ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Liver stiffness is associated with right heart dysfunction, cardiohepatic syndrome, and prognosis in pulmonary hypertension☆

Zvonimir A. Rako, MD,[a,1] Athiththan Yogeswaran, MD,[a,1] Selin Yildiz,[a] Peter Weidemann,[a] Daniel Zedler,[a] Bruno Brito da Rocha,[a] Vitalii Kryvenko, MD, PhD,[a] Simon Schäfer,[a] Hossein Ardeschir Ghofrani, MD,[a,b,c] Werner Seeger, MD,[a] Nils C. Kremer, MD,[a] and Khodr Tello, MD[a]

From the [a]Department of Internal Medicine, Justus-Liebig-University Giessen, Universities of Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Giessen, Germany; [b]Department of Pneumology, Kerckhoff Heart, Rheuma and Thoracic Center, Bad Nauheim, Germany; and the [c]Department of Medicine, Imperial College London, London, UK.

KEYWORDS:
pulmonary hypertension;
cardiohepatic syndrome;
hepatovenous flow;
shear wave elastography;
risk stratification

BACKGROUND: Pulmonary hypertension (PH) can lead to congestive hepatopathy, known as cardiohepatic syndrome (CHS). Hepatic congestion is associated with increased liver stiffness, which can be quantified using shear wave elastography. We aimed to investigate whether hepatic shear wave elastography detects patients at risk in the early stages of PH.

METHODS: Sixty-three prospectively enrolled patients undergoing right heart catheterization (52 diagnosed with PH and 11 with invasive exclusion of PH) and 52 healthy volunteers underwent assessments including echocardiography and hepatic shear wave elastography. CHS was defined as increased levels of ≥2 of the following: gamma-glutamyl transferase, alkaline phosphatase, and bilirubin. Liver stiffness was defined as normal (≤5.0 kPa) or high (>5.0 kPa).

RESULTS: Compared with normal liver stiffness, high liver stiffness was associated with impaired right ventricular (RV) and right atrial (RA) function (median [interquartile range] RV ejection fraction: 54 [49; 57]% vs 45 [34; 51]%, $p < 0.001$; RA reservoir strain: 49 [41; 54]% vs 33 [22; 41]%, $p < 0.001$), more severe tricuspid insufficiency ($p < 0.001$), and higher prevalence of hepatovenous backflow (2% vs 29%, $p < 0.001$) and CHS (2% vs 10%, $p = 0.038$). In the patient subgroup with precapillary PH ($n = 48$), CHS and high liver stiffness were associated with increased European Society of Cardiology/European Respiratory Society 2022 risk scores ($p = 0.003$).

CONCLUSIONS: Shear wave liver elastography yields important information regarding right heart function and may complement risk assessment in patients with (suspected) PH.

☆ Each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Reprint requests: Khodr Tello, MD, Department of Internal Medicine, Justus-Liebig-University Giessen, Klinikstrasse 32, 35392 Giessen, Germany. Telephone: +49 (0)641 985 56087. Fax: +49 (0)641 985 42599.

E-mail address: Khodr.Tello@innere.med.uni-giessen.de.

[1] Contributed equally.

https://doi.org/10.1016/j.healun.2024.02.013

J Heart Lung Transplant 2024;43:1105–1115

Pulmonary hypertension (PH) is characterized by increased right ventricular (RV) afterload, leading to dilatation and dysfunction of the right side of the heart.[1-3] As the disease progresses, congestion and backflow into the venous circulation increase.[4] Secondary organ dysfunction may occur as systemic congestion affects the perfusion and function of various organs, which in turn may result in systemic complications and increased mortality.[5] Consequently, it has been hypothesized that dysfunction of the right side of the heart and congestion have an impact on the anatomical architecture and stiffness of the liver.[6] In addition, congestive stress in the liver system leads to increases in various biomarkers, including gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), and bilirubin.[7,8] In this context, the term "cardiohepatic syndrome" (CHS) was introduced,[9,10] which was defined as an elevation of at least 2 of the 3 aforementioned biomarkers.[8] CHS was closely associated with prognosis in patients with tricuspid regurgitation (TR) undergoing transcatheter edge-to-edge valve repair.[8]

In addition to noninvasive, laboratory-based biomarkers, imaging technology has shown promise for the assessment of disease severity in patients with PH. Several imaging-based measurements of right-sided heart function (e.g., RV and right atrial [RA] strain) are available, and sono-elastographic assessment of hepatic stiffness represents another promising technique.[11-14] Ultrasound elastography is commonly used to assess hepatic stiffness, potentially revealing pathologic liver conditions, and was previously shown to correlate with histopathologic findings.[15] It is noninvasive, cost-effective, easily applied, repeatable, and expeditious.[16] However, it has not been well investigated whether shear wave liver elastography is a suitable tool to assess hepatic sequelae of right-sided heart dysfunction in PH. It is also not fully understood whether ultrasound-based evaluation of liver stiffness is associated with CHS, disease severity, and prognosis in patients with PH.

We hypothesized that detection of early-stage right-sided heart failure, before progression of apparent hepatic and systemic congestion, is important to detect patients at risk. Therefore, in this prospective study, we examined the relevance of liver elastography and CHS in patients with PH.

Methods

Study design and population

We prospectively recruited all consecutive patients who underwent right heart catheterization (RHC), echocardiography, and shear wave liver elastography at the University Hospital Giessen between January 2021 and March 2022. Both incident and prevalent patients were recruited. RHC was performed via the internal jugular vein under local anesthesia, as previously described.[17] The diagnosis of PH was made by a multidisciplinary board including physicians, radiologists, and surgeons according to current guidelines.[1] Accordingly, PH was defined as a mean pulmonary arterial pressure (mPAP) of >20 mm Hg. Precapillary PH was defined as a pulmonary arterial wedge pressure (PAWP) of ≤15 mm Hg and a pulmonary vascular resistance (PVR) of >2 wood units (WU), whereas isolated postcapillary PH was defined as PAWP >15 mm Hg and PVR ≤2 WU. Combined post- and precapillary PH was defined as PAWP >15 mm Hg and PVR >2 WU. CHS was defined as elevation of at least two of the following biomarkers above sex-specific thresholds: GGT (>39 U/liter for female patients and >59 U/liter for male patients), AP (>105 U/liter for female patients and >130 U/liter for male patients), and bilirubin (>1.2 mg/dl for both sexes). We also included healthy volunteers undergoing liver ultrasonography and echocardiography who had no signs of heart failure and no history of lung or liver disease as a control group. RHC was not performed in this subgroup owing to a lack of clinical indication.[1] The study complies with the Declaration of Helsinki and was approved by the local Ethics Committee of the Medical Faculty of the University of Giessen. All participants gave written informed consent.

