Doppler-Derived Renal Venous Stasis Index in the Prognosis of Right Heart Failure

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Background—Persistent congestion with deteriorating renal function is an important cause of adverse outcomes in heart failure. We aimed to characterize new approaches to evaluate renal congestion using Doppler ultrasonography.

Methods and Results—We enrolled 205 patients with suspected or prediagnosed pulmonary hypertension (PH) undergoing right heart catheterization. Patients underwent renal Doppler ultrasonography and assessment of invasive cardiopulmonary hemodynamics, echocardiography, renal function, intra-abdominal pressure, and neurohormones and hydration status. Four spectral Doppler intrarenal venous flow patterns and a novel renal venous stasis index (RVSI) were defined. We evaluated PH-related morbidity using the Cox proportional hazards model for the composite end point of PH progression (hospitalization for worsening PH, lung transplantation, or PH-specific therapy escalation) and all-cause mortality for 1-year after discharge. The prognostic utility of RVSI and intrarenal venous flow patterns was compared using receiver operating characteristic curves. RVSI increased in a graded fashion across increasing severity of intrarenal venous flow patterns (P<0.0001) and was significantly associated with right heart and renal function, intra-abdominal pressure, and neurohormonal and hydration status. During follow-up, the morbidity/mortality end point occurred in 91 patients and was independently predicted by RVSI (RVSI in the third tertile versus referent: hazard ratio: 4.72 [95% CI, 2.10–10.59; P=0.0001]). Receiver operating characteristic curves suggested superiority of RVSI to individual intrarenal venous flow patterns in predicting outcome (areas under the curve: 0.789 and 0.761, respectively; P=0.038).

Conclusions—We propose RVSI as a conceptually new and integrative Doppler index of renal congestion. RVSI provides additional prognostic information to stratify PH for the propensity to develop right heart failure.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov/. Unique identifier: NCT03039959. (J Am Heart Assoc. 2019;8: e013584. DOI: 10.1161/JAHA.119.013584.)

Key Words: cardiorenal syndromes • intrarenal venous flow patterns • pulmonary hypertension • renal Doppler ultrasonography • venous congestion

Heart failure (HF) is a major cause of death worldwide and the leading cause of hospitalization in both the United States and Europe. In addition to low cardiac output, persistent congestion with deterioration of renal function due to progressive right ventricular (RV) failure has been identified as an important cause of adverse outcomes in HF.

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Accompanying Data S1, Tables S1 through S13, Figures S1 through S5 available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013584

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Clinical Perspective

What Is New?

- Doppler-derived intrarenal venous flow patterns having been shown to predict adverse outcomes in patients with heart failure; however, these approaches do not reflect the continuum of renal congestion because classification of intrarenal venous flow into different categories may miss important changes within those categories.
- In patients with suspected pulmonary hypertension undergoing right heart catheterization, we developed a continuous index from intrarenal venous flow patterns, and we propose the renal venous stasis index as a conceptually new and integrative Doppler measure of renal congestion.
- Our study suggests that renal venous stasis index may be superior to individual intrarenal venous flow pattern in predicting outcome in patients with pulmonary hypertension.

What Are the Clinical Implications?

- Renal venous stasis index provides additional prognostic information to stratify pulmonary hypertension for the propensity to develop right heart failure.
- Longitudinal studies are needed to clarify the role of renal venous stasis index in the management of pulmonary hypertension.

Congestion may lead to a vicious circle of renal dysfunction, increases in intra-abdominal pressure, neurohormonal activation, excessive renal tubular sodium reabsorption, fluid overload, and diuretic resistance, leading to further RV stress. Elevation of right atrial pressure (RAP) is transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure within the encapsulated kidney, which decreases net glomerular filtration rate (GFR) and oxygen delivery. Similar pathophysiological mechanisms are expected to occur during increases in intra-abdominal pressure. Congestion may also directly compress vessels in the renal parenchymal regions or reduce vessel compliance. Consequently, changes in vessel shape and function may lead to transient and cardiac cycle-dependent stasis of renal venous flow and to changes in intrarenal venous flow (IRVF) patterns.

Doppler ultrasonography was recently proposed to evaluate renal congestion, with different IRVF patterns and the intrarenal venous impedance index having been shown to predict diuretic response and adverse outcomes in patients with HF or undergoing cardiac surgery. However, these approaches do not reflect the continuum of renal congestion: classification of IRVF patterns into different categories may miss important changes within those categories, and the venous impedance index does not distinguish between IRVF patterns with different degrees of venous stasis. We sought to identify and rigorously characterize a new approach to evaluate the continuum of renal congestion based on Doppler renal venous flow.

