

University of Groningen

Author response to Letter to the Editor

Scheiner, Bernard; Northup, Patrick G.; Lisman, Ton; Mandorfer, Mattias

Published in:
Liver International

DOI:
[10.1111/liv.14499](https://doi.org/10.1111/liv.14499)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Scheiner, B., Northup, P. G., Lisman, T., & Mandorfer, M. (2020). Author response to Letter to the Editor: 'AB0, von Willebrand factor/Factor VIII and portal vein thrombosis in decompensated cirrhosis: Too late to unmask the culprit?'. *Liver International*, 40(7), 1790-1791. <https://doi.org/10.1111/liv.14499>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Author response to Letter to the Editor: 'ABO, von Willebrand factor/Factor VIII and portal vein thrombosis in decompensated cirrhosis: Too late to unmask the culprit?'

We thank Bitto et al¹ for the interest in our study in which we tested the hypothesis whether ABO blood type would be a risk factor for portal vein thrombosis (PVT) in patients with advanced chronic liver disease (ACLD).² In line with our findings, Bitto et al provide data demonstrating that von Willebrand factor levels significantly differ between patients with O and non-O blood types in early stage ACLD, but not when they have more advanced disease.¹ These data thus confirm that the impact of liver disease severity on von Willebrand factor (VWF) levels overrules the effect of blood type.

The authors comment that the factor VIII/protein C (FVIII/PC) ratio better mirrors the procoagulant state of cirrhosis than VWF or FVIII levels, which is why the PVT risk in patients with ACLD is independent of blood type. In other words, the authors are suggesting that hypercoagulability rather than endothelial dysfunction-related VWF-release followed by VWF-mediated platelet thrombus formation is the main driver of PVT in ACLD. This is an interesting thought which is in line with the use of anticoagulants (rather than antiplatelet agents) in the management of PVT. However, we wish to provide additional comments.

Firstly, it remains unclear whether a hyperactive hemostatic system is causally related to PVT in ACLD. An alternative theory is that reduction of portal flow is the main driver of PVT development and TIPS implantation which redirects blood flow by decreasing resistance has been reported to be similarly effective as anticoagulation.³ Even though markers of hypercoagulability may be associated with risk of PVT, this association is not necessarily causal. Notably, some of the markers used to signal hypercoagulability are strongly associated with severity of liver disease, and it may very well be that liver disease severity on its own (unrelated to hemostatic changes) drives the increase in PVT risk.

Secondly, although ratios have become popular in the studies of coagulation in liver disease, and have been associated with clinical features, there are important caveats to the use of these ratios. The hypercoagulable state of a patient with cirrhosis is directly identified using thrombomodulin (TM)-modified thrombin generation assays. As we have argued previously, we feel it is mandatory to report endogenous thrombin potential in the presence of TM (ETP + TM) values instead of derivatives such as ETP ratios, as they may be misleading and do not always confer hypercoagulability.⁴ A similar

argument applies to FVIII/PC ratios which might be useful predictors, but do not necessarily indicate hypercoagulability.

Finally, the call for studies on the effect of blood type on PVT in early stage ACLD is interesting, but as outlined in our manuscript, such studies will be difficult to conduct and of modest clinical impact given the rarity of PVT in these patients.

CONFLICT OF INTEREST

The authors have nothing to disclose regarding the work under consideration for publication. However, the authors disclose the following financial activities outside the submitted work: BS received travel support from AbbVie and Gilead. MM has received travel support from Gilead and served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, Collective Acumen, and WL Gore & Associates. PGN and TL have nothing to disclose.

Bernard Scheiner^{1,2}

Patrick G. Northup³

Ton Lisman⁴ 

Mattias Mandorfer^{1,2} 

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

²Vienna Hepatic Hemodynamic Laboratory, Medical University of Vienna, Vienna, Austria

³Center for the Study of Hemostasis in Liver Disease, Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, VA, USA

⁴Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
Email: j.a.lisman@umcg.nl

ORCID

Ton Lisman  <https://orcid.org/0000-0002-3503-7140>

Mattias Mandorfer  <https://orcid.org/0000-0003-2330-0017>

REFERENCES

1. Bitto N, Tosetti G, La Mura V, Primignani M. ABO, von Willebrand factor/Factor VIII and portal vein thrombosis in decompensated cirrhosis: too late to unmask the culprit? *Liver Int.* 2020. [Epub ahead of print]. <https://doi.org/10.1111/liv.14493>
2. Scheiner B, Northup PG, Gruber AB, et al. The impact of ABO blood type on the prevalence of portal vein thrombosis in patients with advanced chronic liver disease. *Liver Int.* 2020. [Epub ahead of print]. <https://doi.org/10.1111/liv.14404>
3. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. *Gastroenterology.* 2019;156:1582-1599.
4. Potze W, Sanyal AJ, Lisman T. Reply to: "procoagulant imbalance in patients with non-alcoholic fatty liver disease". *JHepatol.* 2017;66:250-251.