ORIGINAL RESEARCH

Prognostic Value of Hepatic Native T1 and Extracellular Volume Fraction in Patients with Pulmonary Arterial Hypertension

Jiajun Guo, BMSc*; Lili Wang, BMSc*; Jiaqi Wang, BMSc; Ke Wan, MD; Chao Gong, MD; Xiaoling Chen, BMSc; Jinghua Guo, BMSc; Yuanwei Xu, MD; Juan He, BMSc; Lidan Yin, BMSc; Shoufang Pu, BMSc; Bi Wen, BMSc; Chen Chen, MD; Yuchi Han, MD; Yucheng Chen, MD

BACKGROUND: Right heart failure may lead to impaired liver perfusion and venous congestion, resulting in different extents of liver fibrosis. However, whether hepatic tissue deterioration determined by native T1 mapping and extracellular volume fraction using cardiac magnetic resonance imaging is associated with poor outcomes in patients with pulmonary arterial hypertensive remains unclear.

METHODS AND RESULTS: A total of 131 participants with pulmonary arterial hypertension (mean age, 36±13 years) and 64 healthy controls (mean age, 44±18) between October 2013 and December 2019 were prospectively enrolled. Hepatic native T1 and extracellular volume fraction values were measured using modified Look–Locker inversion recovery T1 mapping sequences. The primary end point was all-cause mortality; the secondary end point was all-cause mortality and repeat hospitalization attributable to heart failure. Cox regression models and Kaplan–Meier survival analysis were used to identify the association between variables and clinical outcome. During a median follow-up of 34.5 months (interquartile range: 25.3–50.8), hepatic native T1 (hazard ratio per 30-ms increase, 1.22 [95% CI, 1.07–1.39]; \(P=0.003\)) and extracellular volume fraction (hazard ratio per 3% increase, 1.18 [95% CI, 1.04–1.34]; \(P=0.010\)) values were associated with a higher risk of death. In the multivariate Cox model, hepatic native T1 value (hazard ratio per 30-ms increase, 1.15 [95% CI, 1.04–1.27]; \(P=0.009\)) remained as an independent prognostic factor for the secondary end point.

CONCLUSIONS: Hepatic T1 mapping values were predictors of adverse cardiovascular events in participants with pulmonary arterial hypertension and could be novel imaging biomarkers for poor prognosis recognition.

Key Words: cardiovascular magnetic resonance — hepatic T1 mapping — prognosis — pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive disease leading to right heart failure and death. Therefore, evaluation of right heart function is crucial in both the diagnosis and treatment of PAH.

Right heart failure may lead to impaired liver perfusion and venous congestion, resulting in differing extents of liver fibrosis depending on the degree of right heart failure. The extent of liver fibrosis is associated with right atrial pressure, right atrial dilation, and right ventricular (RV) dilation. A retrospective study including 9455 patients with pulmonary hypertension showed that the cumulative incidence rates of nonalcoholic fatty liver disease were significantly higher in patients with pulmonary hypertension (7.3%) than in those without pulmonary hypertension (3.5%; log-rank test, \(P<0.001\)). Furthermore, the former patient group was more likely to develop liver cirrhosis than was the latter group. The gold standard for the diagnosis and
staging of liver fibrosis is liver biopsy; however, less invasive and time-consuming and cost-effective diagnostic methods such as transient elastography are preferred. Nevertheless, both liver biopsy and transient elastography can only provide information on liver injury. In previous studies, T1 mapping sequences of cardiac magnetic resonance imaging (MRI) were a powerful tool for the evaluation of myocardial fibrosis and useful in splenic, skeletal muscle, hepatic, inflammation, edema, and fibrosis evaluations. Furthermore, hepatic T1 mapping analysis can distinguish different degrees of congestive hepatopathy and is strongly correlated with liver stiffness validated by magnetic resonance elastography. Evaluation of liver involvement by hepatic T1 mapping analysis may afford additional benefits to patients with right heart failure, especially to those with PAH.

We hypothesized that patients with higher hepatic native T1 and extracellular volume fraction (ECV) values present poor clinical outcomes. The aim of this study was to evaluate the prognostic significance of hepatic T1 mapping values derived from cardiac MRI in patients with PAH.

**METHODS**

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was approved by the ethics committee of West China Hospital, and registered in the Chinese clinical trial registry (ChiCTR1800019314 and ChiCTR1900025518). All participants underwent the same cardiac MRI and right heart catheterization protocol and provided written informed consent.

**Subjects and Study Design**

Participants diagnosed with PAH were prospectively and consecutively recruited between October 2013 and December 2019 at West China Hospital. All PAH diagnoses were in accordance with the criteria established per the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines. The inclusion criteria were as follows: (1) participants with mean pulmonary arterial pressure $\geq 25$ mm Hg, pulmonary artery wedge pressure $\leq 15$ mm Hg, and pulmonary vascular resistance $>3$ Wood units; and (2) participants who underwent cardiac MRI within 72 hours of right heart catheterization. The exclusion criteria were as follows: (1) participants with poor-quality cardiac MRI images; (2) participants with complex congenital heart disease types including transposition of the great arteries, double-outlet right ventricle, and univentricular heart; (3) participants $<18$ years of age; and (4) participants diagnosed with hepatitis B or C or other hepatic diseases that may lead to liver cirrhosis. Meanwhile, 64 healthy volunteers who underwent cardiac MRI were recruited as controls. A portion of participants have been previously reported in a study of RV eccentricity index (n=57) and RV remodeling in Eisenmenger Syndrome (n=46).

**Image Acquisition**

Cardiac MRI was performed on a 3.0-T scanner (Magnetom Tim Trio; Siemens Healthineers, Erlangen, Germany) with a 32-channel phased-array cardiac coil during breath-holding and electrocardiographic gating. Modified Look–Locker inversion recovery sequences were performed before and after contrast administration. Steady-state free precession was used for cine image acquisition along consecutive short axes from the base to the apex, as well as 2-, 3-, and 4-chamber views along the long axes according to a standardized protocol. ECV values were calculated using serum hematocrit measured within 72 hours after the cardiac MRI scan.
Image Analysis
Biventricular volumes and ejection fraction were analyzed using dedicated software (QMass version 8.1; Medis Medical Imaging Systems, Leiden, the Netherlands) in accordance with the standardized protocol of the Society of Cardiovascular Magnetic Resonance postprocessing guideline.21 Biventricular functional parameters were analyzed by carefully delineating endocardial and epicardial contours of the myocardium, including papillary muscles and trabeculations but no epicardial fat. Biventricular volumes were indexed to the body surface area. The right atrial area was measured at the end-systolic phase. All image analyses were initially blindly executed by J.G. (with 3 years of MRI experience) and L.W. (with 5 years of MRI experience). The controversial results were checked blindly by senior cardiac MRI reader Y.C. (with more than 10 years of CMR experience).