Methods

Study Design and Participants

We prospectively enrolled consecutive hospital inpatients aged ≥18 years with suspected or prediagnosed pulmonary hypertension (PH) who were undergoing invasive right heart catheterization (RHC) between January 2017 and September 2017 at the Department of Pulmonology, University Hospital Giessen and Marburg, Giessen, Germany. PH is the most common precursor to RV failure and thus represents an ideal scenario for studying congestion. Suspicion of PH was determined on clinical grounds including echocardiographic evaluation, in accordance with the most recent guidelines for the diagnosis and treatment of PH. Patients with prediagnosed PH had received the diagnosis based on previous RHC. Diagnosis and classification of PH and pulmonary vasoactive treatment were based on current guidelines. PH was defined as invasively measured mean pulmonary arterial pressure (PAP) ≥25 mm Hg at rest. Patients were assigned a diagnosis of pulmonary arterial hypertension (group 1), PH due to left heart disease (group 2), PH due to lung diseases and/or hypoxia (group 3), chronic thromboembolic PH (group 4), or PH with unclear and/or multifactorial mechanisms (group 5) by a multidisciplinary board. Patients receiving PH therapy could enter the study without restrictions. HF was diagnosed according to current guidelines.

 Patients were excluded if they had chronic kidney disease stage 5, preexisting acute kidney injury, non–end-stage renal disease with extracorporeal or peritoneal ultrafiltration due to diuretic-resistant fluid overload, prediagnosed glomerulonephritis, autosomal dominant polycystic kidney disease, or postrenal obstruction; if they were recipients of solid-organ transplants; or if they had received NSAIDs within 72 hours before RHC. The exclusion criteria acute kidney injury and chronic kidney disease were diagnosed by an adjudication committee of 3 expert nephrologists. Chronic kidney disease was considered as estimated GFR (eGFR; creatinine–cystatin C equation) <60 mL/min per 1.73 m² or the presence of microalbuminuria independent of eGFR. Acute kidney injury was defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within the prior 7 days (determined by all available serum creatinine values from hospital and outpatient medical records within the previous 90 days). Diuretic-resistant fluid overload was defined as the inability to achieve an adequate negative fluid...
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balance when the following 4 therapeutic options had been exploited: (1) restriction of fluid intake to <1.5 L/day and sodium chloride intake to ≤6.0 g/day; (2) (continuous) intravenous infusion of furosemide (minimum 500 mg/day); (3) sequential nephron blockade with the addition of a thiazide diuretic (eg, hydrochlorothiazide minimum 25 mg/day or xipamide minimum 20 mg/day); (4) addition of an aldosterone antagonist if tolerable with serum potassium level (spironolactone minimum 25 mg/day or eplerenone minimum 50 mg/day). RHC data, echocardiography, renal function, IRVF patterns, laboratory measurements, intra-abdominal pressure, and bioimpedance data were evaluated separately, as described in the next section, by examiners who were blinded to the other data. All patients were included in the Giessen PH registry.18

The study was approved by the local Human Research Ethics Committee (AZ 237/16) and complied with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (identifier: NCT03039959). All participants gave signed informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

**Procedures and Measurements**

**Renal Doppler ultrasonography**

Ultrasound and spectral Doppler analyses were performed in duplicate by 2 independent nephrologists with experience in Doppler ultrasound, using an EPIQ 5 system (Philips Healthcare) with a sector transducer frequency range of 2.5–5.0 MHz. The analyses were performed after a Swan-Ganz catheter had been inserted for RHC assessment (described in the next section) and the patient had rested in a supine position for ≥10 minutes. Color Doppler images were used to identify interlobar vessels. Pulsed Doppler waveforms of the interlobar arteries and veins were recorded simultaneously with the patient in a resting decubitus position. Except for renal resistive index (RRI), which was assessed in both kidneys, all renal Doppler ultrasonography studies were performed in the right kidney (except in cases of unsatisfactory image quality) because left renal vein phasicity may be attenuated because of entrapment in the fork between the abdominal aorta and the superior mesenteric artery. In addition, the left ovarian or testicular veins drain into the left renal vein, which, in the rare event of ovarian or testicular varicosity, may affect renal venous flow.

All values were recorded as means of at least 3 measurements obtained in different interlobar vessels over 3 cardiac cycles during sinus rhythm. If atrial fibrillation was present, an index beat (the beat following 2 preceding cardiac cycles of equal duration) was used for each measurement. Venous impedance index and RRI were calculated as follows:

\[
\text{Venous impedance index} = \left( \frac{\text{maximum flow velocity} - \text{minimum diastolic flow velocity}}{\text{maximum flow velocity}} \right) /
\]

(maximum flow velocity–minimum diastolic flow velocity)/maximum flow velocity.9 A side-to-side difference in RRI of >5% between the kidneys was considered indicative for significant renal artery stenosis.19 RRI <0.7 was regarded as normal.20

IRVF patterns were characterized by a blinded adjudication committee comprising a nephrologist, an angiologist, and a pulmonologist blinded to clinical, laboratory, and RHC data. If 2 reviewers disagreed, a third reviewer provided input and consensus was developed. The IRVF patterns were broadly categorized into continuous (noncongestive) and discontinuous (nadir velocity=0) flow patterns. We further classified the discontinuous IRVF patterns into 3 stages: pulsatile, biphasic (with venous peaks during systole and diastole), and monophasic (with venous peak during diastole; Figure 1).