Transthoracic echocardiography

Two- and three-dimensional echocardiography, including strain echocardiography and pulsed wave (PW) Doppler echocardiography, were conducted according to current guidelines.[18] Examinations were performed with the Philips Epiq 7G ultrasound device (Philips Healthcare, Netherlands) and the X5-1 ultrasound probe. The patients were positioned in a left-lateral lying position. RV-focused images for right cardiac dimensional and functional parameters were obtained as previously recommended.[18,19] RV strain was measured with the "AutoStrain RV" tool (Koninklijke Philips N.V., the Netherlands), providing RV free wall longitudinal strain (RV FWLS). RA strain was measured using the kit "AutoStrain LA" (Koninklijke Philips N.V.). Endocardial borders of the right atrium were manually tracked. To capture 3D echocardiographic images, "HM ACQ" was applied and RV volumetry was performed with the option "3D Auto RV" (Koninklijke Philips N.V.), providing RV end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction (RV EF). Flow within the hepatic vein was evaluated using PW Doppler as previously described in the subxiphoidal

view.[20,21] The hepatovenous flow profile was captured by PW Doppler. Normal hepatovenous flow is characterized by anterograde systolic flow (S wave), anterograde early diastolic flow (D wave), and slightly retrograde late diastolic flow (A wave), as shown in Figure 1 and described previously.[21] Hepatovenous flow was regarded as pathologic when distinct hepatovenous backflow was apparent either during systole as a result of pronounced TR (Figure 1F)[20] or during late diastole as a result of increased RV filling pressures (Figure 1G).[4]

