Dear Editors,

We would like to thank reviewers for their valuable comments. Point to point answers for each comment are presented below with appropriate changes in the main text.

Answering 1st reviewer

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.)".

   The changes have been made as suggested by the reviewer in the introduction section of the manuscript.

Answering 2nd reviewer

Thank you for Your review and your important remarks. Indeed we are planning further investigations and mechanistic studies, to determine Nogo-A expression in healthy and diseased liver.

Answering 3rd reviewer

1. "..to confirm the presented results and improve scientific and practical values (suggestions that Nogo-A and PlGF 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".

   Thank you for this very important point. We agree that a larger control group would yield more reliable conclusions concerning the differences of biomarkers in patients with liver cirrhosis when compared to healthy individuals. In our study design, the control group was intended to help determine whether the differences of plasma levels of biomarkers in test subjects and healthy individuals were statistically significant. We have based the size of the control sample on similar research by other authors (Grønbaek H. et al. Soluble CD163, a marker of Kupffer cell activation, is related to portal hypertension in patients with liver cirrhosis. Aliment Pharmacol Ther. 2012 Jul;36(2):173-80; La Mura V. et al. Von Willebrand factor levels predict clinical outcome in patients with cirrhosis and portal hypertension. Gut. 2011 Aug;60(8):1133-8).
   When this was confirmed, we proceeded to evaluate the performance of biomarkers in portal hypertension. The predictive value of biomarkers in diagnosing clinically significant and severe portal hypertension was determined using data from patients with cirrhosis only. These subjects were divided into groups according to hepatic venous pressure gradient. We did not measure hepatic venous pressure gradient in healthy controls, thus did not include them in the analysis.

2. "..I wonder why median and range values of PlGF plasma levels was included in the Results, but only median Nogo-A values were presented".

   The distribution of PlGF values was not normal, therefore we used nonparametric statistical tests and expressed PlGF values as median and range. The distribution of values of Nogo-A was normal, therefore we expressed Nogo-A values as mean and standard deviation.

Answering 4th reviewer

1. "How many patients were examined for peripheral and hepatic PlGF and Nogo-A levels, respectively?

   Periphearl PlGF and Nogo-A levels were examined in 100 patients. Hepatic levels of PLGF and Nogo-A were examined in 30 patients. Changes were made in the Methods and Patients part of the manuscript accordingly.

2. "Peripheral and hepatic PlGF and Nogo-A levels differed from each other. In addition, there were no correlation between peripheral and hepatic PlGF and Nogo-A levels. Hepatic PlGF and Nogo-A levels did not correlate with HVPG. The authors should discuss these findings"

   Thak you for this important point.
   PlGF levels in hepatic vein did not differ from levels in the peripheral vein, suggesting that PlGF levels remain stable after passing to systemic circulation. The reason why hepatic PlGF levels did not correlate to HVPG needs further research and we are planning to explore this phenomenon with higher study sample.
   Nogo-A levels at the hepatic vein were significantly higher than in the peripheral vein, suggesting that the protein undergoes some metabolism processes in the systemic circulation. Again, this phenomenon needs further mechanistic studies. We are planning to also further explore the lack of correlation between higher levels at the hepatic vein and HVPG. Changes were made to the Discussion part of the manuscript accordingly.

3. "Discussion. "Van Steenkiste et al reported the increase of PlGF expression in cirrhotic liver, increase in plasma PlGF levels in patients with alcoholic hepatitis and a linear correlation between plasma PlGF levels and HVPG.[16]" I can't find this description in the reference 16"

   The above mentioned data can be found in the Supporting information section of the online version of the article – Supplementary table 2 and Supplementary table 3.

4. "Abstract. They should use the abbreviations of CSPH and SPH after the first appearance".

   We have made changes to the abstract, as proposed by the reviewer.

5. “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”.

   We have used Youden’s index to determine best sensitivity and specificity. Changes in the manuscript were made accordingly.

We would like to thank the scientific editor for the valuable comments. Point to point answers for each comment are presented below with appropriate changes in the main text.

1. For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'"

   Our corresponding author JK holds A2 English language certificate which has been uploaded to the system. This certificate has been previously used in several accepted sumbmisions to the World Journal of Gastroenterology as proof of language proficiency. He has once more revised the manuscript for minor language errors.

2. **Audio core tip was uploaded in the system**.
3. Comment MR1 "Please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - image files.ppt" on the system"
   Figures were organized as requested and uploaded in the system.

4. Comment MR2 "..you need to provide the grant application form(s)"
   The study was sponsored by the Research Fund of Lithuanian University of Health Sciences (SV5-074/BN17-99, grant No. LSMU-21). Grant application form and grant funding approval document were uploaded to the system.

5. Comment MR3 "Please upload the primary version (PDF) of the Institutional Review Board's official approval"
   Uploaded

6. Comment MR4 "Please upload the primary version (PDF) of the Informed Consent Form"
   Uploaded

7. Comment U5"Please provide the Corresponding author's name, title, and detailed address"
   Required information was provided

8. Comment MR6 "Please explain all the abbreviations in the abstract"
   All abbreviations have been explained in the abstract. Nogo-A is not an abbreviation, it is the name of the protein.

9. Comment MR7 "Please don't include abbreviations in the key words"
   Nogo-A is not an abbreviation, it is the name of the protein.

10. “Please provide all authors’ abbreviation names and manuscript title here”
    Names and manuscript title provided as requested
11. Comment MR8 “Please distinguish between the title of the article series”.
    The titles were revised and corrected
12. Comment MR9 Statistical analysis
    Statistical significance was expressed as $^{a}P<0.05$.
13. Comments 10, 11, 12, 13, 14
    Article highlight section was completed.
14. Comment MR15
    The list of references was revised and corrected.
15. Comment MR16
    Abbreviations were deleted from figure and table titles; abbreviations were explained in the legend.