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Published in:
Journal of Hepatology

DOI:
[10.1016/j.jhep.2022.05.029](https://doi.org/10.1016/j.jhep.2022.05.029)

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

Publication date:
2022

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

Citation for published version (APA):

Mandorfer, M., Scheiner, B., & Lisman, T. (2022). On coagulation in advanced chronic liver disease and the origin of freshwater eels. *Journal of Hepatology*, 77(3), 886-887. <https://doi.org/10.1016/j.jhep.2022.05.029>

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On coagulation in advanced chronic liver disease and the origin of freshwater eels

To the Editor:

We would like to thank Dr. Tripodi for his interest in our work.¹

The conundrum of haemostatic balance in patients with advanced chronic liver disease (ACLD) shares several similarities with the mystery of the freshwater eel. Reports on the presumed origin of the European eel go back to Aristotle who, due to the absence of reproductive organs at the yellow eel stage, considered them a spontaneous generation, *e.g.* derived from mud. It was not until 1922 that Johannes Schmidt located the origin of all European eel (*Anguilla anguilla*) to the Saragossa Sea (Atlantic Ocean) by capturing the smallest eel larvae. Nonetheless, the spawning of the European eel has never been observed in the wild, and thus, key aspects of its biology remain obscure. Notably, Aristotle also recognized the capability of blood to clot, which – in the context of ACLD – remains enigmatic in 2022. Although our knowledge on mechanisms leading to bleeding and thrombosis in patients with ACLD is steadily increasing, bleeding and clot formation are hard to study ‘in the wild’, limiting the available evidence mostly to experimental, genetic, and blood-/plasma-based laboratory investigations.

In this regard, different stages of ACLD have been extensively characterized by quantifying levels of coagulation factors and proteins involved in fibrinolysis,^{2,3} with studies indicating profound differences throughout the course of ACLD. Functional assays such as thromboelastography⁴ and rotational thromboelastometry have reinforced the clinical observation of a capable haemostatic system in the vast majority of patients with ACLD,⁵ although readouts of the latter method may be suggestive of hypocoagulability.⁶ Furthermore, seminal work by Tripodi *et al.*² and other groups⁷ revealed laboratory evidence supporting a hypercoagulable state at advanced stages, as identified by increased endogenous thrombin potential in thrombomodulin-modified thrombin generation assays (TM-TGA). It has been hypothesized that this presumed hypercoagulable state promotes further deterioration via the development portal vein thrombosis (PVT) or even liver disease progression due to parenchymal extinction via a ‘congestive escalator’.⁸ However, TM-TGA are poorly standardized and require considerable expertise, and thus, the ratio of factor VIII/protein C (FVIII/PC) has been applied in several studies attempting to link the presumed ‘hypercoagulable state’ to clinically meaningful endpoints. Intriguingly, this simplification led to positive results that were well-perceived by the community. However, the Achilles’ heel of all laboratory-based ‘coagulation’ tests is that they cannot be considered as surrogates for haemostasis in ACLD, as they are largely unrelated to clinical endpoints. This even applies to TM-TGA (which is considered as the most capable test for detecting the presumed ‘hypercoagulable

state’), as it failed to predict thrombotic events including PVT in our¹ and another well-conducted longitudinal study.⁹

This could be explained by considerable variations in *ex vivo* thrombin generation capacity over time (an aspect that seems understudied), which may compromise the predictive ability of baseline values that have been acquired (long) before the occurrence of the clinical outcome. While this emphasizes the need for further studies on the clinical significance of TM-TGA results, the findings of our studies may have put the final nails in the coffin of the (mis)use of FVIII/PC as a surrogate for the presumed ‘hypercoagulable state’. First, its association with TM-TGA results is confounded by liver disease severity. Second, it is unrelated to bleeding and thrombotic events. Third, its link with clinical endpoints is much better explained by associated well-established disease-driving mechanisms that are not directly related to coagulation.

Accordingly, we very much agree with Dr. Tripodi when he refers to ‘laboratory biomarkers’ or ‘biochemical hypercoagulability’ and underlines the potentially overwhelming contribution of circumstantial risk factors to bleeding and thrombosis in ACLD, which – apart from the contribution of portal hypertension to gastrointestinal bleeding events – seems poorly defined.

Finally, accumulating evidence suggests that plasma-based studies only scratch the surface of the pathophysiology of thrombosis in ACLD. Recent observations regarding the composition of portal vein ‘thrombi’¹⁰ question current paradigms, as intimal hyperplasia rather than fibrin-rich thrombi seemed to be their main constituent. As a heretical thought, one may even conclude that very limited histological data⁸ has provided more insights into the potential role of thrombosis in liver disease progression than a multitude of conventional coagulation studies. Accordingly, it may be hypothesized that one has to delve into the thrombotic crime scene (*i.e.*, the tissues of the portal and intrahepatic vasculature) and the Saragossa Sea to gain further insights into ‘thrombus’ formation and the spawning of the European/American eel, respectively.

