q3 to reviewer #1 to the discussion section of the manuscript. However, considering the following reasons, we have carefully decided to give up this proposal.

(1). This study was to evaluate the effect of the magnitude of elevated platelet counts after splenectomy on the formation of portal vein thrombosis (PVT) postoperatively. Therefore, the study excluded the patients with platelet counts not increased on the first or third days after splenectomy.

(2). In responding to Q3 raised by reviewer #1, I elaborated on the design of the prospective study that our team will conduct. As the confidentiality of the research plan may be involved, our team finally decided not to add this part of the explanation to the discussion section of the manuscript after careful consideration. We hope this can be understood by you.

Q4: The authors did not answer the Q5 to reviewer #1, the reviewer asked for the reactionary elevation of platelet count as due to anemia (or infection with lymphocytosis), and if this was a "statistical confounder" in their results, and could cause bias? Please answer this specific query.

Authors response: Thanks for your question. We have carefully studied your comments, as well as the Q5 raised by reviewer #1. It must be acknowledged that your concerns are very reasonable, because reactive thrombocytosis caused by anemia or infectious with lymphocytosis may indeed affect the formation of PVT after splenectomy. However, in order to avoid the influence of these confounding factors on the statistical analysis, we paid great attention to this issue when designing this study.

(1). Reactive thrombocytosis is closely related to various medical conditions, including infection, anemia, trauma or surgery[1]. Post-splenectomy reactive thrombocytosis is a very common event in patients undergoing the splenectomy, with an incidence of 75-90%[2, 3]. When studying the risk factors of PVT after splenectomy, the interference of thrombocytosis caused

by anemia or infection cannot be ignored. Studies have reported that iron deficiency or hemolytic anemia are contributors to reactive thrombocythemia[4]. However, the 483 patients who underwent splenectomy that we finally included in this study were patients with hepatitis B virus related cirrhosis complication with portal hypertension. The patients who underwent splenectomy due to splenomegaly caused by hematological diseases (article 2 of the exclusion criteria in the materials and methods section of the manuscript) are excluded. These excluded patients included the patients with iron deficiency or hemolytic anemia as you concerned about. Therefore, this factor will not affect the research results.

(2). The most prominent pathogen causing post-splenectomy infection is Streptococcus pneumoniae[5]. Appropriate prophylactic use of broad-spectrum antibiotics in the perioperative period can effectively reduce the risk of infection after splenectomy[6]. In fact, all patients in this study who underwent splenectomy due to portal hypertension received prophylactic antibiotics preoperatively and postoperatively. The patients in this study cohort did not present incision infection or intra-abdominal infection, pneumonia, etc. during postoperative hospitalization.

In addition, although the mortality rate of overwhelming post-splenectomy infection (OPSI) is high at 50-70%[7], the incidence of OPSI in patients undergoing splenectomy is low at 0.13%[8]. Most studies have found that young children (under the age of 2) or individuals who underwent splenectomy due to hematologic diseases have the highest risk of OPSI[9-11]. However, the patients enrolled in this study were adults (over the age of 18), and patients who underwent splenectomy for hematological diseases were also excluded. There were no cases of OPSI in this study cohort during more than 2 years of follow-up.

Actually, the infection with lymphocytosis you are worried about will hardly affect the results of

this study. Primary lymphocytosis is usually seen in young children and is associated with genetic defects, while secondary lymphocytosis is presented in adults due to malignancy, rheumatic disease, or infection[12]. Infectious lymphocytosis is an acute infectious disease caused by virus, which is mainly characterized by significantly increased peripheral blood leukocyte and lymphocyte counts[13]. Infectious lymphocytosis is predominantly seen in children and is very rare in adults[14]. The 483 adult patients enrolled in this study had low peripheral blood leukocyte and lymphocyte counts due to portal hypertension complicated with hypersplenism (**Table 1**). These patients were not diagnosed as infection with lymphocytosis during the perioperative period.

In summary, the reactionary elevation of platelet count as due to anemia (or infection with lymphocytosis) was not a “statistical confounder” in the results of this study.

Table 1: The characteristics of peripheral blood routine in 483 adult patients with portal hypertension.

