Letters to the Editors

Letter: changes in FIB-4 cut-off points for viral hepatitis

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Sirs, I read with great interest the recently published article by Koh *et al.*,[1] who proposed to improve the diagnostic accuracy of FIB-4 for advanced fibrosis in patients with chronic delta hepatitis by reducing the cut-off point from 3.25 to 2.03. I would like to share my thoughts and experience on the FIB-4 cut-off points for viral hepatitis.

FIB-4 is calculated by age, AST, ALT and platelet count, and is widely used for the prediction of liver fibrosis stage. In the study of Koh *et al.*,[1] ALT and AST had the highest mean values, although age and platelet count had the lowest mean value in the HDV group. However, ALT does not seem to have any significant effect, since the square root of the mean ALT value for each viral hepatitis group was similar. The product of age times AST is also close for each group, so the differences among the FIB-4 results of the HBV, HCV and HDV groups can be derived from the platelet count. In my opinion, age bias may be an important factor in this study cohort to explain the poor diagnostic performance for HDV compared to HBV and HCV. If no significant differences existed for age between each group, then HDV-infected patients would have higher FIB-4 values, which may result in the higher diagnostic power of FIB-4 for HDV-infected patients.

Koh *et al.*[1] evaluated the diagnostic accuracy of only the FIB-4 cut-off point of 3.25 and just for advanced fibrosis. However, Kayadibi *et al.*[2] explored significant liver fibrosis (METAVIR F2-4) and cirrhosis (METAVIR F4) in chronic HBV monoinfected patients by decreasing the upper (3.25) and increasing the lower (1.45) cut-off points of FIB-4 that had first been established in HIV/HCV co-infected patients. Cut-off points should be determined for each disease condition, since the pre-test probability of the disease of interest can affect the selected cut-off point, and the cut-off value is not universal.[3] In addition, the nature of the disease may be important in the selection of the cut-off points, as patients with different viral hepatitis types may be misclassified by the use of FIB-4 cut-off points initially established for HIV/HCV co-infected patients.

Koh *et al.*[1] used just a single cut-off point, while Kayadibi *et al.*[2] used both lower and upper cut-off points. In clinical practice, the use of a single cut-off point may not result in a sufficiently high sensitivity and specificity to rule out (or rule in) an outcome of interest, whereas the use of low and high cut-off points results in high sensitivity and specificity.[3] As shown in Table 1, FIB-4 cut-off points of 1.62 and 2.40 generated higher diagnostic performances than did cut-off points of 1.45 and 3.25.[2]

Table 1 | Analytical performances of previously determined FIB-4 cut-off points for fibrosis stages

Fibrosis stage	Cut-off point	Sensitivity (%)	Specificity (%)	Youden's index	Accuracy (%)
METAVIR F2-4	1.45	64.4	86.7	0.51	78.6
	1.62	64.4	90.6	0.55	81.1
	2.40	47.9	97.7	0.46	79.6
	3.25	16.4	100.0	0.16	69.7
METAVIR F4	1.45	80.5	81.9	0.62	81.6
	1.62	80.5	85.0	0.66	84.1
	2.40	61.0	97.5	0.59	90.0
	3.25	22.0	100.0	0.22	84.1

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In conclusion, different FIB-4 cut-off points should be determined for each type of viral hepatitis to increase the diagnostic power, which can vary due to the pre-test probability and the nature of the disease. The use of two cut-off points is therefore more advantageous than the use of a single cut-off point.

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LINKED CONTENT

This article is linked to Takyar et al and Surana and Koh papers. To view these articles visit https://doi.org/10.1111/apt.13974 and https://doi.org/10.1111/apt.13834.

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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 cut-off 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 health care and possible therapy. Dr Kayadibi shows that the specificity and sensitivity of the lower FIB-4 cut-off can be improved with adjusted cut-offs in HBV mono-infection.[2] This is likely true for HDV infected individuals as well, though our colleagues must appreciate the 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.

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The authors' declarations of personal and financial interests are unchanged from those in the original article.[1]

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