To reflect the full continuum of renal congestion, we defined and evaluated a new, continuous ratio, the renal venous stasis index (RvSI). RvSI indicates the proportion of the cardiac cycle during which there is no renal venous outlet flow and is calculated as follows: (cardiac cycle time–venous flow time)/cardiac cycle time (Figure 2).

**Right heart catheterization**

On the day of RHC, each patient took his or her usual dose of medication at 07:00 AM except for the maintenance dose of diuretics. In patients with long-term oxygen treatment, oxygen was applied via nasal cannula at the previously prescribed flow rate. A Swan-Ganz catheter (7F balloon tipped; Baxter Healthcare) was inserted under local anesthesia in the right internal jugular vein. RHC was performed according to current guidelines,14 with assessment of mean PAP, RAP, pulmonary vascular resistance, pulmonary capillary wedge pressure, cardiac output (thermodilution method), cardiac index, mean arterial pressure, and mixed venous oxygen saturation immediately after renal ultrasonography (for details see Data S1).

**Echocardiography**

Echocardiography was performed by experienced echocardiographers 1 day before RHC using Vivid E9 and Vivid S5 systems (GE Healthcare). Right heart parameters (RV myocardial performance index [Tei index], tricuspid annular plane systolic excursion, systolic PAP, right atrial size, basal diameter of the right ventricle, inferior vena cava diameter, and systolic free wall myocardial velocity) and left heart parameters (left atrial and ventricular diameters and the ratio of mitral inflow velocity to lateral annular relaxation velocity [E/e’]) were measured as recommended.21

**Other measures**

Body composition (including hydration status) was analyzed by bioimpedance spectroscopy using the body composition...
Before catheterization, hydration status was also evaluated by clinical assessment (edema) and ultrasound (ascites and pleural effusion). Intra-abdominal pressure was measured via an indwelling urinary catheter in all patients using the transvesical method as previously described (Data S1). The mean arterial pressure was calculated as follows: \[\text{systolic blood pressure} + (2 \times \text{diastolic blood pressure})]/3\]. The abdominal perfusion pressure was determined as mean arterial pressure minus intra-abdominal pressure. The renal filtration gradient can be estimated as glomerular filtration pressure minus proximal tubular pressure. In the presence of elevated intra-abdominal pressure, proximal tubular pressure may be assumed to equal intra-abdominal pressure, and thus glomerular filtration pressure can be estimated mean arterial pressure minus intra-abdominal pressure. The renal filtration gradient was therefore calculated as follows: mean arterial pressure – \((2 \times \text{intra-abdominal pressure})\). Intra-abdominal pressures from 4 to 7 mm Hg were considered as normal range, whereas values ≥12 mm Hg were considered as intra-abdominal hypertension. Six-minute walk distance and New York Heart Association functional class were assessed 1 day before RHC according to current guidelines. Loop diuretic doses were converted to furosemide equivalents with 20 mg torasemide equal to 80 mg furosemide for oral diuretics and 20 mg torasemide equal to 40 mg furosemide for intravenous diuretics. Thiazide diuretics included hydrochlorothiazide and xipamide. If triamterene was taken, it was used in a fixed diuretic combination with hydrochlorothiazide. Aldosterone antagonists included spironolactone and eplerenone.

**Laboratory methods**

Laboratory methods are detailed in Data S1. Briefly, blood samples were collected on the day of RHC from the Swan-Ganz catheter after the patient had rested in a supine position for ≥60 minutes. Urine samples were collected from first morning-void specimens. BNP (B-type natriuretic peptide), copeptin, creatinine, and cystatin C were measured using chemiluminescence, time-resolved amplified cryptate emission, photometric-enzymatic, and immunoturbidimetric methods.
methods, respectively. We chose BNP and copeptin as biomarkers of neurohormonal activation because both are commonly used for diagnosis and determining prognosis in HF. The eGFR was determined using both creatinine and creatinine–cystatin C Chronic Kidney Disease–Epidemiology Collaboration equations.

Follow-Up and End Points
Clinical outcomes were evaluated for 1 year after discharge. Patients were closely followed during the observation period by clinical visits or telephone interviews. Changes of medication for clinical reasons were permitted (the primary physician caring for the patient was blinded to the IRVF patterns and RVSI results). Use of diuretics was at the discretion of the treating physician. At 1 year, all patients were recontacted for follow-up analyses at the nephrology outpatient department. If the primary cause of PH was surgically treated (eg, pulmonary thromboendarterectomy in patients with chronic thromboembolic PH or lung transplantation), the patients were followed until the surgical procedure. If a patient died outside of the hospital, telephone calls to the general practitioner or the family members were performed to confirm the date of death.

We evaluated the first occurrence of a composite end point of PH-related morbidity (any hospitalization for worsening of PH, lung transplantation, or need for escalation of PH-specific therapy) and death from any cause. In addition, the following components of the composite end point were each analyzed separately: unscheduled hospitalization due to fluid overload with requirement for an increase in diuretic therapy (eg, due to pulmonary or peripheral edema, pleural effusion, ascites, or recent increase of body weight by ≥10%); need for escalation or change of PH-specific therapy due to clinical and echocardiographic progress of PH; and death from any cause. Patients who underwent pulmonary thromboendarterectomy were considered as withdrawn alive. All available medical records were collected, and morbidity and mortality data were evaluated according to the predefined end point components in a blinded fashion by a clinical end point adjudication committee including medical experts in nephrology, PH, and cardiology who were unaware of the IRVF patterns and RVSI results and not responsible for the primary care of the patient.