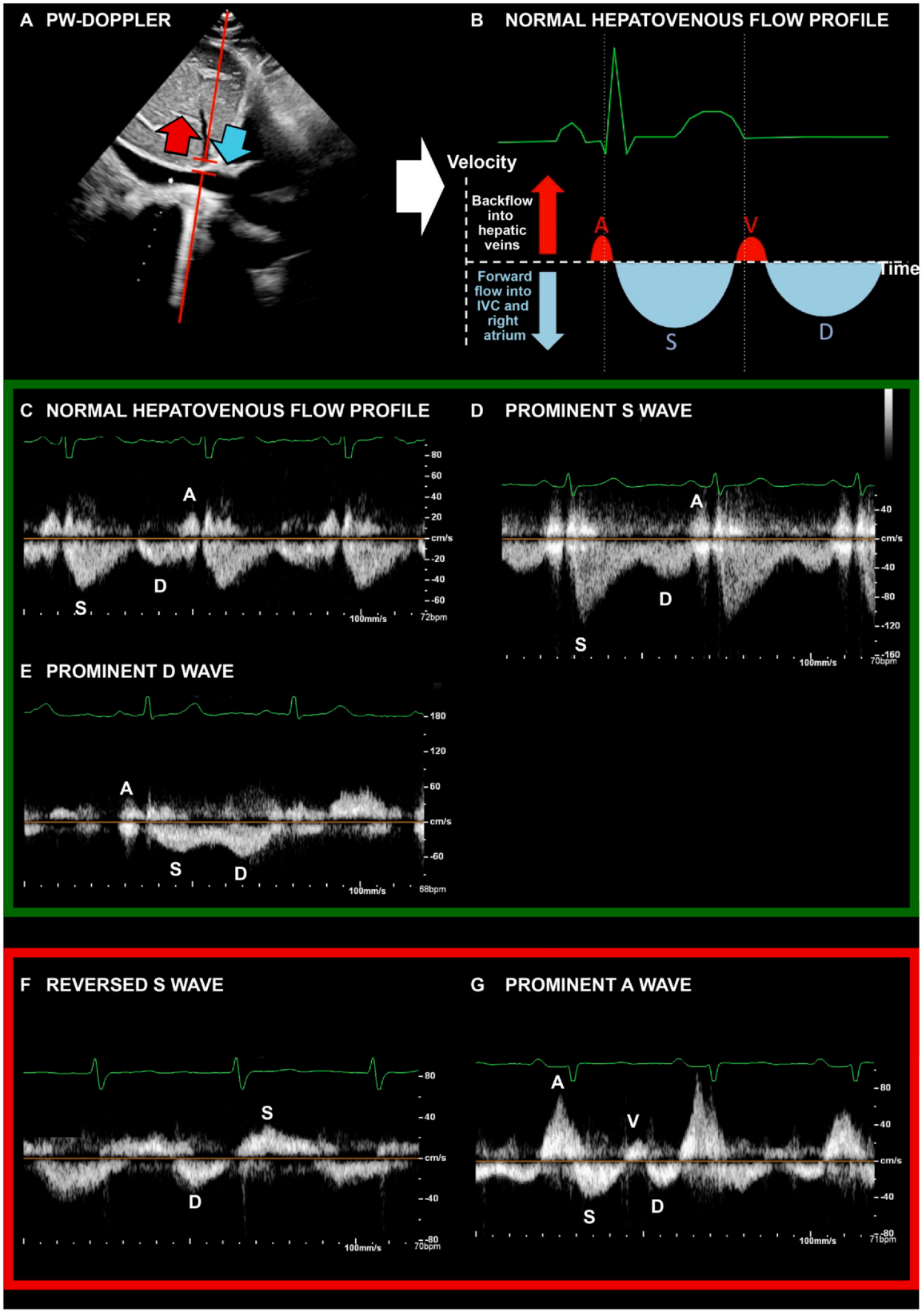


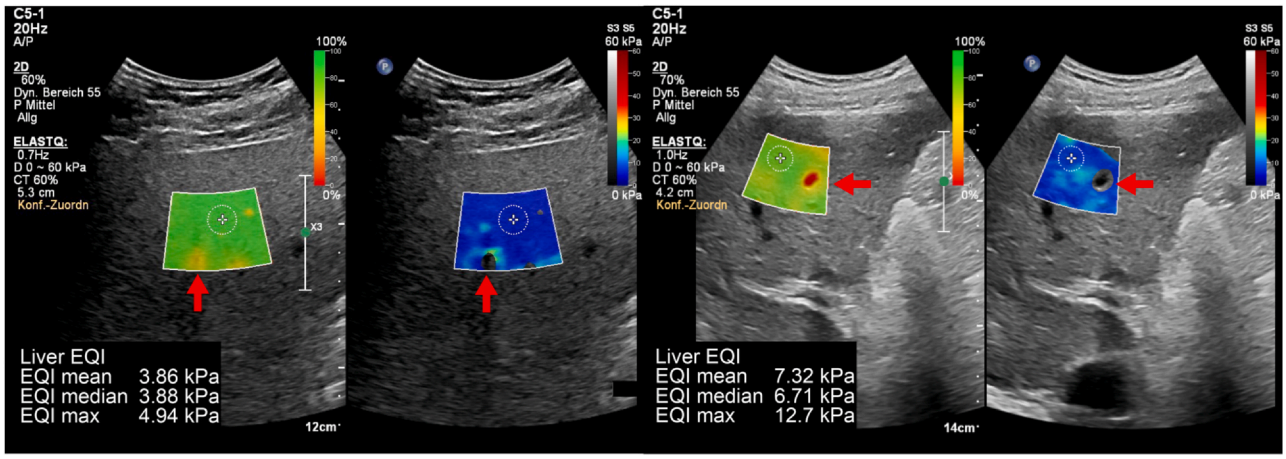
Figure 1 Acquisition and interpretation of hepatovenous flow profiles. (A) Sonographic imaging of the hepatovenous entry site into the IVC. This is where the PW Doppler is positioned to obtain hepatovenous flow profiles. In PW Doppler, upward flow indicates hepatovenous backflow (red arrow) and downward flow indicates forward flow (blue arrow). (B) Schematic example of a normal hepatovenous flow profile in relation to the ECG curve.[20, 21] The "A" wave (immediately after the P wave in the ECG) results from late-diastolic right atrial (RA) contraction and represents a slight hepatovenous backflow. The "S" wave takes place in systole and represents hepatovenous forward flow due to RA relaxation and reduced RA pressure during systolic RV contraction and displacement of the TV toward the apex. The "V" wave represents a slight hepatovenous backflow in end-systole just before TV opening and results from a rise in RA pressure (according to the v wave in pressure recording). The "V" wave may not be detectable. The "D" wave represents hepatovenous forward flow due to a decrease in RA pressure caused by RA emptying into the right ventricle after TV opening. (C-G) Examples of different types of flow profiles. Green framing (C-E) indicates predominant forward flow, which was considered mainly normal, including moderate tricuspid regurgitation resulting in blunting of the S wave (E). Red framing (F, G) indicates significant backflow into the hepatic veins which was considered pathologic, including backflow occurring (F) during systole as a result of pronounced tricuspid regurgitation and (G) during late diastole as a result of increased RV filling pressures. ECG, electrocardiogram; IVC, inferior vena cava; TV, tricuspid valve.

Two-dimensional (2D) shear wave liver elastography

Patients were positioned in a slightly supine left-lateral position. Elastography was performed with the Philips Epiq 7G ultrasound unit and the C5-1 abdominal probe according to current guidelines.[11,22] Hepatic stiffness was measured by 2D shear wave elastography using the tool "ElastQ" (Koninklijke Philips N.V.) and denoted as Young's modulus in kPa.[15] The B-mode ultrasound image was depicted on screen and the region of interest was selected, clean of larger hepatic vessels or biliary ducts and with a distance of at least 1 cm to the liver capsule (Figure 2). Each image was captured in breath-hold in normal expiration. A color-coded map of confidence indicated feasible sites for elastographic measurements (Figure 2). At least 5 distinct sites were recorded. As recommended by current guidelines,[11,22] a ratio of the interquartile range to the median value (IQR/median) of ≤30% for Young's Modulus was applied as a criterion for quality of measurement. Patients who did not meet this quality criterion were excluded from the analysis. Mean values of the single measurements were determined and used for further analysis.

Statistical analyses

All variables were checked for normality based on the Shapiro-Wilk test. For normally distributed parameters, mean (standard deviation) values are shown and Student's *t*-tests were used to compare means between groups. Non-normal parameters are presented as medians [Q1; Q3] and the Wilcoxon rank sum test was used to compare medians between groups. Categorical parameters were compared using the chi-square test. All statistical analyses were performed with R version 4.0.4 (The R Foundation, Vienna).



Healthy control, male, aged 48 years **Patient with PH-HFpEF, male, aged 69 years**

Figure 2 Liver elastography. Example liver elastography images and measurements from (A) a 48-year-old healthy male volunteer and (B) a 69-year-old male patient with PH-HFpEF are shown. In each example, the hepatic B-mode image is depicted twice, as seen by the examiner. The left image contains a map of confidence, indicating appropriate regions to measure liver stiffness in a color-coded manner, as indicated by the reference bar (see top right). Green color indicates good quality of measurement, whereas yellow, orange, and red colors indicate inadequate regions for elastographic evaluation. The right image contains a color-coded map for tissue stiffness, as indicated by the reference bar (see top right). EQI, ElastQ Imaging; PH-HFpEF, pulmonary hypertension due to heart failure with preserved ejection fraction.

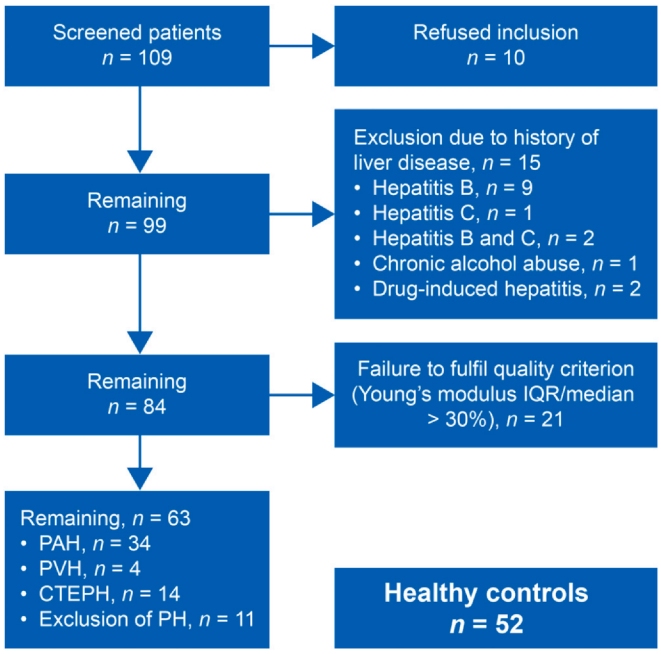


Figure 3 Flow chart of patients enrolled in the study and excluded patients. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PVH, pulmonary venous hypertension.

