

University of Groningen

Reply

von Meijenfeldt, Fien A.; Stravitz, R. Todd; Lee, William M.; Lisman, Ton

Published in:
Hepatology

DOI:
[10.1002/hep.32286](https://doi.org/10.1002/hep.32286)

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:
2022

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

Citation for published version (APA):
von Meijenfeldt, F. A., Stravitz, R. T., Lee, W. M., & Lisman, T. (2022). Reply. *Hepatology*, 75(3), 770-771.
<https://doi.org/10.1002/hep.32286>

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.

Correspondence

Xuefeng Luo, Department of Gastroenterology and Hepatology, Sichuan University-University of Oxford Huaxi Joint Center for Gastrointestinal Cancer, West China Hospital, Sichuan University, #37 Guoxue Road, Chengdu, Sichuan, 610041, China.
Email: luo_xuefeng@wchscu.cn

ORCID

Guofeng Liu  <https://orcid.org/0000-0002-2835-9547>
Li Yang  <https://orcid.org/0000-0003-3821-9342>

REFERENCES

1. Meijenfeldt FA, Stravitz RT, Zhang J, Adelmeijer J, Zen Y, Durkalski V, et al. Generation of neutrophil extracellular traps

in patients with acute liver failure is associated with poor outcome. *Hepatology*. 2022;75:622–33.

2. Cho Y, Szabo G. Two faces of neutrophils in liver disease development and progression. *Hepatology*. 2021;74:503–12.
3. Williams CD, Bajt ML, Sharpe MR, McGill MR, Farhood A, Jaeschke H, et al. Neutrophil activation during acetaminophen hepatotoxicity and repair in mice and humans. *Toxicol Appl Pharmacol*. 2014;275:122–33.
4. Antoniadou CG, Quaglia A, Taams LS, Mitry RR, Hussain M, Abeles R, et al. Source and characterization of hepatic macrophages in acetaminophen-induced acute liver failure in humans. *Hepatology*. 2012;56:735–46.
5. Blasi A, Patel VC, Adelmeijer J, Azarian S, Aziz F, Fernández J, et al. Plasma levels of circulating DNA are associated with outcome, but not with activation of coagulation in decompensated cirrhosis and ACLF. *JHEP Rep*. 2019;1:179–87.

Reply

We thank Dr. Liu and colleagues for their interest in our manuscript. We agree that the lower plasma levels of the neutrophil extracellular trap (NET)-marker, myeloperoxidase (MPO)-DNA complex, in patients with acetaminophen-induced acute liver failure (ALF) might be explained by the shorter duration of disease at blood sampling compared with non-acetaminophen-induced ALF. We disagree, however, that it has been established at what stage in human acetaminophen-induced ALF neutrophil influx in the liver takes place and would like to emphasize that the data referred to by Dr. Liu and colleagues are derived from studies in mice. It would be of interest to assess NET formation in serial blood samples to document NET formation over time and its possible contribution to progression of disease.




We agree that subsets of neutrophils are involved in tissue repair after liver injury, but when neutrophils are activated to form NETs, these beneficial features are likely lost.^[1] Our study suggests that in ALF, NET formation primarily causes damage, as high plasma levels of MPO-DNA complexes were associated with poor outcome. Notably, the vast majority of studies on the role of neutrophils in liver injury and repair have used mouse models of liver injury. Whether these results are relevant for ALF in humans should be further explored.

The second comment raised on the activation of coagulation by NETs in liver disease is important and has been the subject of studies in our group. There is convincing evidence from experimental studies that NETs activate coagulation, but there is limited evidence that NETs are involved in activation of coagulation in patients with liver disease. We previously

showed that MPO-DNA complex levels were not associated with markers of coagulation activation in patients with acute-on-chronic liver failure^[2] and in patients undergoing liver transplantation.^[3] It has also been demonstrated that NETs inhibit the fibrinolytic system in vitro, but it is unclear whether this mechanism plays a role in fibrinolysis regulation in vivo. We recently demonstrated that coagulation or fibrinolytic potential in patients with ALF were not associated with outcome.^[4] Thus, it may be that the mechanism by which NETs contribute to progression of ALF is not through activation of coagulation. We agree that additional (histological) studies to explore the role of NETs in progression of liver disease and their link to coagulation are of interest.

CONFLICT OF INTEREST

Dr. Lee consults for SeaGen, Forma, Karuna, Pfizer, Genentech, and Cortexyme. He received grants from Bristol-Myers Squibb, Intercept, Aurora, Gilead, Ocera, Cumberland, Eiger, and Alexion.

Fien A. von Meijenfeldt¹
R. Todd Stravitz² 
William M. Lee³ 
Ton Lisman¹ 

¹*Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

²*Hume-Lee Transplant Center of Virginia Commonwealth University, Richmond, Virginia, USA*

³University of Texas-Southwestern Medical
Center, Dallas, Texas, USA

Correspondence

Ton Lisman, Surgical Research Laboratory,
Department of Surgery, University Medical
Center Groningen, BA33, Hanzeplein 1, 9713 GZ
Groningen, the Netherlands.
Email: j.a.lisman@umcg.nl

ORCID

R. Todd Stravitz  <https://orcid.org/0000-0001-9901-854X>

William M. Lee  <https://orcid.org/0000-0002-2783-5441>

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

REFERENCES

1. Kolaczowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol.* 2013;13(3):159–75.
2. Blasi A, Patel VC, Adelmeijer J, et al. Plasma levels of circulating DNA are associated with outcome, but not with activation of coagulation in decompensated cirrhosis and ACLF. *JHEP Rep.* 2019;1(3):179–87.
3. von Meijenfeldt FA, Burlage LC, Bos S, Adelmeijer J, Porte RJ, Lisman T. Elevated plasma levels of cell-free DNA during liver transplantation are associated with activation of coagulation. *Liver Transpl.* 2018;24(12):1716–25.
4. Driever EG, Stravitz RT, Zhang J, et al. VWF/ADAMTS13 imbalance, but not global coagulation or fibrinolysis, is associated with outcome and bleeding in acute liver failure. *Hepatology.* 2021;73(5):1882–91.