Figure 2. Renal venous stasis index (RVSI). The RVSI is a novel Doppler-based parameter to estimate severity of renal congestion. Pulsed-wave Doppler samples of renal congestion patterns in the interlobar renal vessel are shown. The upward Doppler signal shows the intrarenal arterial flow, which is used to measure cardiac cycle time; the downward Doppler signal shows the venous flow, used to measure venous flow time. Under physiological conditions, the index is zero due to the presence of a continuous venous flow, whereas it increases with rising severity of congestion. The figure illustrates the method of measurement of RVSI in different congestion stages. ms indicates milliseconds.

Figure 3. Study flow chart. The diagram describes the protocol used for the enrollment of patients in this study.
### Table 1. Clinical Characteristics, Invasive Hemodynamics, Echocardiographic Data, Renal Function, and Neurohormonal and Hydration Status According to RVSI Tertile

| Demographics | All patients(N=205) | RVSI 0(n=59) | RVSI Tertiles | RVSI Tertiles | RVSI Tertiles | P Value* |
|--------------|---------------------|--------------|---------------|---------------|---------------|----------|
|              |                     | First, 0 to ≤0.12 |               | Second, >0.12 to ≤0.32 | Third, >0.32(n=49) |         |
| Age, y       | 68.0 (57.0–78.0)    | 68.0 (55.0–73.0) | 67.0 (51.0–75.5) | 72.5 (61.0–78.0) | 74.0 (65.0–81.0) | 0.0152   |
| Male, n (%)  | 87 (42.4)           | 24 (40.7)     | 17 (34.7)     | 17 (35.4)     | 29 (59.2)     | 0.0488   |
| Body mass index, kg/m² | 27.82±6.07         | 29.03±6.05    | 26.05±6.37    | 28.30±6.84    | 27.67±4.52    | 0.075    |
| Baseline clinical data |                     |               |               |               |               |         |
| Oxygen supply, n (%) | 118 (57.6)          | 28 (47.5)     | 28 (57.1)     | 32 (66.7)     | 30 (61.2)     | 0.224    |
| PaO₂ †       | 69.32±11.71         | 71.09±10.74   | 68.11±11.21   | 68.00±10.01   | 69.67±14.57   | 0.0474   |
| PaCO₂ ‡      | 38.57±8.98          | 40.20±11.68   | 37.76±7.30    | 37.38±7.88    | 38.59±7.66    | 0.367    |
| 6MWD, m      | 277.23±136.05       | 309.76±118.16 | 285.08±156.43 | 283.77±131.30 | 223.80±127.02 | 0.0098   |
| NYHA classification, n (%) |                    |               |               |               |               |         |
| 1–2          | 44 (21.5)           | 15 (25.4)     | 12 (24.5)     | 13 (27.1)     | 4 (8.2)       | 0.178    |
| 3–4          | 161 (78.5)          | 44 (74.6)     | 37 (75.5)     | 35 (72.9)     | 45 (91.8)     |          |
| Laboratory data |                     |               |               |               |               |         |
| Leukocytes, × 10⁹/L | 7.43±2.49           | 7.33±2.53     | 7.72±2.29     | 7.14±2.68     | 7.56±2.47     | 0.674    |
| Hemoglobin, g/dL | 13.27±2.09          | 13.95±1.83    | 13.53±2.06    | 13.49±2.18    | 13.02±2.31    | 0.504    |
| Sodium, mmol/L | 139.56±3.07         | 139.32±3.15   | 139.73±2.72   | 140.15±3.14   | 139.10±3.22   | 0.343    |
| Potassium, mmol/L | 3.67±0.42          | 3.65±0.40     | 3.64±0.34     | 3.63±0.44     | 3.73±0.47     | 0.612    |
| Uric acid, mg/dL | 6.77±2.52           | 6.26±2.18     | 5.89±2.07     | 6.65±2.31     | 8.38±2.82     | <0.0001  |
| Albumin, g/dL | 38.20±3.22          | 38.91±3.18    | 37.49±3.25    | 38.09±2.96    | 38.18±2.42    | 0.162    |
| C-reactive protein, mg/L | 5.22 (1.52–11.44) | 3.13 (1.07–8.60) | 3.70 (0.50–11.58) | 5.22 (2.05–11.48) | 7.20 (3.18–14.51) | 0.0172   |
| Comorbidities, n (%) |                    |               |               |               |               |         |
| Hypertension  | 128 (62.4)          | 35 (59.3)     | 29 (59.2)     | 32 (66.7)     | 32 (65.3)     | 0.800    |
| Diabetes mellitus | 48 (23.4)           | 12 (20.3)     | 9 (18.4)      | 9 (18.4)      | 18 (36.7)     | 0.092    |
| Atrial fibrillation | 56 (27.3)          | 7 (11.9)      | 14 (28.6)     | 9 (18.8)      | 26 (53.1)     | <0.0001  |
| Maintenance therapy |                    |               |               |               |               |         |
| ACEI or ARB, n (%) | 83 (40.5)           | 23 (39.0)     | 18 (36.7)     | 20 (41.7)     | 22 (44.9)     | 0.858    |
| β-Blocker | 103 (50.2)          | 25 (42.4)     | 18 (36.7)     | 27 (56.3)     | 33 (67.3)     | 0.0095   |
| Loop diuretic dose, mg/d² | 40 (0.0–60.0) | 20 (0.0–40.0) | 20 (0.0–55.0) | 30 (0.0–55.0) | 80 (40.0–170.0) | <0.0001  |
| PH-specific therapy (%) |                    |               |               |               |               |         |
| Treatment-naive | 116 (56.6)          | 42 (71.2)     | 21 (42.9)     | 25 (47.9)     | 30 (61.2)     | 0.0292   |
| Monotherapy | 49 (23.9)           | 8 (13.6)      | 18 (36.7)     | 11 (22.9)     | 12 (24.5)     |          |
| Dual therapy | 28 (13.7)           | 6 (10.2)      | 7 (14.3)      | 12 (25.0)     | 3 (6.1)       |          |
| Triple therapy | 12 (5.9)           | 3 (5.1)       | 3 (6.1)       | 2 (4.2)       | 4 (8.2)       |          |
| Hemodynamics |                       |               |               |               |               |         |
| Mean PAP, mm Hg | 34.84±14.63          | 24.10±9.62    | 34.78±12.79   | 41.10±16.03   | 41.69±12.39   | <0.0001  |
| PVR, dynes·cm⁻⁵ | 394 (214–604)       | 229 (110–420) | 422 (214–589) | 516 (279–679) | 495 (313–833) | <0.0001  |
| RAP, mm Hg | 5.76±5.63           | 2.46±3.66     | 3.88±3.76     | 5.56±3.72     | 11.80±6.06    | <0.0001  |
| Cardiac index, L/min/m² | 2.73±0.98          | 2.98±1.01     | 2.88±1.16     | 2.67±0.68     | 2.32±0.89     | 0.0032   |
| PCWP, mm Hg | 9.0 (5.0–13.0)      | 7.0 (4.0–10.0) | 8.0 (5.0–12.0) | 9.5 (6.0–14.8) | 12.0 (8.0–18.0) | <0.0001  |