We would like to conclude that our study failed to substantiate the link between the haemostatic balance and haemostasis-related clinical outcomes. However, it shifted another unknown unknown to the long list of known unknowns in our field: We have learned that FVIII/PC should not be used as an indicator of the presumed ‘hypercoagulable state’ – surrogate markers for bleeding and thrombosis in ACLD have yet to be established.

Financial support

No funding specific to this work was received.

Conflict of interest

M.M. served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, Collective Acumen, and W. L. Gore & Associates and received travel support from AbbVie and

Gilead. Be.Sc. received travel support from AbbVie, Ipsen, and Gilead. T.L. has nothing to disclose.

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

Authors' contributions

Drafting of the manuscript (M.M.) and revision for important intellectual content as well as 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.2022.05.029>.

References

Author names in bold designate shared co-first authorship

- [1] **Scheiner B, Balcar L**, Nussbaumer RJ, Weinzierl J, Paternostro R, Simbrunner B, et al. Factor VIII/protein C ratio independently predicts liver-related events but does not indicate a hypercoagulable state in ACLD. *J Hepatol* 2022;76(5):1090–1099.
- [2] **Fisher C, Patel VC**, Stoy SH, Singanayagam A, Adelmeijer J, Wendon J, et al. Balanced haemostasis with both hypo- and hyper-coagulable features in critically ill patients with acute-on-chronic-liver failure. *J Crit Care* 2018;43:54–60.
- [3] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology* 2009;137(6):2105–2111.
- [4] Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (N Y)* 2012;8(8):513–520.
- [5] Raeven P, Baron-Stefaniak J, Simbrunner B, Stadlmann A, Schwabl P, Scheiner B, et al. Thromboelastometry in patients with advanced chronic liver disease stratified by severity of portal hypertension. *Hepatol Int* 2020;14(6):1083–1092.

- [6] Kleinegris MC, Bos MH, Roest M, Henskens Y, Ten Cate-Hoek A, Van Deursen C, et al. Cirrhosis patients have a coagulopathy that is associated with decreased clot formation capacity. *J Thromb Haemost* 2014;12(10):1647–1657.
- [7] Lebretton A, Sinegre T, Lecompte T, Talon L, Abergel A, Lisman T. Thrombin generation and cirrhosis: state of the art and perspectives. *Semin Thromb Hemost* 2020;46(6):693–703.
- [8] Wanless IR. The role of vascular injury and congestion in the pathogenesis of cirrhosis: the congestive escalator and the parenchymal extinction sequence. *Curr Hepatol Rep* 2020;19(1):40–53.
- [9] Turon F, Driever EG, Baiges A, Cerda E, Garcia-Criado A, Gilibert R, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. *J Hepatol* 2021;75(6):1367–1376.
- [10] **Driever EG, von Meijenfeldt FA**, Adelmeijer J, de Haas RJ, van den Heuvel MC, Nagasami C, et al. Nonmalignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus. *Hepatology* 2022;75(4):898–911.

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A good step toward low-cost prognostication of liver-related outcome awaits more validation

To the Editor:

We read the article “Development and validation of a model to predict incident chronic liver disease in the general population: the CLivD score” with great interest.¹ The study demonstrates the possibility of prognosticating the risk of liver-related outcomes using easily accessible information, and highlights potential room for further validation and optimization.

Although the CLivD model was developed using European cohorts, we observed similar overall risk-stratification capacity in the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was a study conducted by the US Center of Disease Control in 1988–1994 to obtain nationally representative information on the health and nutritional status of the US population.^{2,3} The study used a complex, multistage, probability sampling design to select

participants representative of the civilian, non-institutionalized US population. The mortality data of NHANES III participants were last collected in 2015. We calculated CLivD Model_{lab} and Model_{non-lab} in 5,783 participants aged 40–70 years in NHANES III, representing an estimated population of 187 million. We used weighted Cox proportional hazard analysis to examine the effectiveness of CLivD models to predict liver-related mortality, which included chronic liver disease, cirrhosis, and liver cancer as the underlying cause of death (UCOD 024, 093, 094, and 095). The NHANES III data showed that both Model_{lab} and Model_{non-lab} effectively risk-stratified liver-related mortality (Fig. 1A,B). In both models, no liver-related death was seen in the minimal risk category (green), and the highest mortality was seen in the high-risk category (red). Between the 2 models, Model_{lab} performed better than Model_{non-lab} (C-statistics 0.733 vs. 0.637). The high-risk category by Model_{lab} had a hazard ratio (HR) of 7.7 (1.4–43.5, p = 0.02) over