

Letter: diagnostic accuracy of M30 levels for identifying patients with non-alcoholic steatohepatitis

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SIRS, I read with interest the study by Shen *et al.*,¹ which investigated the diagnostic accuracy of the cell apoptotic marker cytokeratin-18 M30 and total cell death markers cytokeratin-18 M65/M65ED for the assessment and monitoring of non-alcoholic fatty liver disease (NAFLD). According to the results reported in Table 2, M30 achieved an area under the receiver operating characteristic (AUROC) curve for discriminating non-alcoholic steatohepatitis (NASH) from non-NASH of only 0.66 [95% confidence interval (CI): 0.57–0.75].

This value seems to be significantly lower than that originally reported by Wieckowska *et al.*,² who showed that serum M30 accurately predicted 'definitive NASH' (according to the NIDDK NASH Clinical Research Network scoring system)³ in patients with suspected NAFLD with an AUROC of 0.93. Similarly, we have previously reported that M30 levels had an AUROC of 0.83 for distinguishing between 'simple steatosis' and 'definitive NASH'.⁴

The lower diagnostic performance seen in the study by Shen *et al.*¹ may be attributed to problems inherent in the histological classification of their patients with NAFLD. Indeed, as the results presented in Table S2 seem to

suggest, the authors performed a comparison between 'definite NASH' vs. 'borderline NASH' plus 'simple steatosis' (the latter two categories grouped together). To allow comparisons with previous studies, the authors should compare 'definite NASH' with 'simple steatosis' (i.e. without the inclusion of subjects with 'borderline NASH').

In addition, the authors in their article refer to the recent endpoints and clinical trial design for non-alcoholic steatohepatitis.⁵ According to this classification system, the presence or absence of steatohepatitis is categorised according to gestalt recognition of the pattern of disease. Therefore, the authors should also reassess the diagnostic accuracy of the biochemical markers using the histological classification proposed by Sanyal *et al.*⁵

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Letter: diagnostic accuracy of M30 levels for identifying patients with non-alcoholic steatohepatitis – authors' reply

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SIRS, We thank Dr Yilmaz for the comments.¹ According to his suggestion, we compared 32 'definite non-alcoholic steatohepatitis (NASH)' patients (NAS \geq 5)

with 42 'simple steatosis' (NAS \leq 2).² If we excluded patients with 'borderline NASH', the area under the receiver operating-characteristics curve (AUROC) of CK-18 M30, M65 and M65ED in differentiating 'definite NASH' was 0.77 (95% confidence interval: 0.66–0.88), 0.82 (0.72–0.92) and 0.85 (0.76–0.94) respectively. These results would be comparable to Yilmaz's report.³ However, we have a strong concern that it may lead to misinterpretation.

As shown in Figure S3 of our paper, all biomarkers increased in a stepwise fashion with increasing features of NASH.⁴ The difference between 'definite NASH' and 'simple steatosis' would certainly be more dramatic than comparing 'definite NASH' with all other non-alcoholic fatty liver disease (NAFLD) patients. How-