Results

Baseline characteristics

In total, 109 patients were screened for study enrollment (Figure 3). Ten patients refused study enrollment and 15 patients were excluded owing to history of liver disease. Another 21 patients were excluded because the IQR/median ratio of their Young's modulus values was > 30%, meaning their data did not meet the quality criterion for liver elastography. A total of 63 patients were therefore included in this study, of whom 34 (54%) were diagnosed with pulmonary arterial hypertension (PAH), four (6%) with pulmonary venous hypertension (PVH), and 14 (22%) with chronic thromboembolic PH (CTEPH). PH was ruled out by RHC in the remaining 11 patients (17%). Of the patients with manifest PH diagnosis ($n = 52$), 14 patients (27%) were incident and 38 patients (73%) were prevalent cases, of whom 12 patients had PH-targeted monotherapy and 26 had combined therapy. In addition, 52 volunteers were included as healthy controls. Baseline characteristics are presented in Table 1. The patients with PH had significantly higher liver stiffness than the controls (5.92 [5.16; 6.91] kPa vs 4.00 [3.58; 4.63] kPa, $p < 0.001$).

Liver stiffness is associated with severity of right-sided heart dysfunction

We examined the hemodynamic characteristics of patients with high liver stiffness (defined as values above 5.0 kPa).[23] Patients with high liver stiffness had significantly impaired PVR (5.3 [2.9; 9.1] WU vs 2.6 [1.6; 5.2] WU, $p = 0.020$) and cardiac index (2.6 [2.2; 2.9] l/min/m^2 vs 3.1 [2.8; 3.3] l/min/m^2, $p = 0.009$) compared with the group with normal liver stiffness (Table 2). Central venous pressure (CVP; 7.3 [3.4] mm Hg vs 5.9 [3.3] mm Hg, $p = 0.154$) and PAWP (11.0 [8.0; 13.0] mm Hg vs 8.0 [6.0; 10.8] mm Hg, $p = 0.158$) did not differ between the 2 groups. Notably, patients with high liver stiffness had significantly impaired RV and RA function, as shown in Table 2. RV longitudinal systolic function (TAPSE: 20.0 [3.9] mm vs 24.9 [3.7] mm, $p < 0.001$; S′: 11.2 [2.5] cm/sec vs 12.7 [1.9] cm/sec, $p < 0.001$), fractional area change (FAC; 36.0 [28.0; 43.4]% vs 46.2 [41.9; 53.2]%, $p < 0.001$), three-dimensional RV EF (45.4 [34.5; 50.9]% vs 54.3 [48.8; 57.3]%, $p < 0.001$), and RV FWLS (−22.6 [−25.8; −18.1]% vs −28.3 [−29.9; −25.3]%, $p < 0.001$) were significantly lower in patients with high liver stiffness than in those with normal liver stiffness (Table 2). High liver stiffness was also associated with a significantly higher grade of TR than normal liver stiffness ($p < 0.001$).

RA conduit (−15.4 [8.3]% vs −31.8 [10.4]%, $p < 0.001$) and reservoir strain (32.9 [21.6; 41.3]% vs 48.6 [40.5; 53.5]%, $p < 0.001$) were also significantly decreased in patients with high liver stiffness, while RA contractile strain (−15.8 [9.4]% vs 15.5 [6.5]%, $p = 0.867$) was not altered (Table 2). RA dimensions were significantly increased in patients with high liver stiffness (RA end-systolic area; 17.1 [13.2; 22.4] cm^2 vs 13.7 [11.8; 16.4] cm^2, $p = 0.002$). The diameter of the inferior vena cava (IVC; 17.8 (5.4) mm vs 18.0 (3.0), $p = 0.856$) showed no difference between the groups with high and normal liver stiffness. Relevant hepatic venous backflow was more common in patients with high liver stiffness compared with those with normal liver stiffness (29% vs 2%, $p < 0.001$; Table 2).

Consistent with these findings, patients with high liver stiffness were more likely to have CHS than those with normal liver stiffness (10% vs 2%, $p = 0.038$; Table 1). Conversely, patients with CHS had significantly greater liver stiffness than those without CHS (6.26 [5.91; 8.68] kPa vs 4.68 [3.86; 5.93] kPa, $p = 0.031$).

Although age differed significantly between the groups with high liver stiffness and normal liver stiffness, multivariate linear regression analysis showed that liver stiffness was independent of age (Table S1).

CHS and liver stiffness are associated with prognosis in precapillary PH

We then examined the relevance of CHS and liver stiffness in patients with precapillary PH ($n = 48$). The baseline characteristics of this study subgroup are shown in Table 3. The prevalence of CHS was high (10%) in these patients. Interestingly, patients with CHS were significantly more likely than those without CHS to be at high risk based on the European Society of Cardiology/European Respiratory Society (ESC/ERS) 2022 risk stratification scheme (Figure 4). Similarly, patients with high liver stiffness were significantly more likely to be at high risk than those with normal liver stiffness (Table 3).

