PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 73421

Title: β-Arrestin-2 Predicts the Clinical Response to β-Blockers in Cirrhotic Portal Hypertension Patients: A Prospective Study

Provenance and peer review: Invited manuscript; externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06151472

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Egypt

Manuscript submission date: 2021-11-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-21 07:59

Reviewer performed review: 2021-11-21 15:23

Review time: 7 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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) [ ] Accept (General priority) [ ] Minor revision [Y] 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 was a prospective paper which investigated the role of β-arrestins-2 in the setting of patients with cirrhosis and portal hypertension, receiving beta blockers for primary prophylaxis of variceal bleeding. The Authors enrolled 91 patients and followed up them for 18 months, or until the first episode of bleeding. My comments. 1. The enrolment period was not reported 2. The Authors said that the starting propranolol dose was 40 mg BID, with progressive titration until a dose of 360 mg when appropriate. The mean daily dose was only of 60 mg, however. 3. Why the patients underwent upper GI endoscopy every 12 wks? 4. The Authors said that NSBB responders were those who did not bleed during the period. Nevertheless, they considered also an endoscopic NSBB response (at what time period, considering that each patient performs 6 EGD during the observational period). What was the leading indication to response? 5. How was β-arrestins-2 measured in serum? 6. The Authors proposed two different cut-off values for β-arrestins-2 (one able to identify patients with low likelihood of bleeding, the other able to identify a longer bleeding-free interval time). What is the best cut-off to use in the clinical setting? 7. There are few typos which should corrected 8. The Authors discussed the potentially dangerous role of NSBB in patients with SBP and refractory ascites in the discussion section of this paper. This point is largely debated until now, since controversial data have been reported in literature. Notwithstanding, how many patients experienced refractory ascites and SBP in this cohort? 9. Among the potential pitfalls of this study, the Authors should add the need to externally validate these results in larger cohorts

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Provenance and peer review: Invited manuscript; externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03550401

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Egypt

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Reviewer accepted review: 2021-11-22 05:59

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Review time: 3 Days and 20 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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SPECIFIC COMMENTS TO AUTHORS

The author investigate the changes in expression and role of β-Arrestin-2 in predicting the long-term response to non-selective beta-blockers in cirrhotic portal hypertensive patients. And found higher serum level was associated with longer bleeding-free intervals, which was a potential non-invasive biomarker for selecting portal hypertension patients for non-selective beta-blockers therapy.   1. The data that was lost of follow-up needs to be shown, whether any of the patients had an end-point event. It is necessary to consider whether the exclusion of these cases has a potential impact on the outcome.   2. Please use a scale to indicate the size of the picture, not the magnification 3. In table 1, the frequency of large should be 36.7%   4. Page 10, the sentence "There was a significant change in the antral expression of β-Arr-2 after treatment with NSBB compared to baseline. The change was 42.9% vs. 18.6% respectively for low expression, 37.4% vs. 36.3% respectively for moderate, and 19.7% vs. 45.1% respectively for strong expression, (McNemar Bowker's $\chi 2$ =16.18, P = 0.001). ", it is difficult to read, the author needs to indicate the change in the proportion of all cohort before and after treatment. 5. Page 10-11: Multinomial regression showed that NSBB dose (P = 0.02, OR = 0.95, 95% CI: 0.91-0.99) and the ΔPVCI (P = 0.005, OR = 1.58, 95% CI: 0.001- 0.002) were the only independent predictors of reduced β-Arr-2 expression. For multivariate regression, the author need to list the result as tables, including which factors are included in the multiple regression.   6. Please indicate the full name for the abbreviation in the figure legend.   7. We have doubts about the APRI and Platelets values of patients. All patients are cirrhotic patients with esophageal varices. Why is the average APRI value around 1.75? I hope the author can check the data, and what is the reference range of AST?   8.

During follow up, NSBB non-responders represented 82.4% of patients with low β-Arr-2 expression (n=14/17), 45.5% for moderate expression (n=15/33), and 4.9% for strong expression (n=2/41), ($\chi 2$ =35.10, P < 0.001). This was hard to read. There were only 31 patients in non-responders group？ What about 41 and 33 patients？ 9. The name of section of "Survival analysis", which may make readers mistakenly believe that the author performed a survival analysis. But the author only did a Kaplan-Meier curve to analyze the bleeding time. In addition, the author should analyze the bleeding of all cohort during follow-up based on the cut-off value. 10. By Cox-regression analysis, a low serum β-Arr-2 level (P < 0.001, OR= 0.13, 95% CI: 0.09-0.13), a low grade of β-Arr-2 expression in the gastric antrum (P < 0.001, OR= 0.15, 95% CI: 0.1- 0.3), and platelet count (P = 0.008, OR= 0.91, 95% CI: 0.85- 0.98), were the only independent predictors for variceal bleeding. Cox regression needs to show the factors included in the regression analysis in the form of a table. 11. In addition, a low grade of β-Arr-2 expression in the gastric antrum (P <0.001, OR= 0.15, 95% CI: 0.1- 0.3). How is this classified? The grade of β-Arr-2 Expression is handled as a three-category variable or a binary variable.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

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no more comments