RV free wall strain and right atrial (RA) global longitudinal strain were analyzed on the four-chamber view along the long axes by using QStrain software (version 3.0, Medis). Endocardial contours were carefully delineated on RV end-diastolic images and then automatically tracked. Manual adjustments were needed for deviations of the tracked contours. Finally, a contour tracking video was generated, and checked values of RV free wall strain and RA global longitudinal strain were recorded.

Three regions of interest were carefully delineated in the same location in the pre- and postcontrast T1 mapping sequence in the liver parenchyma. Fat and blood vessels in the liver were not included in the regions of interest (Figure 1). Mean T1 values of 3 hepatic regions of interest in the pre- and postcontrast T1 mapping sequences were recorded. Hematocrit was evaluated within 72 hours after cardiac MRI. The hepatic ECV value was calculated as: Hepatic ECV value=$\kappa \times (1-\text{hematocrit}), \kappa = [(1/\text{hepatic post-contrast T1})-(1/\text{hepatic native T1})]/[(1/\text{blood after contrast T1})-(1/\text{blood native T1})]$ (more details are shown in Data S1).

Right Heart Catheterization
Right heart catheterization was performed using a 5F transfemoral catheter under local anesthesia in accordance with the standard procedure.22 The pressure value for the superior vena cava, and RA, RV, pulmonary blood vessel, left atrial, and left ventricular pressures were recorded when stable readings were obtained (more details are shown in Data S1).

Figure 1. Hepatic native T1 and ECV values measured by cardiac magnetic resonance. A, B Pre- and post-contrast T1 mapping images of a patient with PAH. C, D Pre- and postcontrast T1 mapping images of a healthy volunteer. ECV indicates extracellular volume fraction; and PAH, pulmonary arterial hypertension.
Follow-up and Clinical Outcomes

All participants underwent regular follow-ups over the phone or by visiting the clinic every 3 to 6 months after the baseline visit, in accordance with guidelines. The primary end point was defined as all-cause mortality. The secondary end point was defined as a combination of all-cause mortality and heart failure–related repeat hospitalization. Time to event was defined as the interval between the time of the right heart catheterization and the time of the event.

Statistical Analysis

The normality of variables was assessed by the Kolmogorov–Smirnov method. All continuous variables are expressed as mean (SD) or median (interquartile range) values. All categorical variables are presented as percentages. Independent sample t-test and Mann–Whitney U test were used to compare continuous variables, and the χ² test was used for categorical variables. Pearson’s and Spearman’s rank correlation coefficients were used to assess bivariate correlation depending on the normality of variables. Variables related to adverse cardiac events were identified by univariate Cox analysis. Forward stepwise multivariate Cox analyses with entry and removal P values of 0.05 and 0.10 were performed to validate the independent prognostic value of hepatic native T1 and ECV values. Receiver operating characteristic curves were used to determine cutoff values using the Youden method. Two-tailed P values of <0.05 were defined as statistically significant. Statistical analyses were performed using SPSS 26.0 (IBM, Armonk, NY) and R software (version 4.0.1; R Project for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and Other Characteristics

A total of 131 participants and 64 healthy volunteers were included (Figure 2). The mean age of PAH participants was 36.4±13.7 years, and 37 (28.0%) of them were men. The mean age of healthy volunteers was 42.8±17.9 years, and 33 (51.6%) of them were men. The mean age for PAH diagnosis was 34.8±13.2 years. The cohort was composed of 88 participants (67.4%) with congenital heart disease–related PAH, 12 participants (9.1%) with connective tissue disease–related PAH, and 31 participants (23.5%) with idiopathic PAH. A total of 103 participants were treatment naïve, while 90 PAH participants underwent monotherapy, 31 underwent combination therapy, and 10 underwent no medical therapy after a clinical visit at West China Hospital.

The demographic, clinical, hemodynamic, and cardiac MRI parameters of PAH participants and healthy volunteers are shown in Table 1 and Table S1. A mean RA pressure of 10 mm Hg was used as the cut-off value for evaluation of compensation and decomposition of PAH participants. Participants with mean RA pressure ≥10 mm Hg had higher hepatic native T1 values, higher hepatic ECV values, higher NT-proBNP (N-terminal pro-B-type natriuretic peptide), larger RA areas, lower SvO₂ values, and a lower 6-minute walk distance (6MWD).

Hepatic Native T1 Value in Evaluating Liver Dysfunction and Disease Severity

Hepatic native T1 and ECV values were both significantly higher in PAH participants than in healthy volunteers (hepatic native T1 value: 831.0±110.4 ms

Figure 2. Flow diagram shows included participants with PAH and patients who were excluded by exclusion criteria.

CMR indicates cardiac magnetic resonance; PAH, pulmonary arterial hypertension; and RHC, right heart catheterization.
### Table 1. Demographic Information of Patients With PAH and Healthy Controls