continued
### Table 1. Continued

| Echocardiographic parameters | All patients (N=205) | RVSI Tertiles | P Value* |
|-----------------------------|---------------------|--------------|----------|
|                             | RVSI 0 (n=59)       | First, 0 to ≤0.12 (n=49) | Second, >0.12 to ≤0.32 (n=48) | Third, >0.32 (n=49) |
| **Renal function**          |                     |               |          |
| Serum creatinine, mg/dL†    | 1.01±0.45           | 0.92±0.40    | 0.79±0.21 | 0.98±0.36 | 1.35±0.55 | <0.0001 |
| Cystatin C, mg/L            | 1.10 (0.91–1.52)    | 0.98 (0.81–1.24) | 1.01 (0.88–1.18) | 1.27 (0.97–1.62) | 1.53 (1.10–2.09) | <0.0001 |
| Urea, mg/dL†                | 47.44±35.85         | 40.97±26.71  | 34.29±13.13 | 44.69±25.25 | 71.10±54.75 | <0.0001 |
| eGFR (CKD-EPI creatinine equation), mL/min/1.73 m²** | 74.45±26.12 | 80.07±24.52 | 87.31±18.86 | 72.69±24.01 | 56.57±26.75 | <0.0001 |
| eGFR (CKD-EPI creatinine–cystatin C equation), mL/min/1.73 m²*** | 68.58±26.86 | 77.68±27.65 | 80.80±20.25 | 64.06±22.56 | 49.84±24.49 | <0.0001 |
| Renal filtration gradient, mm Hg†† | 69.30±12.46 | 73.70±10.60 | 69.62±13.32 | 69.81±11.12 | 63.20±12.81 | <0.0001 |
| Urine PCR, mg/g creatinine  | 58.8 (40.2–114.2)  | 51.5 (36.4–72.6) | 55.3 (37.5–85.4) | 58.0 (39.9–92.9) | 116.2 (49.1–190.8) | <0.0001 |
| Urine ACR, mg/g creatinine  | 11.4 (6.3–29.7)    | 9.3 (5.2–16.0) | 9.0 (5.7–18.5) | 10.3 (6.7–19.0) | 29.7 (11.7–107.8) | <0.0001 |
| Urine x1MCR, mg/g creatinine| 10.9 (6.0–19.1)    | 8.7 (5.1–16.5) | 8.7 (5.7–15.1) | 12.0 (6.5–21.4) | 15.4 (7.6–32.7) | 0.0092 |
| **Renal Doppler ultrasonography** |                     |               |          |
| Venous impedance index      | 0.84±0.26           | 0.44±0.12    | 1.00±0    | 1.00±0    | 1.00±0    | <0.0001 |
| RRI                         | 0.71±0.07           | 0.69±0.08    | 0.69±0.07 | 0.73±0.07 | 0.74±0.06 | <0.0001 |