Variable	Training cohort			Validation cohort		
	Without PVT (*n* = 203)	PVT (*n* =135)	*P*	Without PVT (*n* = 80)	PVT (*n* = 65)	*P*
RBC† ($\times10^{12}$/L)	3.59 (3.20-3.93)	3.57 (3.21-3.90)	0.69	3.74 (3.49-4.02)	3.55 (3.22-3.93)	0.044
HLB† (g/L)	89.3 (78.1-103)	93.2 (82.1-104)	0.093	89.5 (79.5-107)	91.1 (82.8-101)	0.965
WBC† ($\times10^{9}$/L)	2.51 (1.83-3.40)	2.18 (1.48-2.87)	0.007	2.46 (1.95-3.21)	2.09 (1.58-2.92)	0.06
N† ($\times10^{9}$/L)	1.35 (0.98-2.09)	1.27 (0.85-2.00)	0.177	1.38 (1.06-1.98)	1.15 (0.87-1.77)	0.147
L† ($\times10^{9}$/L)	0.79 (0.56-1.14)	0.50 (0.38-0.79)	<0.001	0.78 (0.51-1.11)	0.63 (0.45-0.91)	0.045
PLT† ($\times10^{9}$/L)	48.0 (36.0-64.5)	33.8 (26.0-47.9)	<0.001	46.0 (32.1-57.0)	35.0 (27.0-48.0)	0.012

† Continuous variables were presented as the median and interquartile range (IQR). PVT, portal vein thrombosis. RBC, red blood cells. HLB, hemoglobin. WBC, white blood cells. N, neutrophil count. L, lymphocyte count. PLT, platelet count.

Reference

1 Schafer AI. Thrombocytosis. *N Engl J Med* 2004; **350**(12): 1211-1219 [PMID: 15028825 DOI: 10.1056/NEJMra035363]

2 Boxer MA, Braun J, Ellman L. Thromboembolic risk of postsplenectomy thrombocytosis. *Arch Surg* 1978; **113**(7): 808-809 [PMID: 678089 DOI: 10.1001/archsurg.1978.01370190030004]

3 Oida T, Kano H, Mimatsu K, Kawasaki A, Kuboi Y, Fukino N, Kida K, Amano S. Thrombocytosis following splenectomy: with or without additional organ resection. *Hepatogastroenterology* 2012; **59**(116): 1033-1035 [PMID: 22580653 DOI: 10.5754/hge10032]

4 Schafer AI. Thrombocytosis and thrombocythemia. *Blood Rev* 2001; **15**(4): 159-166 [PMID: 11792116 DOI: 10.1054/blre.2001.0162]

5 Sinwar PD. Overwhelming post splenectomy infection syndrome - review study. *Int J Surg* 2014; **12**(12): 1314-1316 [PMID: 25463041 DOI: 10.1016/j.ijsu.2014.11.005]

6 Luu S, Spelman D, Woolley IJ. Post-splenectomy sepsis: preventative strategies, challenges, and solutions. *Infect Drug Resist* 2019; **12**: 2839-2851 [PMID: 31571940 PMCID: PMC6748314 DOI: 10.2147/IDR.S179902]

7 Standage BA, Goss JC. Outcome and sepsis after splenectomy in adults. *Am J Surg* 1982; **143**(5): 545-548 [PMID: 7081557 DOI: 10.1016/0002-9610(82)90158-1]

8 Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late postsplenectomy infection. *Br J Surg* 1991; **78**(6): 716-721 [PMID: 2070242 DOI: 10.1002/bjs.1800780626]

9 Werbin N, Lodha K. Malign effects of splenectomy--the place of conservative treatment. *Postgrad Med J* 1982; **58**(676): 65-69 [PMID: 7048272 PMCID: PMC2426301 DOI: 10.1136/pgmj.58.676.65]

10 Kyaw MH, Holmes EM, Toolis F, Wayne B, Chalmers J, Jones IG, Campbell H. Evaluation of severe infection and survival after splenectomy. *Am J Med* 2006; **119**(3): 276 e271-277 [PMID: 16490477 DOI: 10.1016/j.amjmed.2005.07.044]

11 Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *J Infect* 2001; **43**(3): 182-186 [PMID: 11798256 DOI: 10.1053/jinf.2001.0904]

12 Koumadoraki E, Madouros N, Sharif S, Saleem A, Jarvis S, Khan S. Hemophagocytic Lymphohistiocytosis and Infection: A Literature Review. *Cureus* 2022; **14**(2): e22411 [PMID: 35345677 PMCID: PMC8942143 DOI: 10.7759/cureus.22411]

13 Horwitz MS, Moore GT. Acute infectious lymphocytosis. An etiologic and epidemiologic study of an outbreak. *N Engl J Med* 1968; **279**(8): 399-404 [PMID: 4298693 DOI: 10.1056/NEJM196808222790803]

14 Arribas JM, Fernandez GH, Escalera GI, Pardilla AI, Martin TA, Gonzalez De La Rosa JB. [Acute infectious lymphocytosis associated to Giardia lamblia and Blastocystis hominis coinfection]. *An Esp Pediatr* 2001; **54**(5): 518-520 [PMID: 11333485]