| Characteristic                  | PAH patients (n=131) | RAP<10 mmHg (n=84) | RAP≥10 mmHg (n=44) | Healthy controls (n=64) |
|--------------------------------|----------------------|--------------------|--------------------|------------------------|
| Age, y, mean (SD)              | 36 (13)              | 35 (14)            | 40 (13)*            | 44 (18)                |
| Male patients, n (%)           | 37 (28.2)            | 21 (25.0)          | 15 (34.1)           | 33 (51.6)              |
| BMI, kg/m², mean (SD)          | 21.0 (3.6)           | 20.9 (3.6)         | 21.4 (3.5)          | 22.3 (2.8)             |
| BSA, m², mean (SD)             | 1.6 (0.2)            | 1.6 (0.2)          | 1.6 (0.2)           | 1.6 (0.2)              |
| Age at diagnosis, y, mean (SD) | 34.6 (13.0)          | 32.9 (12.6)        | 38.6 (13.2)*        | ...                    |
| CHD-PAH                        | 88 (67.2)            | 53 (63.1)          | 32 (72.7)           | ...                    |
| CTD-PAH                        | 12 (9.2)             | 9 (10.7)           | 3 (6.8)             | ...                    |
| Idiopathic PAH                 | 31 (23.7)            | 22 (26.2)          | 9 (20.5)            | ...                    |
| Low risk                       | 30 (22.9)            | 21 (25.0)          | 9 (20.5)            | ...                    |
| Moderate risk                  | 64 (48.9)            | 38 (45.2)          | 24 (54.5)           | ...                    |
| High risk                      | 34 (26.0)            | 24 (28.6)          | 10 (22.7)           | ...                    |
| I                              | 13 (9.9)             | 10 (11.9)          | 3 (6.8)             | ...                    |
| II                             | 75 (57.3)            | 49 (58.3)          | 24 (54.5)           | ...                    |
| III                            | 28 (21.4)            | 16 (19.0)          | 12 (27.3)           | ...                    |
| IV                             | 2 (1.5)              | 1 (1.2)            | 1 (2.3)             | ...                    |
| 6MWD, m, mean (SD)             | 433.6 (95.9)         | 447.4 (85.8)       | 405.6 (109.3)*      | ...                    |
| NT-proBNP, pg/mL, median (interquartile range) | 473.0 (149.0– 1780.5) | 436.5 (133.3– 1077.0) | 1398.0 (247.0–3224.0)* | ... |
| Troponin T, ng/L, median (interquartile range) | 9.5 (6.3–15.4) | 8.3 (5.7–14.3) | 11.9 (7.5–17.7)* | ... |
| TBIL, μmol/L, mean (SD)        | 18.9 (10.7)          | 17.1 (8.6)         | 21.9 (13.1)*        | ...                    |
| DBIL, μmol/L, mean (SD)        | 7.1 (6.5)            | 5.7 (3.1)          | 9.8 (8.6)*          | ...                    |
| IBIL, μmol/L, mean (SD)        | 11.7 (6.1)           | 11.4 (6.2)         | 12.0 (5.3)          | ...                    |
| ALP, μmol/L, mean (SD)         | 73.1 (28.7)          | 69.8 (26.9)        | 79.7 (31.7)         | ...                    |
| GGT, μmol/L, mean (SD)         | 40.9 (39.3)          | 34.0 (32.4)        | 54.6 (48.0)*        | ...                    |
| ALT, μmol/L, mean (SD)         | 22.6 (19.2)          | 19.9 (11.6)        | 28.0 (28.1)         | ...                    |
| AST, μmol/L, mean (SD)         | 26.1 (14.2)          | 24.3 (12.1)        | 29.8 (17.3)*        | ...                    |
| Creatinine, μmol/L, mean (SD)  | 64.3 (15.4)          | 63.7 (15.6)        | 64.8 (15.4)         | ...                    |
| eGFR, ml/min per 1.73m², mean (SD) | 110.2 (17.7) | 112.4 (17.4) | 105.2 (17.7) | ... |
| Endothelin-receptor antagonists | 19 (14.5)            | 9 (10.7)           | 10 (22.7)           | ...                    |
| Phosphodiesterase type 5 inhibitors | 7 (5.3)              | 1 (1.2)            | 6 (13.6)*           | ...                    |
| Oral beraprost sodium          | 5 (3.8)              | 2 (2.4)            | 3 (6.8)             | ...                    |
| Endothelin-receptor antagonists | 112 (85.5)           | 73 (86.9)          | 37 (84.1)           | ...                    |
| Phosphodiesterase type 5 inhibitors | 35 (26.7)            | 24 (28.6)          | 11 (25.0)           | ...                    |
| Monotherapy                    | 90 (68.7)            | 56 (66.7)          | 32 (72.7)           | ...                    |
| Combination therapy            | 31 (23.7)            | 22 (26.2)          | 9 (20.5)            | ...                    |
| No medication therapy          | 10 (7.6)             | 6 (7.1)            | 3 (6.8)             | ...                    |
| mRAP, mmHg, mean (SD)          | 8.0 (5.3)            | 5.0 (2.7)          | 13.9 (3.8)*         | ...                    |
| mPAP, mmHg, mean (SD)          | 61.4 (18.6)          | 59.1 (17.5)        | 65.5 (20.3)         | ...                    |
| PVR, Woods unit, mean (SD)     | 17.3 (15.1)          | 15.2 (9.4)         | 20.6 (21.2)         | ...                    |
| Cardiac index, L/min per m², mean (SD) | 2.1 (0.7)        | 2.1 (0.7)          | 2.0 (0.7)           | ...                    |
| SvO₂, %, mean (SD)             | 63.3 (8.6)           | 64.6 (15.6)        | 60.8 (9.0)*         | ...                    |
| RVEDVI, mL/m², mean (SD)       | 117.7 (59.2)         | 118.9 (58.9)       | 116.7 (61.2)        | 73.8 (16.6)            |
| RVESVI, mL/m², mean (SD)       | 76.8 (47.7)          | 77.7 (48.2)        | 76.3 (48.1)         | 34.5 (10.6)            |
| RVEF, %, mean (SD)             | 37.2 (13.3)          | 36.7 (12.9)        | 37.6 (14.6)         | 55.7 (13.1)            |
| LVEDVI, mL/m², mean (SD)       | 79.5 (53.5)          | 79.6 (50.2)        | 71.4 (45.9)         | 78.2 (12.6)            |
| LVESVI, mL/m², mean (SD)       | 36.8 (27.5)          | 36.9 (26.0)        | 32.9 (23.7)         | 29.6 (7.3)             |
| LVEF, %, mean (SD)             | 54.7 (9.4)           | 54.4 (9.4)         | 55.3 (9.8)          | 62.5 (4.8)             |

(Continued)
versus 717.3±70.5 ms, P<0.001; hepatic ECV value: 33.3±8.3% versus 30.3±5.1%, P=0.02).

Hepatic native T1 value was not related to alanine aminotransferase or aspartate aminotransferase concentrations, which suggested that liver involvement attributable to right heart failure may not lead to necrosis of hepatocytes. However, gamma-glutamyl transpeptidase, a biomarker that increases during liver congestion, was related to the hepatic native T1 value (r=−0.19, P=0.026), confirming the clinical significance of hepatic native T1 value elevation to some extent.

