PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 05040484

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Doctor, Professor, Research Scientist

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-22 18:14

Reviewer performed review: 2021-01-22 19:13

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This article is interesting, but I have a few comments: 1) hepatitis D infection is possible only with co-infection with hepatitis B, so pure hepatitis D does not exist: there are hepatitis B without D and hepatitis B with D. I think the terminology should be corrected. 2) you write "1028 subjects (HCV = 701, HBV = 240 and HDV = 86)", but 701 + 240 + 86 = 1027: you have lost one subject. 3) AUROC should always be reported with a confidence interval. 4) APRI index is used in hepatology for similar cases. It is also quite easy to calculate. I think it would be logical to compare the predictive characteristics of this index and yours to show which one is better. 5) according to Table 4, the platelet count in the blood has a high negative predictive value and a low positive predictive value. This means that if a patient has a platelet count of more than 140, he/she is almost guaranteed to have no cirrhosis, but if it is less, then this means practically nothing. This information should be added to the Discussion and in the same place it should be described what to do with patients with platelets below 140: should they be subjected to other, more reliable methods for detecting compensated cirrhosis (Fibroscan and others) or not. This should also be specified as a limitation of your method.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 02663375

Position: Editorial Board

Academic degree: MD

Professional title: Academic Research, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-23 16:13

Reviewer performed review: 2021-01-23 20:05

Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [Y] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The aim of this study was to assess whether platelets or other laboratory markers can be used as a simple method to identify the development of cirrhosis. This topic isn't new, and several studies have been published decades ago. On the other hand, the role of platelet count in the diagnosis of cirrhosis is very well known, and an answer to the aim of this study can be found in several articles that were published more than a decade ago. Some examples: - Cheung et al. in a series of 4462 patients of national (U.S.), multicenter, ethnically diverse cohort, found that a platelet count of < 150/L can be used in routine clinical practice to exclude or confirm the presence of advanced fibrosis [Cheung RC, Currie S, Shen H, et al. Can we predict the degree of fibrosis in chronic hepatitis C patients using routine blood tests in our daily practice? J Clin Gastroenterol. 2008 Aug;42(7):827-34] -Renou et al report that thrombopenia detected in patients with chronic hepatitis C constitutes an accurate marker of hepatic fibrosis and an excellent predictive noninvasive marker of cirrhosis in the absence of clinical, biological, endoscopic, or ultrasonographic signs of portal hypertension or hepatocellular failure [Renou C, Muller P, Jouve E, et al. Prevalence of moderate isolated thrombocytopenia as a strong predictive marker of cirrhosis inpatient with chronic hepatitis C. Am J Gastroenterol. 2001;96:1657–1659]. -Qamar et al. report that, in patients with compensated cirrhosis, thrombocytopenia (defined as a platelet count <150 000/μL) is the most common peripheral blood alteration, occurring in almost 78% of patients [Qamar AA, Grace ND, Groszmann RJ, et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol. 2009;7:689–695]. Therefore, this study lacks any interest. On the other hand, in primary care settings, simple nonproprietary biomarkers of liver fibrosis are nowadays available. Among them, the APRI score (AST to Platelet Ratio Index) is a

very simple one. It would have been of interest to know if platelet count alone was more accurate than the APRI score. Line 75: The journal has a worldwide readership that may be unaware of these specific U.S. programs. Therefore, it must be stated here that this are both U.S. programs and not worldwide programs. Line 114: Again, please specify that this applies to U.S. Line 177: Why only the platelet count? The methods should have been set before knowing the results. Lines 243-244: it seems all the way round, since the PPV was 48%. Lines 261-263: I do not agree with this statement. The Fib-4 score is very simple, it is not a proprietary biomarker and is easily obtained using a formula available also online. It should be explained why platelet count alone is better than the freely available biomarkers that incorporate platelet count in them. The APRI test is even more simple that Fib-4. The authors should have compared the accuracy of Fib-4 or APRI against platelet count. Lines 266-267: this is a limitation in the USA not in other parts of the world.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 02904354

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Chief Physician, Associate Professor, Doctor, Postdoc

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-01-22 04:24

Reviewer performed review: 2021-01-24 13:20

Review time: 2 Days and 8 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The role of PLT in evaluating the severity of liver diseases and portal hypertension complications has been widely explored in patient with chronic liver diseases. For example, APRI "aspartate aminotransferase (AST) to platelet ratio index" has been well recognized to identify the presence of liver fibrosis. The role of PLT in other conditions should be reviewed. By comparison, the present study is clearly written, but study design is less competitive. Some comments are listed as follows. Title section: The title "Platelet count as a Screening Tool for Compensated Cirrhosis in Chronic Viral Hepatitis" cannot show the novelty and advantages of the present study. Abstract section: The methods section said "Youden's Index", but the results section did not give such data. Except for the AUROC, what are the specificity and sensitivity? What are "All other tested markers"? Please give the detailed markers? "143 k/uL". Please take it as the universally used unit. "it performed equally well in the validation cohort (n=309)." What is the AUROC in the validation cohort? Conclusions should be more specified to "liver cirrhosis". Introduction section: Introduction should pay more attention to the role of PLT in evaluating the severity of liver diseases and portal hypertension complications, but not other contents. The words "expert consensus suggests that thrombocytopenia, with a laboratory cutoff value of <150/uL" should be supported by some references. What is "Alas"? Language expression should be greatly improved.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 03024263

