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CORRESPONDENCE

Letter to the editor: Serum thrombospondin-2 as biomarker in liver diseases, a look beyond NASH

To the editor,

With great interest, we read the study by Kozumi et al.[1] demonstrating that thrombospondin-2 (THBS2) is a valuable biomarker for NASH and advanced liver fibrosis. In particular, the authors showed that serum THBS2 levels promise to stratify patients with NAFLD according to the risk of hepatic complications, such as liver cancer and decompensated cirrhotic events. Concomitantly to this report, we published data showing that THBS2, along with thrombospondin-1 (THBS1) and pigment epithelium-derived factor (PEDF), was able to inhibit vascular growth in intrahepatic cholangiocarcinoma (iCCA), while promoting cancer-associated lymphangiogenesis.[2] We concluded that targeting these proteins could be a potential strategy to counteract the invasiveness of iCCA. Notably, among the presented data, we showed that serum THBS2 levels were significantly higher in patients with iCCA (92.3 ng/ml) compared with healthy donors (HDs) (24.6 ng/ml) (Figure 1A); no difference in serum THBS1 and PEDF expressions were found. In particular, THBS2 exhibited an area under the curve of 0.82 (95% CI, 0.681–0.957; $p = 0.0005$) when comparing iCCA versus HDs, resulting in a positive predictive value of 95% (Figure 1B). Our results predicted THBS2 as a potential noninvasive biomarker for the detection of iCCA. Recently, to extend our analysis in populations of patients with biopsy-proven NASH with advanced fibrosis (≥ F3) and patients with HCC cirrhosis, the latter not specifically considered in the study by Kozumi et al.,[1] we found increased serum THBS2 levels with respect to HDs (Figure 1A,B). Hence, in addition to confirming the diagnostic value of circulating THBS2 levels in the frame of NASH, these data shed light on the pathogenic features of the most recurring liver diseases. In fact, considering iCCA, HCC, and NASH as a unique population, the serum levels of THBS2 showed a diagnostic ability in discriminating advanced liver disease from HDs (Figure 1C,D). Moreover, these data should be integrated with recent observations indicating the ability of THBS2 serum levels in detecting pancreatic cancer and distal cholangiocarcinoma.[3]

In the light of these considerations, we suggest the need to enroll a large cohort of patients in a multicenter research trial to strengthen these promising observations and to better define THBS2 efficacy in detecting liver and gastric diseases, particularly in early stages of cancer.

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CONFLICT OF INTEREST

Nothing to report.

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Abbreviations: HD, healthy donor; iCCA, intrahepatic cholangiocarcinoma; THBS, thrombospondin.

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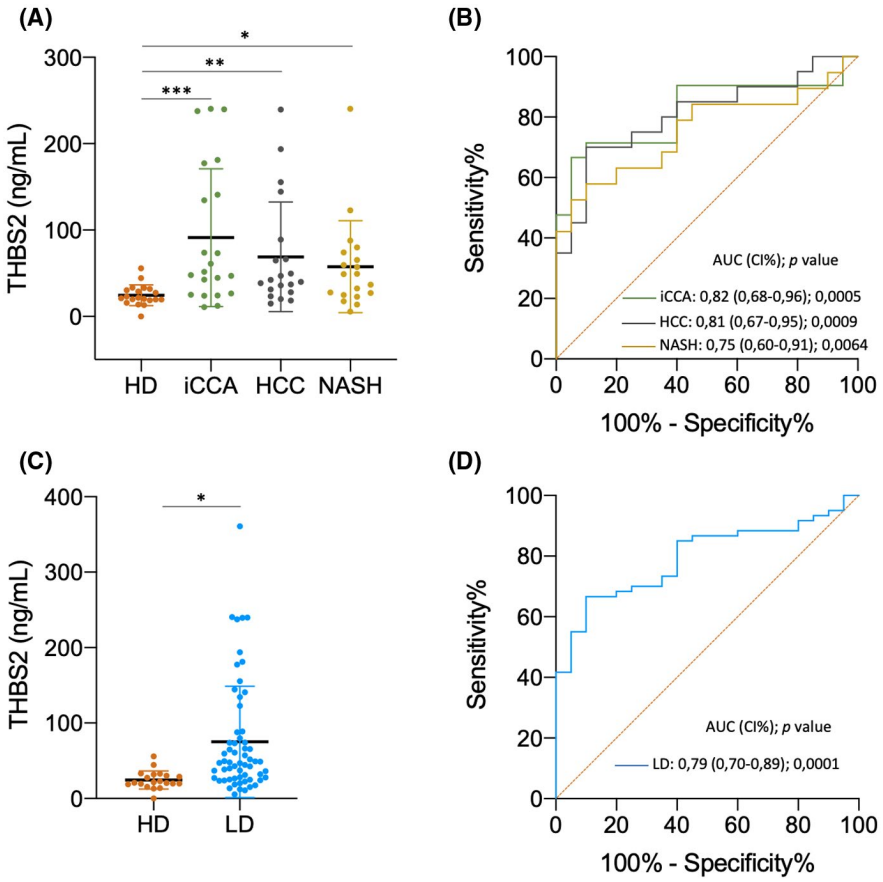

FIGURE 1 Serum thrombospondin-2 (THBS2) levels in liver diseases. (A) Scatter dot plots of serum levels of THBS2 in healthy donors (HD; $n = 20$) and intrahepatic cholangiocarcinoma (iCCA; $n = 21$), HCC ($n = 20$), and NASH ($n = 19$) groups. (B) Receiver operator characteristic curves for THBS2 in serum samples for the indicated groups compared with HDs. (C) Scatter dot plots of serum levels of THBS2 in HD ($n = 20$) and liver disease (LD; $n = 60$) groups. (D) Receiver operator characteristic curves for THBS2 in serum samples for the LD group compared with HDs. Means and SD are indicated. Angle bisector represents the line of identity that marks the lower limit for a successful diagnostic test; area under the curve (AUC) is indicated; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ (Mann-Whitney *U*-test). Adapted from Carpino et al.[2]

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