



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47730

**Title:** Plasma Nogo-A and placental growth factor levels are associated with portal hypertension in patients with liver cirrhosis

**Reviewer’s code:** 03253490

**Reviewer’s country:** Turkey

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-25 17:47

**Reviewer performed review:** 2019-03-26 07:58

**Review time:** 14 Hours

| SCIENTIFIC QUALITY                                     | LANGUAGE QUALITY  | CONCLUSION   | PEER-REVIEWER STATEMENTS                                  |
|--|---|--|---|
| <input type="checkbox"/> Grade A: Excellent            | <input type="checkbox"/> Grade A: Priority publishing                 | <input type="checkbox"/> Accept                    | Peer-Review:  |
| <input checked="" type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language polishing | (High priority)                                    | <input checked="" type="checkbox"/> Anonymous             |
| <input type="checkbox"/> Grade C: Good                 |   | <input type="checkbox"/> Accept                    | <input type="checkbox"/> Onymous                          |
| <input type="checkbox"/> Grade D: Fair                 | <input type="checkbox"/> Grade C: A great deal of language polishing  | (General priority)                                 | Peer-reviewer’s expertise on the topic of the manuscript: |
| <input type="checkbox"/> Grade E: Do not publish       | <input type="checkbox"/> Grade D: Rejection                           | <input checked="" type="checkbox"/> Minor revision | <input checked="" type="checkbox"/> Advanced              |
|  |   | <input type="checkbox"/> Major revision            | <input type="checkbox"/> General                          |
|  |   | <input type="checkbox"/> Rejection                 | <input type="checkbox"/> No expertise                     |
|  |   |  | Conflicts-of-Interest:                                    |
|  |   |  | <input type="checkbox"/> Yes                              |
|  |   |  | <input checked="" type="checkbox"/> No                    |

**SPECIFIC COMMENTS TO AUTHORS**

Gelman et al. aimed to determine plasma levels of Placental growth factor (PIGF) and Nogo-A in patients with liver cirrhosis, Clinically significant portal hypertension (CSPH) and severe portal hypertension (SPH) and potential to predict portal hypertension. The



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study is well designed and well written. Some issues raised: 1-Please give more detail about PIGF actions (as a pro-angiogenic factor, enhancing the proliferation, migration and survival of endothelial cells- stimulates proliferation of mesenchymal fibroblasts and regulates the contractile response of mural cells etc.). Thank you for giving opportunity to review your study.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

- The same title
- Duplicate publication
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##### ***BPG Search:***

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47730

**Title:** Plasma Nogo-A and placental growth factor levels are associated with portal hypertension in patients with liver cirrhosis

**Reviewer's code:** 03024263

**Reviewer's country:** Russia

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-25 14:03

**Reviewer performed review:** 2019-03-26 18:07

**Review time:** 1 Day and 4 Hours

| SCIENTIFIC QUALITY                                     | LANGUAGE QUALITY   | CONCLUSION                                 | PEER-REVIEWER STATEMENTS                      |
|--|--|--|---|
| <input type="checkbox"/> Grade A: Excellent            | <input checked="" type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept            | Peer-Review:                                  |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language                 | (High priority)                            | <input checked="" type="checkbox"/> Anonymous |
| <input type="checkbox"/> Grade C: Good                 | polishing  | <input checked="" type="checkbox"/> Accept | <input type="checkbox"/> Onymous              |
| <input type="checkbox"/> Grade D: Fair                 | <input type="checkbox"/> Grade C: A great deal of                | (General priority)                         | Peer-reviewer's expertise on the              |
| <input type="checkbox"/> Grade E: Do not               | language polishing   | <input type="checkbox"/> Minor revision    | topic of the manuscript:                      |
| publish  | <input type="checkbox"/> Grade D: Rejection                      | <input type="checkbox"/> Major revision    | <input type="checkbox"/> Advanced             |
|  |  | <input type="checkbox"/> Rejection         | <input checked="" type="checkbox"/> General   |
|  |  |  | <input type="checkbox"/> No expertise         |
|  |  |  | Conflicts-of-Interest:                        |
|  |  |  | <input type="checkbox"/> Yes                  |
|  |  |  | <input checked="" type="checkbox"/> No        |

**SPECIFIC COMMENTS TO AUTHORS**

The present study was carried out at a good methodological level and is of great scientific and practical importance. If the role of VEGF and PlGF in the pathogenesis of portal hypertension in liver cirrhosis is well known, the significance of Nogo-A is



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described for the first time. However, it remains unclear how Nogo-A affects the pathogenesis of portal hypertension in liver cirrhosis. The authors suggest that it affects the intrahepatic mechanisms, but they did not conduct these studies, which is a significant drawback. Perhaps this will be the goal of their further research. Indeed, early diagnosis of a clinically significant portal hypertension is of practical importance for the prevention of complications associated with it. However, HVPG measurement is possible only in specialized centers. In addition, the invasiveness of the procedure and the need for repeated use increases the risk of possible complications and increases costs. These limitations have contributed to the development of alternative methods for assessing the severity of portal hypertension, which are well described in the literature. The authors for the first time showed the possibility of using Nogo-A as a non-invasive marker for diagnosis a clinically significant portal hypertension with high specificity (93.1%) and positive predictive value (92.9%).