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-23 05:25

Reviewer performed review: 2021-01-25 18:27

Review time: 2 Days and 13 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The growing need for alternative approaches to the assessment of liver disease severity has driven the development of non-invasive methods in order to overcome the limitations of liver biopsy. The authors showed the possibility of using platelets (a platelet cut-off of 140 K/uL) as a simple method to identify the development of liver cirrhosis in patients with HBV/HCV/HDV infection. Determination of platelet count is a well-known routine laboratory parameter that is usually investigated in patients with suspected chronic liver disease, in particular, liver cirrhosis. In patients with untreated HBV/HCV infection, thrombocytopenia is usually mild-to-moderate, and worsens with disease progression, as patients develop extensive fibrosis and/or cirrhosis. At the same time, platelet counts of <150000 /L are more frequently observed in patients with cirrhosis compared to patients without cirrhosis (64% vs. 6%, respectively) (DOI: 10.1111/j.1572-0241.2000.02325.x). This simple preliminary test is useful in making clinical decisions and in identifying areas of specialized care. However, as numerous studies have shown, it lacks the necessary diagnostic specificity and sensitivity. I see no originality in the presented study. In addition, it is limited by its retrospective design and inclusion of patients from a single institution.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 02567669

Position: Editorial Board

Academic degree: MD

Professional title: Emeritus Professor

Reviewer's Country/Territory: Germany

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-23 10:44

Reviewer performed review: 2021-01-28 20:06

Review time: 5 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript is aimed to find a very simple one-component marker to differentiate patients with chronic hepatitis B/C/D without cirrhosis from those with cirrhosis. Th result is not very surprising, but for the first time, platelet count has been validated as a very useful marker that can be applied in low-cost situations. The study is well designed, the statistics is fine, the description and the interpretation is sound.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 05771703

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Poland

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-01-22 23:40

Reviewer performed review: 2021-01-30 15:12

Review time: 7 Days and 15 Hours

Scientific quality	[ ] Grade A: Excellent　[ ] Grade B: Very good　[Y] Grade C: Good [ ] Grade D: Fair　[ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing　[ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing　[ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority)　[ ] Accept (General priority) [Y] Minor revision　[ ] Major revision　[ ] Rejection
Re-review	[ ] Yes　[Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous　[ ] Onymous Conflicts-of-Interest: [ ] Yes　[Y] No

SPECIFIC COMMENTS TO AUTHORS

In this cross-sectional study, the authors aimed to determine whether platelets or other laboratory markers can be used as a simple method to identify the development of cirrhosis. It should be pointed out, that this study was performed   in a relatively large sample of 1028 subjects. Although the idea of performing the study is interesting, the usage of platelet count in decision-making for the treatment and management of patients with HCV seems to be irrelevant. All treatment-naïve and treatment-experienced patients aged ≥3 years with chronic hepatitis C should be considered for DAA therapy regardless of disease severity in line with the liver societies guidelines (the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver).   The World Health Organization's Global Strategy on viral hepatitis assumes to eliminate this public health threat by 2030 with the treatment coverage for hepatitis C infection reaching, by then, 80% of eligible persons.   1.   The major problem concerns methodology: What were the exclusion criteria (apart from HIV infection) for the study? There could have been patients with concomitant diseases: acute (viral) infectious disease, onco-hematological diseases, which could make the results of platelet count unreliable (as the results within two months of liver biopsy were utilized for analysis).

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Surana et al performed a large-scale cross-sectional study, and found a platelet count >143 K/uL appear to have the most clinical utility in ruling out cirrhosis across all chronic viral hepatitis. The aim of this study is to provide primary-care physicians with an easy way to screen for cirrhosis. In general, the presentation of this study is complete and excellent. I'd like to make several suggestions just for your reference: 1. As we can see from the data, the authors seem to analyze a complete data set. Are patients with missing data being excluded?   2. As the authors stated, "Given the specialized setting of the National Institutes of Health, this population may have a higher prevalence of cirrhosis than the typical primary care setting", The analyzed population selected by the authors and the popularizing population of the study results are not consistent. The two groups of patients have different backgrounds, whether this will affect the study results? 3. The author chose pre-treatment liver biopsies as the gold standard, which seemed to eliminate the effects of drug intervention. However, the reality is that the vast majority of patients will be given antiviral drugs. Please explain the impact of antiviral drugs on the study results and the applicability of the study conclusion. 4. The purpose of the study was to screen for cirrhosis(F4) rather than advanced liver fibrosis(F3). I suggest that the author can use advanced fibrosis(F3) as the research standard, which is more therapeutic or preventative. 5. There are gender differences in platelet count and function. Please analyze the impact of gender differences on the results.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 05040484

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Doctor, Professor, Research Scientist

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-02-26 06:18

Reviewer performed review: 2021-02-26 06:29

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

No comments

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastrointestinal Pathophysiology

Manuscript NO: 62949

Title: Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis

Reviewer's code: 02663375

Position: Editorial Board

Academic degree: MD

Professional title: Academic Research, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-02-26 06:41

Reviewer performed review: 2021-02-26 06:52

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

No further comments