Table 2. Correlation Between Hepatic Native T1 Value and Clinical Parameters

| Characteristic | PAH patients (n=131) | RAP<10 mmHg (n=84) | RAP≥10 mmHg (n=44) | Healthy controls (n=64) |
|----------------|----------------------|--------------------|--------------------|------------------------|
| RA area, cm², mean (SD) | 24.7 (9.1) | 22.6 (8.8) | 29.3 (11.3)* | ... |
| RV-FWS, %, mean (SD) | −19.6 (7.2) | −19.9 (7.1) | −19.5 (7.5) | ... |
| RAGLS, %, mean (SD) | 28.0 (12.1) | 29.2 (10.1) | 25.2 (15.2) | ... |
| Mean hepatic T1 value, ms | 834.0 (105.3) | 802.5 (98.4) | 897.3 (92.1)* | 717.3 (70.5) |
| Hepatic ECV value, % | 33.3 (8.3) | 32.2 (7.4) | 35.4 (9.7) | 30.3 (5.1) |

6MWD indicates 6-minute walk distance; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, peripheral arterial hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RAGLS, right atrial global longitudinal strain; RAP, right atrial pressure; RHC, right heart catheterization; RVESVi, right ventricular end-diastolic volume index; RVESVi, right ventricular global longitudinal strain; RVESVi, right ventricular end-systolic volume index; RV-FWS, right ventricular free wall strain; and TBIL, total bilirubin. *Statistically significant differences between the RAP<10 group and RAP 10 group.

Hepatic native T1 value was also related to ln (NT-proBNP) (r=0.38, P<0.001), 6MWD (r=−0.25, P=0.006), RA area (r=0.23, P=0.008), SvO₂ (r=−0.22, P=0.016), and mean RA pressure (r=0.45, P<0.001) (Table 2). A cutoff value of 881.90 ms defined by the Youden method for hepatic native T1 was used to define the normal native T1 group and elevated native T1 group. The elevated native T1 group showed significant elevation of gamma-glutamyl transpeptidase, NT-proBNP, and mean RA pressure; and reductions in 6MWD, SvO₂, RV free wall strain, and RA global longitudinal strain (Table 3). All of these parameters were confirmed to be valuable in evaluating patients’ risk stratification and disease severity, suggesting that elevation of the hepatic native T1 value was related to the disease process and finally led to poor prognosis.

Survival Analysis in PAH

During the median follow-up period of 34.5 months (interquartile range: 25.3–50.8 months), 21 participants (16.0%) reached the primary end point (all-cause mortality), and 57 participants (43.5%) reached the secondary end point (all-cause mortality, 21 patients; heart failure–related readmissions, 36 patients). The prognostic significance of risk stratification parameters in the 2015 European Society of Cardiology/European Respiratory Society model, liver function indexes, and RV parameters measured by cardiac MRI were analyzed using univariate Cox analyses (Table 4 and Table S2). Hepatic native T1 and ECV values were predictors for both primary and secondary end points. We showed that with every 30-ms increase in the hepatic native T1 value, participants’ mortality risk increased by 21.9%, while with every 3% increase in the hepatic ECV value, the mortality risk increased by 18.2%. In addition, we also developed a multivariate Cox model to validate the independent prognostic significance.
of hepatic native T1 and ECV values. The multivariate Cox model was limited in primary end point for the low occurrence of an event. After adjusting with ln (NT-proBNP), 6MWD, RV ejection fraction, RA area, and SvO2, an increase in the hepatic native T1 value (per 30- ms increase, hazard ratio, 1.15 [95% CI, 1.04–1.28]; \( P =0.005 \)) and 6MWD (per 1-m increase, hazard ratio, 0.99 [95% CI, 0.99–1.00]; \( P =0.044 \)) still remained independently prognostic for the secondary end point (Table 4).

The optimal hepatic native T1 cutoff values by the Youden method for identifying patients with primary end point were 881.90 ms. The Kaplan–Meier curves for survival free of the primary and secondary end points are shown in Figure 3. Patients with hepatic native T1 values >881.90 might have a higher risk of suffering from all-cause mortality.

**DISCUSSION**

The main findings of this study were as follows: (1) Hepatic native T1 and ECV values were abnormally increased in patients with PAH and associated with liver congestion and PAH severity; and (2) increased hepatic native T1 and ECV values were poor prognostic signs for all-cause mortality and heart failure readmissions.

Right heart failure may lead to blockage of venous drainage and increased central venous pressure, which can cause impaired liver perfusion and liver venous congestion. Thus, liver changes can be reasonably considered to be a marker reflecting the severity of right heart failure or even the prognosis of these patients. Liver biopsy or other noninvasive tools for detection of liver pathology changes are widely used in clinical practice to detect liver pathological changes but are limited in detecting myocardial changes.

Cardiac MRI examination is considered as the gold standard for heart function evaluation and has its merits in clarifying myocardial pathological changes, but the clinical significance of cardiac MRI goes far beyond these. In idiopathic inflammatory cardiomyopathy, effective treatment leads to dynamic changes in the T1, T2, and ECV values of skeletal muscles measured by cardiac MRI, which is considered an important tool in treatment monitoring. \(^1^1\) Thus, more attention is required to shed light on other potential aspects of the clinical significance of cardiac MRI.

The clinical significance of hepatic T1 mapping assessed by cardiac magnetic resonance has been shown in previous studies. \(^9^,1^2^,1^4^-1^6^,1^7^\) Hepatic native T1 and ECV values were shown to be elevated in patients with tetralogy of Fallot repair, Fontan palliation, and idiopathic dilated cardiomyopathy. \(^9^,1^2^-1^4^,1^6^-1^7^\) In addition, hepatic T1 mapping analysis can distinguish different degrees of congestive hepatopathy and is strongly correlated with liver stiffness validated by magnetic resonance elastography. \(^1^4^-1^6^-1^7^\) Bogaert et al\(^1^6^\) confirmed the feasibility of predicting right-sided filling status on the basis of liver relaxation times in patients with PAH and suggested its potential value in monitoring therapy response, but their study used a small retrospective