Table 1 Baseline Characteristics

	n	Normal liver stiffness (EQI ≤ 5 kPa)		High liver stiffness (EQI > 5 kPa)	*p*
		Healthy controls *n* = 52	Patients *n* = 14	Patients *n* = 49	
Age, years	115	34.0 [27.8; 47.2]	56.0 [39.8; 60.8]	63.0 [53.0; 72.0]	< 0.001[a]
Female sex, *n* (%)	115	27 (52)	8 (57)	32 (65)	0.187[b]
Body mass index, kg/m^2	115	24.1 [21.8; 26.0]	28.3 [25.9; 32.3]	25.9 [23.3; 30.8]	0.127[a]
PH by subtype, *n* (%)	115				
None		52 (100)	2 (14)	9 (18)	
PAH		0 (0)	8 (57)	26 (53)	
iPAH		0 (0)	5 (36)	12 (46)	
hPAH		0 (0)	0 (0)	1 (4)	
CTD-PH		0 (0)	0 (0)	6 (23)	
PVOD		0 (0)	1 (7)	0 (0)	
CHD		0 (0)	1 (7)	3 (12)	
Others		0 (0)	1 (7)	4 (15)	
PVH		0 (0)	1 (7)	3 (6)	
CTEPH		0 (0)	3 (21)	11 (22)	
6MWD, m	40		350 (127)	367 (127)	0.753[c]
Functional class (WHO/NYHA), *n* (%)	115				< 0.001[b]
1		52 (100)	1 (7)	1 (2)	
2		0 (0)	6 (43)	14 (29)	
3		0 (0)	7 (50)	30 (61)	
4		0 (0)	0 (0)	4 (8)	
BNP, pg/ml	61		26.0 [13.0; 49.0]	69.5 [25.0; 234.2]	0.020[a]
ESC/ERS 2022 risk level, *n* (%)	115				< 0.001[b]
Low		52 (100)	12 (86)	19 (39)	
Medium		0 (0)	2 (14)	28 (57)	
High		0 (0)	0 (0)	2 (4)	
GGT, U/liter	63		25.0 [16.0; 35.2]	31.0 [18.0; 42.0]	0.502[a]
AP, U/liter	63		70.1 (20.2)	78.3 (24.8)	0.215[c]
Bilirubin, mg/dl	63		0.8 [0.7; 1.0]	0.7 [0.5; 1.0]	0.250[a]
CHS, *n* (%)	115		1 (7)	5 (10)	0.038[b]

Abbreviations: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CHD, congenital heart disease; CTD-PH, connective tissue disease-associated pulmonary hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; GGT, gamma-glutamyl transferase; hPAH, heritable pulmonary arterial hypertension; iPAH, idiopathic pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; WHO/NYHA, World Health Organization/New York Heart Association.

Data are presented as *n* (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median [Q1; Q3] for non-normally distributed continuous variables. The *p* values in the right column refer to 2-sample comparisons between normal liver stiffness and high liver stiffness. Therefore, mean values for normal liver stiffness are presented in the main text.

[a]Wilcoxon test.

[b]Chi-square test.

[c]Student's *t*-test.

Discussion

In this large prospective study including patients with (suspected) PH and healthy controls, we showed that hepatic stiffness measured by shear wave elastography is associated with RV and RA dysfunction, CHS, and prognosis.

In recent decades, research has increasingly focused on the interactions between organs. In this context, an essential connection was shown between different organ systems, such as the heart and the kidneys (i.e., cardiorenal syndrome), the liver and the kidneys, or the lungs and the liver (i.e., hepatopulmonary syndrome and portopulmonary hypertension).[24-27] Only recently has more attention been paid to CHS, another form of interaction between the right side of the heart and the liver.[8-10] Of note, the term CHS embraces several types of interaction, including CHS type 2 (congestive hepatopathy) which applies in the context of systemic venous congestion and PH.[9]

In PH, increase in RV afterload induces homeometric adaptation, often accompanied by increased RV stiffness.[2,28] Further increase in RV afterload may lead to exhaustion of adaptive remodeling, leading to systemic congestion.[2]

The underlying pathomechanisms that result in hepatic congestion, CHS, and increased liver stiffness are multifactorial, have been previously described, and can be discerned in the results of the current study. With increased RV stiffness, passive diastolic RV filling is impaired, resulting in restricted RA reservoir and conduit strain,

Table 2 Functional Parameters

	n	Normal liver stiffness (EQI ≤ 5 kPa)		High liver stiffness (EQI > 5 kPa)	*p*
		Healthy controls *n* = 52	Patients *n* = 14	Patients *n* = 49	
Echocardiography					
TAPSE, mm	115	25.5 (3.5)	22.3 (3.4)	20.0 (3.9)	< 0.001[a]
S′, cm/sec	115	12.8 (1.7)	12.3 (2.6)	11.2 (2.5)	< 0.001[a]
FAC, %	77	47.2 [42.5; 53.2]	39.5 [30.4; 43.0]	36.0 [28.0; 43.4]	< 0.001[b]
RV FWLS, %	115	−28.5 [−30.3; −25.8]	−26.0 [−28.9; −21.8]	−22.6 [−25.8; −18.1]	< 0.001[b]
RV EF, %	114	54.7 [50.3; 57.9]	49.7 [43.8; 53.9]	45.4 [34.5; 50.9]	< 0.001[b]
RA ESA, cm^2	115	13.7 [11.7; 16.2]	14.7 [12.3; 17.6]	17.1 [13.2; 22.4]	0.002[b]
RA conduit strain, %	114	−34.5 (8.5)	−21.8 (10.8)	−15.4 (8.3)	< 0.001[a]
RA contractile strain, %	114	−14.6 (6.2)	−18.9 (6.8)	−15.8 (9.4)	0.867[a]
RA reservoir strain, %	114	49.9 [42.5; 54.9]	41.8 [33.0; 49.5]	32.9 [21.6; 41.3]	< 0.001[b]
Tricuspid insufficiency, *n* (%)	115				< 0.001[c]
No TR		24 (46)	3 (21)	4 (8)	
Mild		28 (54)	6 (43)	17 (35)	
Intermediate		0 (0)	5 (36)	20 (41)	
Severe		0 (0)	0 (0)	8 (16)	
sPAP, mm Hg	84	22 [21; 26]	50 [37; 58]	55 [41; 84]	< 0.001[b]
IVC diameter, mm	115	18.2 (2.6)	17.0 (4.3)	17.8 (5.4)	0.856[a]
Hepatovenous flow profile, *n* (%)	114				< 0.001[c]
Normal		52 (100)	12 (92)	35 (71)	
Pathologic		0 (0)	1 (8)	14 (29)	
RHC					
mPAP, mm Hg	63		28.0 [21.3; 37.8]	38.0 [26.0; 52.0]	0.060[b]
CVP, mm Hg	63		5.9 (3.3)	7.3 (3.4)	0.154[a]
PAWP, mm Hg	63		8.0 [6.0; 10.8]	11.0 [8.0; 13.0]	0.158[b]
PVR, WU	63		2.6 [1.6; 5.2]	5.3 [2.9; 9.1]	0.020[b]
Cardiac index, $l/min/m^2$	63		3.1 [2.8; 3.3]	2.6 [2.2; 2.9]	0.009[b]
Liver elastography					
Liver EQI, kPa	115	3.8 [3.5; 4.2]	4.6 [4.2; 4.9]	6.2 [5.7; 7.4]	< 0.001[b]

Abbreviations: CVP, central venous pressure; ESA, end-systolic area; FAC, fractional area change; IVC, inferior vena cava; S′, tricuspid lateral annular systolic velocity; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

Data are presented as *n* (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median [Q1; Q3] for non-normally distributed continuous variables. The *p* values in the right column refer to 2-sample comparisons between normal liver stiffness and high liver stiffness. Therefore, mean values for normal liver stiffness are presented in the main text.