*Continued*
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**Statistical Analysis**

Descriptive statistics were expressed as mean±SD or median (interquartile range [IQR]) for continuous variables, and frequency (percentage) for categorical variables. Patient characteristics were compared between subgroups using ANOVA, Mann-Whitney U tests, or Kruskal–Wallis tests for continuous variables and χ² tests for categorical variables. Intra- and interobserver reliability was evaluated using the intraclass correlation coefficient. To understand the relationships of renal function and RVI with other continuous variables, we performed Spearman and Pearson correlation analysis. Correlation coefficient values >0.3 were considered relevant. Kaplan-Meier analysis was performed to determine the relationship of RVI and IRVF patterns with clinical end points. Risk factors for clinical end points were determined with Cox proportional hazards models. Univariate factors with P<0.05 were entered into the multiple Cox regression model. A stepwise backward procedure was used in multiple Cox regression analysis (likelihood ratio). RVI values >0 were divided into tertiles, and then the hazard rates of each tertile for reaching the clinical end points were calculated in relation to the control group (RVI=0). Receiver operating characteristic curves were used to evaluate RVI and IRVF as predictors of binary clinical end points. Time-to-event information and censoring were ignored when computing the areas under the curves. Receiver operating characteristics were compared with the DeLong test implemented in the R package pROC.

### Table 1. Continued

| Neurohormonal status | All patients (N=205) | RVI Tertiles | P Value* |
|----------------------|----------------------|--------------|----------|
|                      |                      | First, 0 to ≤0.12 (n=94) | Second, >0.12 to ≤0.32 (n=48) | Third, >0.32 (n=49) |
| **BNP, pg/mL**       | 138.0 (50.0–321.0)   | 46.0 (26.0–113.0) | 98.0 (38.0–264.5) | 198.5 (111.3–322.5) | 468.0 (228.5–820.0) | <0.0001 |
| **Copeptin, pmol/L** | 11.1 (5.8–23.3)      | 9.1 (4.6–16.0) | 7.3 (4.9–14.4) | 14.0 (5.2–23.5) | 23.2 (11.1–39.6) | <0.0001 |
| **Urine feNa, %**     | 0.6 (0.4–1.3)        | 0.7 (0.4–1.2) | 0.6 (0.4–1.1) | 0.6 (0.4–1.2) | 1.2 (0.4–2.1) | 0.072 |

**Hydration status**

| Hydration status | All patients (N=205) | RVI Tertiles | P Value* |
|------------------|----------------------|--------------|----------|
|                  |                      | First, 0 to ≤0.12 (n=94) | Second, >0.12 to ≤0.32 (n=48) | Third, >0.32 (n=49) |
| **Peripheral edema, n (%)** | 60 (29.3) | 13 (22.0) | 11 (22.4) | 16 (33.3) | 20 (40.8) | 0.105 |
| **Pleural effusion, n (%)**   | 17 (8.3) | 3 (5.1) | 3 (6.1) | 3 (6.3) | 8 (16.3) | 0.137 |
| **Ascites, n (%)**           | 7 (3.4) | 0 (0) | 1 (2.0) | 0 (0) | 6 (12.2) | 0.0013 |
| **Hydration status as measured by bioimpedance** | 0.71±0.12 | −0.14±1.41 | 0.50±1.78 | 1.18±2.41 | 1.50±2.48 | <0.0001 |
| **ECW/ICW ratio**           | 0.88±0.12 | 0.85±0.11 | 0.85±0.09 | 0.89±0.13 | 0.91±0.13 | 0.0286 |

**Intra-abdominal pressure measurement**

| Abdominal perfusion pressure, mm Hg | All patients (N=205) | RVI Tertiles | P Value* |
|------------------------------------|----------------------|--------------|----------|
|                                    |                      | First, 0 to ≤0.12 (n=94) | Second, >0.12 to ≤0.32 (n=48) | Third, >0.32 (n=49) |
| **Abdominal perfusion pressure, mm Hg** | 76.78±11.81 | 79.46±10.38 | 77.31±10.89 | 76.19±13.32 | 73.61±12.21 | <0.0001 |

Values are mean±SD or median (interquartile range) except as noted. Additional data are provided in the Data S1. ACEI indicates angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; 1MCR; 1-microglobulin/creatinine ratio; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECW, extracellular water; E/e ratio, ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR, estimated glomerular filtration rate; feNa, fractional excretion of sodium; ICW, intracellular water; IVC, inferior vena cava; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVF, left ventricular ejection fraction; MAP, mean arterial pressure; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; PCR, protein/creatinine ratio; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RRI, renal resistive index; RV, right ventricular; RV S', systolic annular tissue velocity of the lateral tricuspid annulus; RVI, renal venous stasis index; 6MWD indicates 6-min walk distance; TAPSE, tricuspid annular plane systolic excursion.