### Table 3. Differences in Clinical and Imaging Parameters Between Elevated and Normal Hepatic Native T1 Value Groups

| Parameter                        | Normal native T1 group* (n=91) | Elevated native T1 group* (n=40) | \( P \) value |
|----------------------------------|--------------------------------|---------------------------------|--------------|
| **Liver functional indexes**     |                                |                                 |              |
| ALT, \( \mu \text{mol/L}, \text{mean (SD)} \) | 20.9 (11.7) | 26.4 (29.6) | 0.921 |
| AST, \( \mu \text{mol/L}, \text{mean (SD)} \) | 24.6 (11.5) | 29.3 (18.6) | 0.304 |
| GGT, \( \mu \text{mol/L}, \text{mean (SD)} \) | 34.7 (33.1) | 54.7 (48.3) | 0.003 |
| **Disease severity indexes**     |                                |                                 |              |
| NT-pro BNP, pg/mL, median (interquartile range) | 345.0 (113.0–1046.0) | 1556.5 (388.5–3523.3) | <0.001 |
| 6MWD, m, mean (SD)               | 449.2 (99.9) | 396.7 (74.8) | 0.006 |
| SvO\(_2\), %, mean (SD)          | 65.2 (7.1)  | 58.8 (10.3) | 0.002 |
| mRAP, mm Hg, mean (SD)           | 6.8 (4.5)   | 10.7 (5.9)  | <0.001 |
| RA area, cm\(^2\), mean (SD)     | 23.8 (8.5)  | 26.9 (10.3) | 0.100 |
| **Right heart functional indexes** |                                 |                                 |              |
| RVEF, %, mean (SD)               | 38.4 (12.7) | 34.1 (14.6) | 0.106 |
| RV-FWS, %, mean (SD)             | −20.6 (7.2) | −17.3 (6.9) | 0.017 |
| RAGLS, %, mean (SD)              | 29.7 (11.5) | 23.8 (12.5) | 0.013 |

6MWD indicates 6-minute walk distance; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RA, right atrial; RAGLS, right atrial global longitudinal strain; RVEF, right ventricular ejection fraction; and RV-FWS, right ventricular free wall strain.

* A cutoff value of 881.90 ms for hepatic native T1 was used to define the normal native T1 group and elevated native T1 group.
cohort and provided no evidence for prognosis prediction, which requires further confirmation. In the current study, hepatic T1 mapping assessed by cardiac magnetic resonance, a novel imaging biomarker, was shown to be elevated in patients with PAH, related to disease severity, and had prognostic significance, also offering a novel method to monitor liver involvement in patients with PAH.

### Table 4. Univariate and Multivariate Cox Regression Analyses of Primary and Secondary End Points in All Patients With PAH

|                          | Primary end point | Secondary end point |
|--------------------------|-------------------|---------------------|
|                          | Unadjusted HR     | P value             | Unadjusted HR     | P value             | Adjusted HR     | P value             |
| Mean hepatic native T1 value, ms (per 30-ms increase) | 1.22 (1.07–1.39)  | 0.003               | 1.15 (1.06–1.25)  | 0.001               | 1.15 (1.04–1.27) | 0.009               |
| Hepatic ECV value, % (per 3% increase) | 1.18 (1.04–1.34)  | 0.010               | 1.09 (1.00–1.20)  | 0.048               |
| RVEF, % (per 1% increase) | 0.95 (0.92–0.99)  | 0.009               | 0.97 (0.95–0.99)  | 0.007               |
| RVEDVi, mL/m² (per 1 mL/m² increase) | 1.00 (1.00–1.01)  | 0.290               | 1.00 (1.00–1.01)  | 0.290               |
| RVESVi, mL/m² (per 1 mL/m² increase) | 1.01 (1.00–1.01)  | 0.046               | 1.01 (1.00–1.01)  | 0.048               |
| RA area, cm² (per 1 cm² increase) | 1.07 (1.03–1.12)  | <0.001              | 1.04 (1.01–1.07)  | 0.007               |
| RV-FWS, % (per 1% increase) | 1.094 (1.03–1.16) | 0.004               | 1.05 (1.02–1.09)  | 0.003               |
| RAGLS, % (per 1% increase) | 0.903 (0.86–0.95) | <0.001              | 0.96 (0.93–0.98)  | 0.001               |
| TBIL, μmol/L (per 1-μmol/L increase) | 1.04 (1.01–1.08)  | 0.007               | 1.01 (0.99–1.04)  | 0.390               |
| GGT, μmol/L (per 1-μmol/L increase) | 1.01 (1.01–1.02)  | <0.001              | 1.01 (1.00–1.01)  | 0.056               |
| ALT, μmol/L (per 1-μmol/L increase) | 1.01 (1.00–1.03)  | 0.007               | 1.01 (1.00–1.03)  | 0.188               |
| AST, μmol/L (per 1-μmol/L increase) | 1.03 (1.01–1.04)  | 0.003               | 1.02 (1.01–1.04)  | <0.001              |
| ln (NT-proBNP) (per 1 increase) | 1.98 (1.44–2.72)  | <0.001              | 1.40 (1.18–1.66)  | <0.001              |
| 6MWD (per 1 m increase) | 0.99 (0.99–1.00)  | 0.001               | 1.00 (0.99–1.00)  | 0.002               | 1.00 (0.99–1.00) | 0.044               |
| SvO₂, % (per 1% increase) | 0.93 (0.89–0.97)  | 0.002               | 0.96 (0.93–0.98)  | 0.002               |
| Cardiac index (per 1 L/min/m² increase) | 0.57 (0.28–1.17)  | 0.126               | 0.82 (0.54–1.22)  | 0.324               |
| mRAP (per 1 mmHg increase) | 1.10 (1.03–1.18)  | 0.008               | 1.04 (0.99–1.09)  | 0.176               |

6MWD indicates 6-minute walk distance; ALT, alanine transaminase; AST, aspartate aminotransferase; ECV, extracellular volume fraction; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; RA, right atrial; RAGLS, right atrial global longitudinal strain; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RV-FWS, right ventricular free wall strain; and TBIL, total bilirubin.

Adjusted HR: adjustment of ln (NT-proBNP), 6MWD, RVEF, RA area, and SvO₂.

Figure 3. Kaplan–Meier curves for patients with PAH.
A. Kaplan–Meier curves for survival and event-free survival of patients with PAH. B. Kaplan–Meier curves for the primary end point according to the cutoff value (881.90 ms) of hepatic native T1. The prognostic cutoff value of hepatic native T1 was defined by the Youden method. C. Kaplan–Meier curves for secondary end point according to the cutoff value (881.90 ms) of hepatic native T1. PAH indicates pulmonary arterial hypertension.
The clinical significance of cardiac structural, functional, and myocardial characterization parameters assessed by cardiac MRI in patients with PAH has been validated in a few previous studies.23–26 Most studies focused on right heart involvement in patients with PAH, but it may be difficult to analyze histological changes in the right ventricle because of the thin RV wall and limited spatial resolution of cardiac MRI.25,27Cardiac functional indexes, especially right heart functional indexes, are important in the prognostication of patients with PAH, but in the era of precise treatment, it may be too late to intervene until RV dysfunction occurs and novel imaging biomarkers are needed. The “liver-heart axis” signifies that the heart and liver are not only functionally related and anatomically in proximity but also pathologically linked. Chronic heart failure may lead to liver fibrosis validated by liver biopsy and often manifests as elevation of hepatic native T1 and ECV values,2,28 while liver cirrhosis may also lead to lower ventricular ejection fraction and diffuse myocardial fibrosis. The vicious circle involving liver and cardiac deterioration may lead to a poor prognosis, indicating the potential clinical value of liver functional or histological indexes in cardiac disease. In our study, patients with PAH with elevated hepatic native T1 and ECV values were more likely to suffer from adverse cardiovascular events, which may indicate the importance of managing liver function in patients with PAH during treatment.