[a]Student's *t*-test.

[b]Wilcoxon test.

[c]Chi-square test.

whereas RA contraction remains preserved (Table 2), as previously described.[29,30] RV stiffening also involves an impaired late-diastolic RA-RV pressure gradient, causing RA contraction to result in a reduced forward ejection, but a mounting venous backflow, following pressure gradients.[4,30] Interestingly, improvement of RV diastolic dysfunction results in normalization of RA passive strain and venous backflow.[30] Alternatively, PH-related RV dilatation and secondary TR can promote systolic venous flow reversal. Correspondingly, patients with increased liver stiffness displayed higher-graded TR (Table 2). As hepatovenous backflow is transferred to the sinusoids, compression of bile canaliculi and impaired biliary drainage occur.[9] Congestion of the venous system, in turn, can lead to changes in the anatomical architecture of the liver. Hepatic stiffness was correlated with aspartate aminotransferase, GGT, AP, and direct bilirubin in a study of hospitalized heart failure patients.[31] Concordantly, patients with CHS in our study had significantly higher elastic values than those without, indicating elevated hepatic stiffness. Taken together, our results demonstrate the link from PH-induced afterload increase and consequent RV and RA dysfunction to hepatovenous congestion that eventually promotes hepatic stiffening.

We found that increased liver stiffness was associated with RV and RA dysfunction, as well as higher-graded TR and hepatovenous flow return, whereas conventional parameters for venous congestion (IVC diameter and CVP) were not significantly altered (Table 2). This indicates that liver elastography and Doppler-derived hepatovenous flow may detect alterations and thus identify patients at risk at earlier stages than conventional markers of congestion. In a subgroup of patients with precapillary PH, which is representative for advanced PH severity, those with increased liver stiffness had significantly increased CVP (Table 3). These results conform with previous studies that

Table 3 Baseline Characteristics and Functional Parameters in Precapillary Pulmonary Hypertension

	n	Combined *n* = 48	Normal liver stiffness (EQI ≤ 5 kPa) *n* = 11	High liver stiffness (EQI > 5 kPa) *n* = 37	*p*
Age, years	48	60.0 [46.8; 69.2]	57.0 [47.5; 60.5]	63.0 [47.0; 70.0]	0.153[a]
Female sex, *n* (%)	48	30 (62)	7 (64)	23 (62)	0.929[b]
Body mass index, kg/m^2	48	26.0 [23.5; 30.8]	28.8 [26.2; 33.0]	25.5 [23.3; 29.4]	< 0.039[a]
PH by subtype, *n* (%)	48				
PAH		34 (71)	8 (73)	26 (70)	
CTEPH		14 (29)	3 (27)	11 (30)	
6MWD, m	36	364 (129)	350 (127)	367 (132)	0.814[c]
Functional class (WHO/NYHA)	48				0.511[b]
1		2 (4)	1 (9)	1 (3)	
2		14 (29)	4 (36)	10 (27)	
3		28 (58)	6 (55)	22 (59)	
4		4 (8)	0 (0)	4 (11)	
BNP, pg/ml	46	54.0 [26.0; 209.8]	26.0 [14.2; 45.8]	83.0 [27.8; 262.2]	0.014[a]
ESC/ERS 2022 risk level, *n* (%)	48				< 0.001[b]
Low		20 (42)	10 (91)	10 (27)	
Medium		26 (54)	1 (9)	25 (68)	
High		2 (4)	0 (0)	2 (5)	
GGT, U/liter	48	30.5 [17.8; 43.5]	26.0 [17.0; 34.5]	33.0 [18.0; 48.0]	0.445[a]
AP, U/liter	48	78.0 (25.0)	73.4 (20.9)	79.4 (26.2)	0.437[c]
Bilirubin, mg/dl	48	0.7 [0.5; 1.0]	0.7 [0.7; 0.8]	0.7 [0.5; 1.0]	0.884[a]
CHS, *n* (%)	48	5 (10)	0 (0)	5 (14)	0.198[b]
Echocardiography					
TAPSE, mm	48	20.1 (4.0)	22.4 (3.2)	19.5 (4.0)	0.024[c]
S′, cm/sec	48	11.4 (2.6)	12.3 (2.9)	11.1 (2.5)	0.224[c]
FAC, %	18	36.0 [26.4; 42.5]	39.7 [39.2; 44.5]	29.0 [25.1; 38.5]	0.113[a]
RV FWLS, %	48	−22.1 [−25.6; −17.6]	−25.7 [−28.7; −22.0]	−21.1 [−24.8; −15.8]	0.007[a]
RV EF, %	47	44.4 [34.6; 50.9]	50.7 [44.6; 53.4]	41.5 [31.7; 49.0]	0.012[a]
RA ESA, cm^2	48	17.2 [13.1; 25.6]	15.9 [12.3; 17.5]	17.6 [14.1; 30.9]	0.120[a]
RA conduit strain, %	47	−16.6 (9.6)	−20.7 (10.1)	−15.3 (9.2)	0.137[c]
RA contractile strain, %	47	−16.3 (9.0)	−21.1 (4.0)	−14.9 (9.6)	0.003[c]
RA reservoir strain, %	47	34.4 [23.1; 42.1]	37.9 [33.6; 48.9]	31.4 [17.8; 41.0]	0.021[a]
Tricuspid insufficiency, *n* (%)	48				0.286[b]
No TR		2 (4)	1 (9)	1 (3)	
Mild		20 (42)	6 (55)	14 (38)	
Intermediate		18 (38)	4 (36)	14 (38)	
Severe		8 (17)	0 (0)	8 (22)	
sPAP, mm Hg	46	58.5 [40.0; 81.8]	44.5 [36.5; 54.5]	64.5 [47.8; 89.0]	0.021[a]
IVC diameter, mm	48	18.4 (5.1)	16.6 (2.9)	18.9 (5.5)	0.081[c]
Hepatovenous flow profile, *n* (%)	47				< 0.001[b]
Normal		33 (69)	10 (100)	23 (62)	
Pathologic		14 (31)	0 (0)	14 (38)	
RHC					
mPAP, mm Hg	48	39.5 [34.5; 52.3]	33.0 [22.0;39.0]	41.0 [37.0; 54.0]	0.002[a]
CVP, mm Hg	48	7.3 (3.3)	4.9 (3.0)	8.0 (3.1)	0.009[c]
PAWP, mm Hg	48	10.0 [7.0; 13.0]	7.0 [6.0; 10.0]	11.0 [8.0; 13.0]	0.029[a]
PVR, WU	48	6.3 [3.6; 9.2]	3.1 [2.1; 6.0]	6.9 [4.3; 9.8]	0.003[a]
Cardiac index, l/min/m^2	48	2.7 [2.3; 3.1]	3.2 [2.7; 3.3]	2.5 [2.2; 2.9]	0.020[a]

