Table 1 Comparison of diagnosis with wd scores and AFP with different cut-offs in patients with chronic hepatitis B

Author	Marker	Cut-off	Sensitivity	Specificity	NLR	PLR
Cai *et al*[1]	wd scores	27.9	0.827	0.674	0.26	2.54
	AFP	20 ng/mL	0.448	0.761	0.73	1.87
Wong *et al*[4]	AFP	20 ng/mL	0.386	0.989	0.62	35.09
		6 ng/mL	0.807	0.804	0.24	4.12

AFP, α-fetoprotein; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

Are the 5-hydroxymethylcytosine-based wd-scores really superior over α-fetoprotein for the early diagnosis of hepatocellular carcinoma?

We read with interest the recent article by Cai *et al*[1] describing the development of 5-hydroxymethylcytosine (5hmC)-based wd-scores that have better accuracy in diagnosing early hepatocellular carcinoma (HCC) than does α-fetoprotein (AFP). Although several gene signatures have been published but not used in practice of early HCC diagnosis,[2] this study showed the potential application of the 5hmC-based wd scores. However, several concerns remain that need to be clarified.

First, the wd-scores' cut-off for early diagnosis of HCC, derived by the maximal Youden index and characterised by a sensitivity of 82.7% and a specificity of 76.4%, is suboptimal; this would result in missed diagnosis of early HCC in 17.3% of patients, and the corresponding negative likelihood ratio of 0.26 is characterised by a small probability for excluding diagnosis.[3] With the area under the receiver operating characteristic curve of 0.846, the performances of the wd-scores in early diagnosis of HCC were not perfect; thus, two cut-offs should be defined to discriminate low and high risk of early HCC. Considering the poor prognosis of HCC and the high cost of medical treatment, early HCC diagnosis should be emphasised with high sensitivity and a likelihood ratio of 0.1 (generating a large and often conclusive change[3] to minimise missed diagnosis). Therefore, the wd-scores' cut-off should be lowered. Of course, a higher cut-off with high specificity for discriminating a high risk of early HCC should also be defined.

Second, in patients with chronic hepatitis B (CHB) or cirrhosis, Cai *et al* reported that a wd-score of 27.9 detected early HCC with a sensitivity of 82.7% and a specificity of 67.4%, respectively, compared with AFP 20 ng/mL, which had a sensitivity of 44.8% and a specificity of 76.1%, respectively (table 1). Moreover, wd-scores demonstrated the capability of diagnosing early HCC in patients who were misclassified with the use of AFP alone; this may be attributed to a higher AFP cut-off, resulting in more missed diagnoses. Will this advantage of wd-scores remain if the AFP cut-off is decreased to attain a sensitivity of 82.7%, thereby resulting in a decrease in missed diagnoses? Actually, a study on patients with CHB receiving entecavir treatment indicated that an AFP cut-off of 20 ng/mL diagnosed HCC with a sensitivity of 38.6%, a specificity of 98.9% and a likelihood ratio of 35.09, which is suitable for confirming but not excluding HCC diagnosis[3]; when the AFP cut-off was decreased to 6 ng/mL, the sensitivity increased to 80.7% (table 1).[4] Moreover, due to the different mechanism for detecting early HCC, AFP alone may also diagnose patients who were misclassified by wd-scores; thus, the authors should clarify this issue.

Finally, while discussing the superiority of wd-scores over AFP alone, cost-effectiveness analysis should not be neglected. AFP test has been routinely available in real-life medical practice at a low cost. However, as novel diagnostic biomarkers, determination of 5hmC-based wd-scores may be expensive and, thus, not routinely available. If wd scores could not classify a significantly higher proportion of patients than AFP alone, its superiority over AFP alone cannot be derived.

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