Limitations

The degree of liver fibrosis or congestion in this study was not validated by liver biopsy or by using FibroScan. We may speculate that patients with PAH with higher hepatic native T1 and ECV values are more likely to suffer from cardiac events, but whether or not this progress is reversible with RA or ventricular function improvement or right-sided heart filling pressure reduction after guideline-directed medical therapy remains unclear and needs further study. Moreover, we predominantly included young and female patients because of the major inclusion of participants with PAH with congenital heart disease, which may not be representative for the PAH phenotype seen currently. The prognostic significance of hepatic T1 mapping analysis still needs further exploration and validation.

ARTICLE INFORMATION

Received April 3, 2022; accepted September 29, 2022.

Affiliations

Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China (J.G., L.W., J.W., C.G., Y.X., J.H., L.Y., S.P., B.W., Y.H.); Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (L.W.); Department of Geriatrics, West China Hospital, Sichuan University, Chengdu, China (K.W.); and Cardiovascular Medicine, Wexner Medical Center, College of Medicine, The Ohio State University, Columbus, Ohio (Y.H.).

Sources of Funding

This research was supported by the 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC18013).

Disclosures

None.

Supplemental Material

Data S1
Table S1
Table S2

REFERENCES

1. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoepfer MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation. 2020;141:678–693. doi: 10.1161/circulation.naha.116.022362
2. Dai DF, Swanson PE, Krieger EV, Liou IW, Carithers RL, Yeh MM. Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. Mod Pathol. 2014;27:1552–1558. doi: 10.1038/modpa thol.2014.79
3. Jördens MS, Luedde M, Roderburg C, Demir M, Luedde T, Kostev K, Loosen SH. Pulmonary hypertension is associated with an increased incidence of NAFLD: a retrospective cohort study of 18,910 patients. J Intern Med. 2021;289:886–983. doi: 10.1111/jjim.13357
4. Serra-Burriel M, Graupera I, Torán P, Thiele M, Roulot D, Wai-Sun Wong V, Neil Guha I, Fabrellas N, Arslanow A, Expósito C, et al. Transient elastography for screening of liver fibrosis: cost-effectiveness analysis from six prospective cohorts in Europe and Asia. J Hepatol. 2019;71:1141–1151. doi: 10.1016/j.jhep.2019.08.019
5. Ilic I, Milovanovic T. The risk-benefit assessment of liver biopsy in times of non-invasive screening for liver fibrosis. J Hepatol. 2020;73:701–702. doi: 10.1016/j.jhep.2020.05.017
6. Li S, Zhou D, Sirajuddin A, He J, Xu J, Zhuang B, Huang J, Yin G, Fan X, Wu W, et al. T1 mapping and extracellular volume fraction in dilated cardiomyopathy: a prognosis study. JACC Cardiovasc Imaging. 2021;15:578–590. doi: 10.1016/j.jcmg.2021.07.023
7. Li Y, Liu X, Yang F, Wang J, Xu Y, Fang T, Pu L, Zhou X, Han Y, Chen Y. Prognostic value of myocardial extracellular volume fraction evaluation based on cardiac magnetic resonance T1 mapping with T1 long and short in hypertrophic cardiomyopathy. Eur Radiol. 2021;31:4557–4567. doi: 10.1007/s00330-020-07650-7
8. Xu J, Zhuang B, Sirajuddin A, Li S, Huang J, Yin G, Song L, Jiang Y, Zhao S, Lu M. MRI T1 mapping in hypertrophic cardiomyopathy: evaluation in patients without late gadolinium enhancement and hemodynamic obstruction. Radiol. 2020;294:275–286. doi: 10.1148/radiol.2019100651
9. Chacko L, Boldrini M, Martone R, Law S, Martinez-Naharro A, Hutt DF, Kotecha T, Patel RK, Razvi Y, Rezk T, et al. Cardiac magnetic resonance-derived extracellular volume mapping for the quantification of hepatic and splenic amyloid. Circ Cardiovasc Imaging. 2021;14:CIRCIMAGING121012506. doi: 10.1161/CIRCIMAG ING.121.012506
10. Liu A, Wijesundara RS, Ariga R, Mahmood M, Leveilt E, Greiser A, Petrou M, Krasopoulos G, Forfar JC, Kharbanda RK, et al. Splenic T1-mapping: a novel quantitative method for assessing adenosine stress adequacy for cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2017;19:1. doi: 10.1186/s12968-016-0318-2
11. Xu Y, Sun J, Wan K, Yu L, Wang J, Li W, Yang F, Sun J, Cheng W, Mui D, et al. Multiparametric cardiovascular magnetic resonance characteristics and dynamic changes in myocardial and skeletal muscles in idiopathic inflammatory cardiomyopathy. J Cardiovasc Magn Reson. 2020;22:22. doi: 10.1186/s12968-020-00616-0
12. Bogaert J, Symons R, Rafouti-Stergiou P, Droogwe N, Dresselaers T, van der Loo M. Assessment of right-sided heart failure in patients with dilated cardiomyopathy using magnetic resonance relaxometry of the liver. Am J Cardiol. 2021;124:103–111. doi: 10.1016/j.amjcard.2021.03.012
13. Dolan RS, Stillman AE, Davarpanah AH. Feasibility of hepatic T1-mapping and extracellular volume quantification on routine cardiac magnetic resonance imaging in patients with infiltrative and systemic disorders. Acad Radiol. 2021;28:S100–S109. doi: 10.1016/j.acra.2021.08.018
14. Kazour I, Serai SD, Xanthakos SA, Fleck RJ. Using T1 mapping in cardiovascular magnetic resonance to assess congestive hepatopathy. *Abdom Radiol*(NY). 2018;43:2679–2685. doi: 10.1007/s00261-018-1528-x