(*continued on next page*)

Table 3 (*Continued*)

	n	Combined *n* = 48	Normal liver stiffness (EQI ≤ 5 kPa) *n* = 11	High liver stiffness (EQI > 5 kPa) *n* = 37	*p*
Liver elastography					
Liver EQI, kPa	48	5.9 [5.2; 6.7]	4.5 [4.3; 4.9]	6.3 [5.7; 7.4]	< 0.001[a]

Abbreviations: 6MWD, 6-minute walk distance; AP, alkaline phosphatase; BNP, brain natriuretic peptide; CHS, cardiohepatic syndrome; CTD-PH, connective tissue disease-associated pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; CVP, central venous pressure; EF, ejection fraction; EQI, ElastQ Imaging; ESA, end-systolic area; ESC/ERS, European Society of Cardiology/European Respiratory Society; FAC, fractional area change; FWLS, free wall longitudinal strain; GGT, gamma-glutamyl transferase; hPAH, heritable pulmonary arterial hypertension; IVC, inferior vena cava; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RV, right ventricular; S′, tricuspid lateral annular systolic velocity; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; WHO/NYHA, World Health Organization/New York Heart Association.

Data are presented as *n* (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median [Q1; Q3] for non-normally distributed continuous variables. The *p* values in the right column refer to 2-sample comparisons between normal liver stiffness and high liver stiffness.

[a]Wilcoxon test.

[b]Chi-square test.

[c]Student's *t*-test.

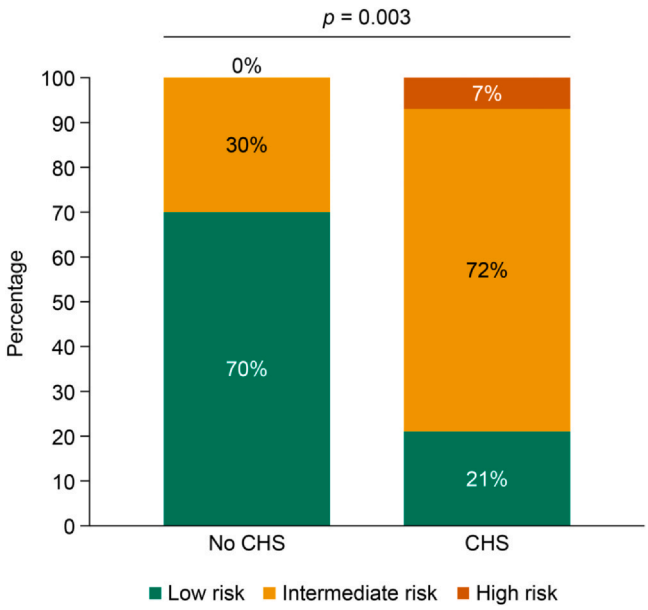


Figure 4 Risk associated with CHS in precapillary pulmonary hypertension. Risk was evaluated using the European Society of Cardiology/European Respiratory Society risk stratification scheme. Significance was assessed using the chi-square test. CHS, cardiohepatic syndrome.

demonstrated increased hepatic stiffness in patients with PAH compared with healthy controls.[32,33]

Finally, we examined whether liver stiffness and CHS are associated with prognosis. The ESC/ERS risk stratification scheme has been shown to be an important tool for assessing prognosis in various types of PH, including PAH, PH associated with interstitial lung disease, and CTEPH.[34-36] We found that CHS and liver stiffness were associated with PH severity and estimated risk of mortality in a subgroup of patients with PAH and CTEPH, as assessed via the ESC/ERS risk score. This is in accordance with previous studies evaluating the prognostic value of liver elastography in the context of heart failure and PH.[31-33,37]

However, our study is limited as it is a single-center study and the results may therefore not be generalizable to other centers/countries. Healthy volunteers were recruited as a control group, but voluntary enrollment may have been prone to selection bias. In addition, owing to the short follow-up time of the patients, a definitive statement about the connection between liver elastography, CHS, and survival is not directly possible. Thus, a prospective, multicenter evaluation is warranted.

In conclusion, we regard shear wave-based liver elastography as a potential tool to complement risk assessment in patients with (suspected) PH.

Author contributions

K.T. supervised the project. K.T., Z.A.R., and A.Y. have substantially contributed to the conception and design of the work. K.T., Z.A.R., A.Y., S.Y., and P.W. have performed the acquisition, analysis, and/or interpretation of data for the work. All authors participated in the drafting and critical revising of the work for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure statement

Dr Rako, Ms Yildiz, Mr Weidemann, Mr Zedler, Mr Brito da Rocha, Dr Kryvenko, and Mr Schäfer report nonfinancial support from the University of Giessen during the conduct of the study. Dr Yogeswaran reports nonfinancial support from the University of Giessen during the conduct of the study, and personal fees from MSD outside the submitted work. Dr Kremer reports nonfinancial support from the University of Giessen during the conduct of the study, and speaking fees from Janssen outside the submitted work.

Dr Ghofrani reports grants from the German Research Foundation and nonfinancial support from the University of Giessen during the conduct of the study, and personal fees from Bayer, Janssen, Pfizer, Xeros, Liquidia, and Takeda, grants and personal fees from Gossamer, Bayer HealthCare, and MSD/Acceleron, and grants from Aires, the German Research Foundation, Excellence Cluster Cardiopulmonary Research, and the German Ministry for Education and Research outside the submitted work. Dr Seeger reports grants from the German Research Foundation and nonfinancial support from the University of Giessen during the conduct of the study, and personal consulting fees from United Therapeutics, Tiakis Biotech AG, Liquidia, Pieris Pharmaceuticals, Abivax, Pfizer, and Medspray BV outside the submitted work. Dr Tello reports nonfinancial support from the University of Giessen during the conduct of the current study and speaker honoraria from Actelion and Bayer outside the submitted work.