*After application of the Bonferroni correction, P=0.0008 was considered significant.

1Blood gas measurements were taken from arterialized capillary ear lobe blood during right heart catheterization. In patients with long-term oxygen treatment, oxygen was applied by nasal cannula at the previously prescribed flow rate. To convert mm Hg to kPa, multiply by 0.133.

2MAP was calculated as follows: systolic blood pressure−[2×diastolic pressure]−3.

3To convert the values for serum creatinine to μmol/L, multiply by 88.4.

4To convert the values for urea to blood urea nitrogen, multiply by 0.467.

5*eGFR was calculated with the CKD-EPI equation based on serum creatinine.

6**eGFR was calculated with the CKD-EPI equation based on serum creatinine and cystatin C.

7The renal filtration gradient was calculated as follows: MAP−2×intra-abdominal pressure.

8Additional bioimpedance data are provided in Data S1.

9Abdominal perfusion pressure was calculated as MAP minus intra-abdominal pressure.

After application of the Bonferroni correction, P=0.0008 was considered significant.

Additional data are provided in the Data S1. ACEI indicates angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; 1MCR; 1-microglobulin/creatinine ratio; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECW, extracellular water; E/e ratio, ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR, estimated glomerular filtration rate; feNa, fractional excretion of sodium; ICW, intracellular water; IVC, inferior vena cava; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVF, left ventricular ejection fraction; MAP, mean arterial pressure; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; PCR, protein/creatinine ratio; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RRI, renal resistive index; RV, right ventricular; RV S', systolic annular tissue velocity of the lateral tricuspid annulus; RVI, renal venous stasis index; 6MWD indicates 6-min walk distance; TAPSE, tricuspid annular plane systolic excursion.

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7The renal filtration gradient was calculated as follows: MAP−2×intra-abdominal pressure.

8Additional bioimpedance data are provided in Data S1.

9Abdominal perfusion pressure was calculated as MAP minus intra-abdominal pressure.
Overall, the significance level was set at $\alpha=0.05$ except in multiple Cox regression analysis, where the significance level was $\alpha=0.10$. The Bonferroni correction was applied to adjust for multiple testing. The size of the RHC cohort was estimated based on feasibility considerations. The power to detect a hazard ratio $>2.0$ at $\alpha=0.05$ between the third tertile RVSI group ($n=49$) versus RVSI=0 ($n=59$) was 50%. The power was calculated in R (3.5.1) using the function `powerCT` from the package `powerSurvEpi (0.1.0)`, based on a method proposed by Freedman.27,29,30 All other statistical analyses were performed using SPSS 23.0 software (IBM Corp).

Results

Patients

Of 270 eligible patients undergoing RHC, 205 patients were enrolled and included in the analysis (Figure 3). None were lost to follow-up. In all patients except 2, renal Doppler studies were performed in the right kidney. IRVF pattern classifications were completely consistent, and RVSI measurements showed excellent reliability in both intra- and interobserver comparisons (Table S1). Patients’ baseline characteristics are shown in Table 1 and Table S2.

Association of RVSI with IRVF patterns and demographic and clinical characteristics

After completion of recruitment, we confirmed the predefined IRVF patterns with invasive hemodynamics and echocardiography and assessed their associations with other parameters (Figure S1 and Table S3). By definition, patients with no renal congestion had RVSI=0 and were assigned as the referent group. As shown, RVSI showed a significant stepwise increase along the predefined IRVF patterns ($P<0.0001$; Figure 4).

Table 1 and Figure 5 show the associations of RVSI tertiles with key clinical parameters (additional parameters are shown in Table S4). Cardiopulmonary hemodynamics (evaluated by RHC) worsened with increasing RVSI tertile, with RAP showing the clearest association. RV systolic function (tricuspid annular plane systolic excursion) showed a significant stepwise decrease along the tertiles, with manifest dysfunction at the highest tertile. Right atrial and ventricular diameter, left atrial diameter, and $E/e’$ ratio significantly increased along the RVSI tertiles.

Patients with no congestion had normal mean serum creatinine and eGFR values. From the second RVSI tertile onward, there was gradual lower eGFR and renal filtration gradient across RVSI tertiles, whereas from RVSI=0 (no congestion) to the first RVSI tertile, there was no significant change in serum creatinine ($P=0.09$), eGFR ($P=0.53$), and cystatin C ($P=0.70$). RRI significantly increased with increasing RVSI tertile. Of note, none of the patients exhibited a significant difference in mean RRI values between kidneys (indicative of renal artery stenosis). There was a significant increase in proteinuria, albuminuria, and tubular proteinuria ($\alpha 1$-microglobulin) with increasing RVSI tertile, but the median values stayed within the physiological range.

RVSI tertiles were associated with levels of BNP and copeptin, as well as hydration status (as measured by bioimpedance), loop diuretic dose, and intra-abdominal pressure. Fluid overload was detected as an extracellular fluid expansion in relation to intracellular fluid depletion. Of note, all patients with ascites were in the highest RVSI tertile and exhibited a monophasic IRVF pattern except 1 patient who was diagnosed with hepatitis C–associated liver cirrhosis and porto-PH who was within the first RVSI tertile.