15. Bogaert J, Claessen G, Dresselaers T, Masri PG, Belge C, Delcroix M, Symons R. Magnetic resonance relaxometry of the liver - a new imaging biomarker to assess right heart failure in pulmonary hypertension. *J Heart Lung Transplant*. 2021;41:86–94. doi: 10.1016/j.healun.2021.09.005

16. Ramachandran P, Serai SD, Veldman GR, Lang SM, Mazur W, Trout AT, Dillman JR, Fleck RJ, Taylor MD, Alsaeid T, et al. Assessment of liver T1 mapping in fontan patients and its correlation with magnetic resonance elastography-derived liver stiffness. *Abdom Radiol*(NY). 2019;44:2403–2408. doi: 10.1007/s00261-019-01990-9

17. Huber AT, Razakamanantsoa L, Lamy J, Giron A, Cluzel P, Kachenoura N, Redheul A. Multiparametric Differentiation of Idiopathic Dilated Cardiomyopathy With and Without Congestive Heart Failure by Means of Cardiac and Hepatic T1-Weighted MRI Mapping. *AJR Am J Roentgenol*. 2020;215:79–86. doi: 10.2214/ajr.19.22009

18. Gaïlé N, Humbert M, Vachieri JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vachiery JL, Teixidor I, et al. 2016 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119. doi: 10.1093/eurheartj/ehv317

19. Wang L, Chen X, Wan K, Gong C, Li W, Xu Y, Wang J, He J, Wen B, Han Y, et al. Diagnostic and prognostic value of right ventricular eccentricity index in pulmonary artery hypertension. *Pulm Circ*. 2020;10:20458940198999778. doi: 10.1177/20458940198999778

20. Gong C, He S, Chen X, Wang L, Guo J, He J, Yin L, Chen C, Han Y, Chen Y. Diverse right ventricular remodeling evaluated by MRI and prognosis in eisenmenger syndrome with different shunt locations. *J Magn Reson Imaging*. 2021;55:1478–1488. doi: 10.1002/jmri.27791

21. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:17. doi: 10.1186/s12968-020-00607-1

22. Callan P, Clark AL. Right heart catheterisation: indications and interpretation. *Heart*. 2016;102:147–157. doi: 10.1136/heartjnl-2015-307786

23. Dong Y, Pan Z, Wang D, Lv J, Fang J, Xu R, Ding J, Cui X, Xie X, Wang X, et al. Prognostic value of cardiac magnetic resonance-derived right ventricular remodeling parameters in pulmonary hypertension: a systematic review and meta-analysis. *Circ Cardiovasc Imaging*. 2020;13:e010568. doi: 10.1161/circimaging.120.010568

24. Leng S, Dong Y, Wu Y, Zhao X, Ruan W, Zhang G, Allen JC, Koh AS, Tan RS, Yip JW, et al. Impaired cardiovascular magnetic resonance-derived rapid semiautomated right atrial longitudinal strain is associated with decompensated hemodynamics in pulmonary arterial hypertension. *Circ Cardiovasc Imaging*. 2019;12:e006882. doi: 10.1161/circimaging.118.008582

25. Saunders LC, Johns CS, Stewart NJ, Oram CJE, Capener DA, Puntmann VO, Elliot CA, Condiffe RC, Kiely DG, Graves MJ, et al. Diagnostic and prognostic significance of cardiovascular magnetic resonance native myocardial T1 mapping in patients with pulmonary hypertension. *J Cardiovasc Magn Reson*. 2018;20:78. doi: 10.1186/s12968-018-0501-8

26. García-Álvarez A, García-Lunar I, Pereda D, Fernández-Jimenez R, Sánchez-González J, Mirels JG, Nuño-Ayala M, Sánchez-Quintana D, Fernández-Friera L, García-Ruiz JM, et al. Association of myocardial T1-mapping CMR with hemodynamics and RV performance in pulmonary hypertension. *J Am Coll Cardiol Imag*. 2015;8:76–82. doi: 10.1016/j.jcmg.2014.08.012

27. Alabed S, Saunders L, Garg P, Shahin Y, Alandejani F, Rolf A, Puntmann VO, Nagel E, Wild JM, Kiely DG, et al. Myocardial T1-mapping and extracellular volume in pulmonary arterial hypertension: a systematic review and meta-analysis. *Magn Reson Imaging*. 2021;79:66–75. doi: 10.1016/j.mri.2021.03.011

28. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol*. 2015;28:932–943. doi: 10.1038/modpathol.2015.40
SUPPLEMENTAL MATERIAL
Data S1. Supplemental Materials and Methods

Cardiovascular MRI scan protocol

Cardiac MRI was performed on a 3.0-T scanner (Magnetom Tim Trio; Siemens Healthineers, Erlangen, Germany) with a 32-channel phased-array cardiac coil during breath-holding and electrocardiography (ECG) gating. Modified Look-Locker inversion recovery (MOLLI) sequences were performed before and after contrast administration. Steady-state free precession was used for cine images acquisition along consecutive short axes from the base to the apex, as well as two-, three-, and four-chamber views along the long axes according to a standardized protocol\textsuperscript{(19)}. The typical scan parameters were as follows: repetition time (TR), 2.6 ms; echo time (TE), 1.3 ms; flip angle, 50°; field of view, 320–340 mm\(^2\); matrix, 256 × 144; and slice thickness, 8 mm with no gap. T1 mapping images were acquired with a motion-corrected MOLLI recovery sequence with a 5b(3b)3b (b: heartbeat) scheme for native T1 mapping (used T1 long sequence) and 4b(1b)3b(1b)2b scheme for post-T1 mapping (used T1 short sequence). Basal, mid, and apical short-axis and four-chamber T1 mapping slices were scanned. T1 mapping images were acquired before and 15 min after the injection of gadolinium agent. The typical scan parameters for the MOLLI sequence were as follows: TR, 2.9 ms; TE, 1.12 ms; flip angle, 35°; bandwidth, 930 Hz/pixel; TI of the first experiment, 100 ms; TI increment, 80 ms; parallel imaging factor, 2; matrix size, 192 × 144; in-plane spatial resolution, 2.4 mm × 1.8 mm; total acquisition time, 11 heartbeats. ECV values were calculated using serum hematocrit (HCT) measured within 72 h since the cardiac MRI scan.
Right heart catheterization scan protocol