Acknowledgments

Editorial assistance was provided by Claire Mulligan, PhD (Beacon Medical Communications Ltd., Brighton, UK).

Financial support

This work was supported by the Excellence Cluster Cardiopulmonary System and the Collaborative Research Center 1213 Pulmonary Hypertension and Cor Pulmonale, grant number SFB1213/1, project B08 (German Research Foundation, Bonn, Germany). For the manuscript, editorial assistance was provided by Dr Claire Mulligan (Beacon Medical Communications, Ltd., Brighton, United Kingdom), funded by the University of Giessen.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2024.02.013.

References

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61:2200879.
2. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53:1801900.
3. Vonk Noordegraaf A, Galie N. The role of the right ventricle in pulmonary arterial hypertension. Eur Respir Rev 2011;20:243-53.
4. Marcus JT, Westerhof BE, Groeneveldt JA, Bogaard HJ, de Man FS, Vonk Noordegraaf A. Vena cava backflow and right ventricular stiffness in pulmonary arterial hypertension. Eur Respir J 2019;54:1900625.
5. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation 2020;141:678-93.
6. Padalino MA, Chemello L, Cavalletto L, Angelini A, Fedrigo M. Prognostic value of liver and spleen stiffness in patients with fontan associated liver disease (FALD): a case series with histopathologic comparison. J Cardiovasc Dev Dis 2021;8:30.
7. Yogeswaran A, Tello K, Lund J, et al. Risk assessment in pulmonary hypertension based on routinely measured laboratory parameters. J Heart Lung Transplant 2022;41:400-10.
8. Stolz L, Orban M, Besler C, et al. Cardiohepatic syndrome is associated with poor prognosis in patients undergoing tricuspid transcatheter edge-to-edge valve repair. JACC Cardiovasc Inter 2022;15:179-89.
9. Poelzl G, Auer J. Cardiohepatic syndrome. Curr Heart Fail Rep 2015;12:68-78.
10. Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. Curr Heart Fail Rep 2014;11:236-40.
11. Ferraioli G, Wong VW, Castera L, et al. Liver ultrasound elastography: an update to the world federation for ultrasound in medicine and biology guidelines and recommendations. Ultrasound Med Biol 2018;44:2419-40.
12. Tello K, Dalmer A, Vanderpool R, et al. Cardiac magnetic resonance imaging-based right ventricular strain analysis for assessment of coupling and diastolic function in pulmonary hypertension. JACC Cardiovasc Imaging 2019;12:2155-64.
13. Crowe T, Jayasekera G, Peacock AJ. Non-invasive imaging of global and regional cardiac function in pulmonary hypertension. Pulm Circ 2018;8. 2045893217742000.
14. Hammerstingl C, Schueler R, Bors L, et al. Diagnostic value of echocardiography in the diagnosis of pulmonary hypertension. PLoS One 2012;7:e38519.
15. Sigrist RMS, Liau J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound elastography: review of techniques and clinical applications. Theranostics 2017;7:1303-29.
16. Dong Y, Sirli R, Ferraioli G, et al. Shear wave elastography of the liver - review on normal values. Z Gastroenterol 2017;55:153-66.
17. Yogeswaran A, Richter MJ, Sommer N, et al. Evaluation of pulmonary hypertension by right heart catheterisation: does timing matter? Eur Respir J 2020;56:1901892.
18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39. e14.
19. Badano LP, Muraru D, Parati G, Haugaa K, Voigt JU. How to do right ventricular strain. Eur Heart J Cardiovasc Imaging 2020;21:825-7.
20. Fadel BM, Almulla K, Husain A, Dahdouh Z, Di Salvo G, Mohty D. Spectral Doppler of the hepatic veins in tricuspid valve disease. Echocardiography 2015;32:856-9.
21. Fadel BM, Mohty D, Husain A, et al. Spectral Doppler of the hepatic veins in rate, rhythm, and conduction disorders. Echocardiography 2016;33:136-40. quiz 5.
22. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (short version). Ultraschall Med 2017;38:377-94.
23. Ferraioli G, Roccarina D. Update on the role of elastography in liver disease. Ther Adv Gastroenterol 2022;15. 17562848221140657.
24. Kumar P, Rao PN. Hepatopulmonary syndrome. N Engl J Med 2020;382:e14.
25. Nassar M, Nso N, Medina L, et al. Liver kidney crosstalk: hepatorenal syndrome. World J Hepatol 2021;13:1058-68.
26. Ronco C, Bellasi A, Di Lullo L. Cardiorenal syndrome: an overview. Adv Chronic Kidney Dis 2018;25:382-90.
27. Krowka MJ, Fallon MB, Kawut SM, et al. International liver transplant society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation 2016;100:1440-52.
28. Trip P, Rain S, Handoko ML, et al. Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension. Eur Respir J 2015;45:1603-12.
29. Tello K, Dalmer A, Vanderpool R, et al. Right ventricular function correlates of right atrial strain in pulmonary hypertension: a combined cardiac magnetic resonance and conductance catheter study. Am J Physiol Heart Circ Physiol 2020;318:H156-64.

30. Wessels JN, Mouratoglou SA, van Wezenbeek J, et al. Right atrial function is associated with right venticular diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension. Eur Respir J 2022;59:2101454.
31. Taniguchi T, Ohtani T, Kioka H, et al. Liver stiffness reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure. JACC Cardiovasc Imaging 2019;12:955-64.
32. Furukawa A, Tamura Y, Yamada K, et al. Liver fibrosis index as a novel prognostic factor in patients with pulmonary arterial hypertension. Heart Vessels 2022;37:601-8.
33. Urabe C, Takaya Y, Nakayama R, Nakamura K, Ito H. Shear wave dispersion slope of the liver can predict adverse outcomes in patients with pulmonary hypertension. Int Heart J 2023;64:230-6.
34. Delcroix M, Staehler G, Gall H, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J 2018;52:1800248.
35. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39:4175-81.
36. Yogeswaran A, Tello K, Faber M, et al. Risk assessment in severe pulmonary hypertension due to interstitial lung disease. J Heart Lung Transplant 2020;39:1118-25.
37. Zhang J, Xu M, Chen T, Zhou Y. Correlation between liver stiffness and diastolic function, left ventricular hypertrophy, and right cardiac function in patients with ejection fraction preserved heart failure. Front Cardiovasc Med 2021;8:748173.