Prognostic value of liver fibrotic markers in patients with heart failure

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Background: One of the major comorbidities in patients with heart failure (HF) is hepatic dysfunction, which may occur with prolonged hepatic hypoperfusion and congestion due to HF. Although several liver fibrotic markers are associated with prognosis in patients with HF, the optimal markers for outcome prediction remain unclear.

Purpose: The aim of this study was to simultaneously investigate the prognostic value of liver fibrotic markers and the associations between these markers and clinical parameters in HF patients without organic liver disease.

Methods: We prospectively examined 211 consecutive patients with chronic HF (116 male, mean age 66 ± 14 years, LVEF 48 ± 17%) between April 2018 and August 2021, excluding those with organic liver disease, using liver magnetic resonance imaging and ultrasound. We measured seven representative liver fibrotic markers, including hyaluronic acid, type III procollagen N-terminal peptide (P-III-P), type IV collagen 7s domain, mac-2 binding protein glycosylation isomer (M2BPGi), platelet ratio index (APRI), fibrosis 4 index (FIB-4), and FibroIndex. The primary outcome of interest was the composite of all-cause death and hospitalisation for HF.

Results: During a median follow-up period of 747 (interquartile range 465-1042) days, the primary outcome occurred in 45 patients (21%), including 15 (7%) all-cause deaths and 30 (14%) hospitalisations for HF. Patients with higher hyaluronic acid and P-III-P levels showed a significantly higher incidence of the primary outcome than those without (P <0.001 and P = 0.005, respectively). Multivariable Cox regression analysis showed that hyaluronic acid and P-III-P levels were independently associated with the risk of the primary outcome (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.18-2.87 and HR 2.89, 95% CI 1.32-6.34, respectively) even after adjustment for the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, whereas other five liver fibrotic markers were not associated with the primary outcome. Discriminative value of the MAGGIC score for the primary outcome was significantly increased by adding hyaluronic acid and P-III-P levels (Harrel’s c-statistics; from 0.717 to 0.752 and 0.745, respectively) with significant net reclassification improvement (38% and 52%, respectively). Hyaluronic acid was predominantly correlated with age, haemoglobin, serum albumin, troponin T, N-terminal pro-brain natriuretic peptide (NT-proBNP), and pulmonary artery compliance (Figure). P-III-P levels were correlated with haemoglobin, estimated glomerular filtration rate, alkaline phosphatase, and NT-proBNP levels (Figure). P-III-P levels were correlated with haemoglobin, estimated glomerular filtration rate, alkaline phosphatase, and NT-proBNP levels (Figure).

Conclusion: Among the representative liver fibrotic markers, hyaluronic acid and P-III-P might be optimal for outcome prediction in HF patients without organic liver disease. Hyaluronic acid and P-III-P levels were predominantly associated with several key prognostic indicators of HF simultaneously.

Figure. Heatmap displaying the correlation between liver fibrotic markers and clinical parameters