RHC was performed using a 5F transfemoral catheter under local anesthesia in accordance with the standard procedure. Blood samples were collected from systemic and pulmonary circulation, and then, oxygen saturation was measured. Cardiac output (CO) was calculated using the Fick method, and the cardiac index was calculated as CO/BSA. Pulmonary vascular resistance (PVR) was calculated using the following formula: 

\[ PVR = \frac{\text{mean pulmonary arterial pressure (mPAP)} - \text{pulmonary capillary wedge pressure (PCWP)}}{\text{CO}}. \]

Subgroup analysis

Although all PAH patients with liver complications were excluded in this study, CTD-PAH may also lead to subclinical liver changes that are ignored clinically. We performed a subgroup survival analysis of CHD-PAH in this study to minimize the bias of cohort selection.
Table S1. Comparison between age- and sex-matched control group and PAH patient

| Characteristic               | All PAH (n=131) | Healthy controls (n=44) | p-value |
|-----------------------------|-----------------|-------------------------|---------|
| Age, mean (SD)              | 36 (13)         | 38 (15)                 | 0.405   |
| Male patients, n (%)        | 37 (28.2)       | 13 (29.5)               | 0.869   |
| BMI, kg/m², mean (SD)       | 21.0 (3.6)      | 22.0 (2.8)              | 0.090   |
| BSA, m², mean (SD)          | 1.6 (0.2)       | 1.6 (0.2)               | 0.159   |
| RVEDVi, ml/m², mean (SD)    | 117.7 (59.2)    | 73.3 (17.5)             | <0.001  |
| RVESVi, ml/m², mean (SD)    | 76.8 (47.7)     | 34.8 (11.0)             | <0.001  |
| RVEF, %, mean (SD)          | 37.2 (13.3)     | 54.0 (7.1)              | <0.001  |
| LVEDVi, ml/m², mean (SD)    | 79.5 (53.5)     | 78.8 (13.7)             | 0.369   |
| LVESVi, ml/m², mean (SD)    | 36.8 (27.5)     | 30.3 (7.2)              | 0.002   |
| LVEF, %, mean (SD)          | 54.7 (9.4)      | 62.0 (4.2)              | <0.001  |
| Mean hepatic T1 value, ms   | 834.0 (105.3)   | 729.5 (66.6)            | <0.001  |
| Hepatic ECV value, %        | 33.3 (8.3)      | 30.3 (7.2)              | 0.007   |

BMI: body mass index; BSA: body surface area; RVEDVi: right ventricular end-diastolic volume index; RVESVi: right ventricular end-systolic volume index; RVEF: right ventricular ejection fraction; LVEDVi: left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction.
Table S2. Subgroup univariate and multivariate cox regression analyses of primary and secondary endpoints in patients with CHD-PAH

|                                | Primary endpoint | Secondary endpoint |
|--------------------------------|------------------|--------------------|
|                                | Unadjusted HR (95% CI) | p-value | Unadjusted HR (95% CI) | p-value | Adjusted HR (95% CI) * | p-value * |
| Mean hepatic native T1 value, ms (per 30 ms increase) | 1.31 (1.09-1.56) | 0.003 | 1.15 (1.01-1.30) | 0.029 | 0.053 |
| Hepatic ECV value, % (per 3% increase) | 1.19 (0.98-1.44) | 0.077 | 1.15 (1.00-1.31) | 0.044 |
| RVEF (per 1% increase) | 0.97 (0.93-1.01) | 0.126 | 0.98 (0.95-1.01) | 0.128 |
| RVESVi (per 1mL/m² increase) | 1.00 (0.99-1.01) | 0.674 | 1.00 (1.00-1.01) | 0.543 |
| RA area, cm² (per 1cm² increase) | 1.08 (1.03-1.14) | 0.001 | 1.04 (1.01-1.08) | 0.025 |
| RV-FWS, % (per 1% increase) | 1.21 (1.09-1.35) | 0.001 | 1.11 (1.05-1.18) | < 0.001 |
| RAGLS, % (per 1% increase) | 0.88 (0.83-0.93) | < 0.001 | 0.93 (0.89-0.96) | < 0.001 |
| Parameter                          | Baseline (increase) | 95% CI   | p-value | 95% CI   | p-value |
|-----------------------------------|---------------------|----------|---------|----------|---------|
| TBIL, μmol/L (per 1μmol/L increase) | 1.05 (1.00-1.09)  | 0.033    | 1.02 (0.99-1.05) | 0.291    |
| ALP, μmol/L (per 1μmol/L increase)  | 1.01 (1.00-1.03)  | 0.055    | 1.01 (1.00-1.02) | 0.065    |
| GGT, μmol/L (per 1μmol/L increase)  | 1.02 (1.01-1.02)  | 0.001    | 1.01 (1.00-1.02) | 0.020    |
| ALT, μmol/L (per 1μmol/L increase)  | 1.03 (1.01-1.05)  | 0.015    | 1.02 (1.00-1.03) | 0.070    |
| AST, μmol/L (per 1μmol/L increase)  | 1.02 (1.00-1.05)  | 0.022    | 1.02 (1.01-1.04) | 0.003    |
| ln (NT-proBNP) (per 1 increase)    | 1.78 (1.25-2.52)  | 0.001    | 1.25 (1.00-1.56) | 0.046    |
| 6MWD (per 1m increase)             | 0.99 (0.99-1.00)  | 0.021    | 1.00 (0.99-1.00) | 0.006    |
| SvO2 (per 1% increase)             | 0.92 (0.87-0.97)  | 0.001    | 0.95 (0.92-0.98) | 0.004    |
| Cardiac index (per 1L/min/m² increase) | 0.36 (0.15-0.83)  | 0.017    | 0.81 (0.47-1.38) | 0.436    |
| mRAP (per 1mmHg increase)          | 1.13 (1.04-1.22)  | 0.003    | 1.03 (0.97-1.11) | 0.318    |

Adjusted HR: adjustment of GGT, ln (NT-proBNP)

RVEF: right ventricular ejection fraction; RVEDVi: right ventricular end-diastolic volume index; RVESVi: right ventricular end-systolic volume index; RV-FWS: right ventricular free-wall strain; RAGLS: right atrial global longitudinal strain; TBIL: TBIL: total bilirubin; DBIL: direct
bilirubin; IBIL: indirect bilirubin; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; ALT: glutamic-pyruvic transaminase; AST: glutamic oxaloacetic transaminase; 6MWD: 6 minute walking distance; mRAP: mean right atrial pressure.