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- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47730

**Title:** Plasma Nogo-A and placental growth factor levels are associated with portal hypertension in patients with liver cirrhosis

**Reviewer’s code:** 02445708

**Reviewer’s country:** Poland

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-27 10:36

**Reviewer performed review:** 2019-03-29 09:18

**Review time:** 1 Day and 22 Hours

| SCIENTIFIC QUALITY                                | LANGUAGE QUALITY  | CONCLUSION   | PEER-REVIEWER STATEMENTS                      |
|---|---|--|---|
| <input type="checkbox"/> Grade A: Excellent       | <input type="checkbox"/> Grade A: Priority publishing       | <input type="checkbox"/> Accept                    | Peer-Review:                                  |
| <input type="checkbox"/> Grade B: Very good       | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority)                                    | <input checked="" type="checkbox"/> Anonymous |
| <input checked="" type="checkbox"/> Grade C: Good | polishing   | <input type="checkbox"/> Accept                    | <input type="checkbox"/> Onymous              |
| <input type="checkbox"/> Grade D: Fair            | <input type="checkbox"/> Grade C: A great deal of           | (General priority)                                 | Peer-reviewer’s expertise on the              |
| <input type="checkbox"/> Grade E: Do not          | language polishing  | <input type="checkbox"/> Minor revision            | topic of the manuscript:                      |
| publish   | <input type="checkbox"/> Grade D: Rejection                 | <input checked="" type="checkbox"/> Major revision | <input type="checkbox"/> Advanced             |
|   |   | <input type="checkbox"/> Rejection                 | <input checked="" type="checkbox"/> General   |
|   |   |  | <input type="checkbox"/> No expertise         |
|   |   |  | Conflicts-of-Interest:                        |
|   |   |  | <input type="checkbox"/> Yes                  |
|   |   |  | <input checked="" type="checkbox"/> No        |

**SPECIFIC COMMENTS TO AUTHORS**

In this study, Authors evaluate plasma levels of placental growth factor (PIGF) and Nogo-A protein (biomarkers of pathological angiogenesis) in patients with liver cirrhosis, clinically significant portal hypertension, and severe portal hypertension. They found:



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a) higher plasma levels of PIGF and b) lower plasma levels of Nogo-A in patients with liver cirrhosis and portal hypertension. Moreover, the Authors suggest that Nogo-A and PIGF “(...) showed moderate predictive value in determining clinically significant and severe PH (...)”. In general, this is an interesting and original paper, especially as Nogo-A protein levels in patients with liver cirrhosis and portal hypertension is concern. However, to confirm the presented results and improve scientific and practical values (suggestions that Nogo-A and PIGF could be biomarkers in determining clinically significant portal hypertension and severe portal hypertension) of the paper, much more control subject (approx. 100) should be examined. Moreover, I wonder why median and range values of PIGF plasma levels was included in the Results, but only median Nogo-A values were presented.

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- No

##### ***BPG Search:***

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- Duplicate publication
- Plagiarism
- No



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47730

**Title:** Plasma Nogo-A and placental growth factor levels are associated with portal hypertension in patients with liver cirrhosis

**Reviewer's code:** 00030389

**Reviewer's country:** Japan

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-25 22:57

**Reviewer performed review:** 2019-03-29 12:53

**Review time:** 3 Days and 13 Hours

| SCIENTIFIC QUALITY                                | LANGUAGE QUALITY  | CONCLUSION   | PEER-REVIEWER STATEMENTS                      |
|---|---|--|---|
| <input type="checkbox"/> Grade A: Excellent       | <input type="checkbox"/> Grade A: Priority publishing       | <input type="checkbox"/> Accept                    | Peer-Review:                                  |
| <input type="checkbox"/> Grade B: Very good       | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority)                                    | <input checked="" type="checkbox"/> Anonymous |
| <input checked="" type="checkbox"/> Grade C: Good | polishing   | <input type="checkbox"/> Accept                    | <input type="checkbox"/> Onymous              |
| <input type="checkbox"/> Grade D: Fair            | <input type="checkbox"/> Grade C: A great deal of           | (General priority)                                 | Peer-reviewer's expertise on the              |
| <input type="checkbox"/> Grade E: Do not          | language polishing  | <input checked="" type="checkbox"/> Minor revision | topic of the manuscript:                      |
| publish   | <input type="checkbox"/> Grade D: Rejection                 | <input type="checkbox"/> Major revision            | <input type="checkbox"/> Advanced             |
|   |   | <input type="checkbox"/> Rejection                 | <input checked="" type="checkbox"/> General   |
|   |   |  | <input type="checkbox"/> No expertise         |
|   |   |  | Conflicts-of-Interest:                        |
|   |   |  | <input type="checkbox"/> Yes                  |
|   |   |  | <input checked="" type="checkbox"/> No        |

**SPECIFIC COMMENTS TO AUTHORS**

The authors measured peripheral and hepatic PIGF and Nogo-A levels in patients with liver cirrhosis and examined the potential to predict portal hypertension. The results are interesting, but there are several concerns. Major comments #1. How many patients



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were examined for peripheral and hepatic PIGF and Nogo-A levels, respectively? #2. Peripheral and hepatic PIGF and Nogo-A levels differed from each other. In addition, there were no correlation between peripheral and hepatic PIGF and Nogo-A levels. Hepatic PIGF and Nogo-A levels did not correlate with HVPG. The authors should discuss these findings. #3. Discussion. "Van Steenkiste et al reported the increase of PIGF expression in cirrhotic liver, increase in plasma PIGF levels in patients with alcoholic hepatitis and a linear correlation between plasma PIGF levels and HVPG.[16]" I can't find this description in the reference 16. Minor comments #1. Abstract. They should use the abbreviations of CSPH and SPH after the first appearance. #2. Statistical analysis. They should describe the method to choose the values with best sensitivity and specificity. For example, maximizing the Youden's index, which is Maximum=Sensitivity + Specificity.

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