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Aliment Pharmacol Ther. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Aliment Pharmacol Ther. 2017 April ; 45(7): 1008–1009. doi:10.1111/apt.13974.

Letter: Changes in FIB-4 cut-off points for viral hepatitis - Authors' Reply

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Sirs

We are greatly appreciative of the interest in our recent manuscript[1] by Dr. Kayadibi [2]and value the opportunity to discuss and clarify his concerns.

Dr. Kayadibi suggests that age bias and differences in platelets may have led to decreased diagnostic accuracy of FIB-4 in our HDV cohort. The significant difference of age in the reported HDV cohort represents the rapid progression of HDV in the general population and the younger age at which HDV infected individuals develop advanced fibrosis and cirrhosis[3]. While it is true that similar ages across viral groups would have improved the diagnostic accuracy of FIB-4, this would not be representative of HDV infection or its global effect[4, 5]. The significant difference in ages across viral groups is further evidence why FIB-4 may not be a sufficiently accurate biomarker for identifying advanced liver disease in HDV infected patients. Regarding the differences in platelets between groups, this is again reflective of the nature of HDV disease and rapid progression with higher necroinflammation demonstrated by histology. The lower platelet counts have been well described in HDV compared to HCV and HBV infected patients[6].

We agree that it is clinically important to assess whether surrogate markers of fibrosis can sufficiently discriminate those patients who do not have advanced fibrosis as well. FIB-4 was initially established in HIV/HCV co-infected patients with two cutoff points to identify patients with and without advanced fibrosis[7]. However, due to the nature of our data and the natural history of HDV patients, our study focused on the ability of validated biomarkers to identify advanced fibrosis. Delta hepatitis tends to be endemic to regions with fewer resources. For these areas, noninvasive fibrosis markers would be best utilized to identify subjects with advanced fibrosis or cirrhosis, as these individuals would require more healthcare and possible therapy. Dr. Kayadibi shows that the specificity and sensitivity of the lower FIB-4 cutoff can be improved with adjusted cutoffs in HBV mono-infection[2]. This is likely true for HDV infected individuals as well, though our colleagues must appreciate the

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Conflicts of interest: None of the authors has financial interests or conflicts of interest related to this research.
The authors' declarations of personal and financial interests are unchanged from those in the original article[1].

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higher necroinflammatory scores on liver biopsies and corresponding higher transaminases in this cohort as described in our paper. Further work should be done to establish noninvasive markers of fibrosis to identify HDV infected patients with and without advanced fibrosis.

Acknowledgments

Financial support: This research was supported by the Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases.

Abbreviations

NIH	National Institutes of Health
HIV	human immunodeficiency virus
APRI	Aspartate aminotransferase to platelet ratio index
FIB-4	Fibrosis 4 score
HDV	Hepatitis D virus
HCV	Hepatitis C virus
HBV	Hepatitis B virus

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