Reply to: 'From coagulation imbalance to prediction of advanced chronic liver disease decompensation: The wind of change?'

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From laboratory tests of coagulation to prognostic biomarkers in advanced chronic liver disease

To the Editor:

We would like to thank Dr. Ponziani and colleagues[1] for their interest in our work[2] and for sharing their interesting data.

In their letter to the editor, the authors analysed the prognostic ability of the ratio between factor VIII and protein C (FVIII/PC) as well as ADAMTS-13 and von Willebrand factor (ADAMTS-13/VWF) in 86 well-characterized patients with mainly compensated advanced chronic liver disease (ACLD). We were pleased to see that the FVIII/PC ratio was highly predictive of outcomes even in their cohort of patients with significantly less severe liver disease.[1] Indeed, the time-dependent AUCs for the prediction of hepatic decompensation or liver-related death at up to 40 months from baseline were excellent (>0.9).[1]

The authors also nicely outlined the rationale for studying ADAMTS-13 and VWF in patients with liver disease.[3] VWF, playing an important role in primary hemostasis by mediating platelet adhesion to the subendothelium, is released upon endothelial perturbation[4] and Toll-like receptor 4 activation[5] and therefore reflects the severity of portal hypertension and bacterial translocation, two major drivers of complications in ACLD.[4,6] Plasma levels of ADAMTS-13, a protease that acts as the major regulator of multimeric VWF size, are significantly reduced in patients with ACLD.[7] Not surprisingly, the ADAMTS-13/VWF ratio did not only predict outcomes in patients with ACLD,[8] but also in a large cohort of patients with acute liver failure.[9]

In their letter,[1] as well as in their previous study,[3] the authors also reported that patients who developed portal vein thrombosis (PVT) during follow-up had lower ADAMTS-13/VWF ratios at baseline and this ratio was the only baseline factor associated with PVT development. While this finding is interesting, it needs to be interpreted with caution as it remains to be elucidated if the ratio really indicates a prothrombotic tendency or if it is simply a surrogate of more advanced liver disease (and thus, PVT risk),[3] as is the case with the FVIII/PC ratio.[2] Notably, owing to the low number of PVT events, no adjustment for conventional indicators of liver disease severity was performed.[1,3]

Nevertheless, if the ADAMTS-13/VWF ratio was indeed directly involved in disease progression/the prothrombotic tendency in patients with ACLD, it may not only be a prognostic biomarker, but possibly even a predictive biomarker (*i.e.*, a predictor of the response to certain treatment strategies). Accordingly, it still seems advisable to investigate coagulation-related biomarker candidates in clinical trials targeting bacterial translocation-induced systemic inflammation (*e.g.*, prophylactic antibiotics) and/or endothelial dysfunction (*e.g.*, statins), as the field of ACLD/portal hypertension is lacking predictive biomarkers to guide personalized therapy.

Some further interesting evidence regarding the biological meaning of the ADAMTS-13/VWF ratio can be derived from a recent study evaluating a large cohort of patients with acute liver failure.[9] In this study, patients who died or underwent liver transplantation had significantly lower ADAMTS-13 activity accompanied by higher VWF levels. Nevertheless, the global coagulation status as assessed by thrombomodulin-modified thrombin generation and clot lysis time assays was comparable.[9]

Finally, a general note of caution needs to be added concerning the use of ratios as markers of a prothrombotic condition. Using ratios of pro- and anticoagulant protein levels/

activities assumes a linear relationship between the biological impact of these variables, a precondition that has not been proven for FVIII and PC or ADAMTS-13 and VWF.[10]

In conclusion, we concur with Ponziani and colleagues that both ratios should primarily be considered as surrogates of liver disease severity and not as indicators of hypercoagulability and/or direct modifiers of PVT development. Nevertheless, we need to intensify our efforts to develop a deeper pathophysiological understanding of the potential involvement of the coagulation system in liver disease progression and cirrhotic PVT in order to expand our armamentarium of disease-modifying/preventive therapies.

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Conflict of interest

Be.Sc. received travel support from AbbVie, Gilead, and Ipsen. M.M. served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, Collective Acumen, Takeda, and W. L. Gore & Associates and received travel support from AbbVie and Gilead. L.B. and T.L. have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Drafting of the manuscript (Be.Sc., M.M., and T.L.) and revision for important intellectual content and approval of the final manuscript (all authors).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.02.011.

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Author names in bold designate shared co-first authorship

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