Correlation analyses (Figure S2 and Table S5) showed relevant and statistically significant relationships between RVSI and cardiopulmonary hemodynamics, echocardiographic parameters, renal function, intra-abdominal pressure, and neurohormonal and hydration status. As expected, tricuspid insufficiency had an impact on RVSI values [median RVSI: 0.00 [IQR: 0.15–0.36] in mild, 0.13 [IQR: 0.17–0.46] in moderate, and 0.33 [IQR: 0.26–0.72] in severe tricuspid insufficiency; $P<0.0001$]. However, in multivariate Cox regression analysis, RVSI was superior to tricuspid insufficiency in predicting the composite end point and all individual components. Furthermore, RVSI values were significantly increased in patients with versus without atrial fibrillation (0.28 versus 0.09; $P<0.0001$); this large difference was not due to interobserver variability (intraclass correlation coefficient was >0.9 in both groups).

Of the echocardiographic and hemodynamic parameters assessed, right atrial area and RAP showed the strongest...
correlations with renal function (Table S6). Arterial blood gas measurements showed no correlation with renal function.

**Analysis of PH subtypes**

Baseline parameters significantly differed across the PH subtype groups, and confirmed the correctness of the classification of each group (Table S7). All 30 patients with PH due to left heart disease had HF with preserved ejection fraction (Table S2). Patients with PH due to left heart disease exhibited the highest RVSI values and were most likely to have a monophasic pattern; they also had the poorest right and left heart function, lowest renal function, and highest BNP levels and intra-abdominal pressures.

**Clinical outcomes**

All 205 patients were included in the analysis of outcomes. During the observational period (12 months [range: 11–13 months]), the composite end point of PH-related morbidity and death from any cause occurred in 91 of 205 patients (Table S8). We observed 64 (31.2%) unscheduled hospitalizations for fluid overload, 71 (34.6%) escalations of PH-specific therapy, and 21 (10.2%) deaths. Five patients underwent pulmonary thromboendarterectomy, and 1 patient underwent lung transplantation.

Patients in higher RVSI tertiles had increased rates of the composite end point (Figure 6) and 2 of the individual components (Figure S3). Analysis of outcomes by IRVF patterns showed broadly similar trends but with some overlap between the groups with biphasic and monophasic IRVF patterns (Figure S4). In multiple Cox regression analysis, RVSI tertiles remained independent predictors of the composite end point and 2 of the individual components (Table 2; univariate analyses are provided in Tables S9–S12).

**Figure 5.** RVSI and associated clinical parameters. Severity of renal congestion can be evaluated by measurement of RVSI using renal Doppler ultrasonography. The figure illustrates the associations of RVSI tertiles with RAP and renal function (A), right ventricular systolic function and RA area (B), neurohormonal status (C), and hydration status (D). Fluid overload as measured by bioimpedance is likely to occur because of hemodynamic alterations and neurohormonal activation leading to a deterioration of renal function and fluid retention. BNP indicates B-type natriuretic peptide; eGFR, estimated glomerular filtration rate (based on Chronic Kidney Disease Epidemiology Collaboration creatinine–cystatin C equation); RA, right atrial; RAP, right atrial pressure; RVSI, renal venous stasis index; TAPSE, tricuspid annular plane systolic excursion; VII, venous impedance index.

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During the observational period, 3 patients developed stage 3 acute kidney injury with diuretic-resistant fluid overload and required RRT; all 3 exhibited a monophasic IRVF pattern with a median RVSI of 0.64 (IQR: 0.59–0.73) at baseline.

**Discussion**

We developed a continuous index from Doppler-derived IRVF patterns and propose the RVSI as a simple, noninvasive, and integrative Doppler measure of renal congestion. In patients undergoing RHC based on clinical grounds, the RVSI was correlated with invasive hemodynamics. Furthermore, our data suggest that the RVSI may be superior to individual IRVF patterns in predicting outcome.

Elevated RAP has been identified as a main driver of deteriorating renal function in acutely decompensated HF. Only 3 HF studies have previously investigated the association of Doppler-derived IRVF patterns and venous impedance index with RAP and their utility in predicting diuretic response and adverse outcomes. Furthermore, we assessed the tricuspid annular plane systolic excursion/systolic PAP ratio as a parameter of right ventricle–pulmonary artery coupling, which was recently demonstrated to be associated with prognosis in patients with pulmonary arterial hypertension and HF with preserved ejection fraction. The association of the tricuspid annular plane systolic excursion/systolic PAP ratio and RVSI further emphasizes the meaning of RVSI as a marker of renal congestion, as it mirrors not only RV failure but also right ventricle–pulmonary artery uncoupling when afterload exceeds contractility.

IRVF depends on extrinsic factors (interstitial pressure and intra-abdominal pressure) and intravenous pressure, which is highly dependent on RAP. Under physiological conditions, intrarenal veins exhibit continuous flow independent of renal function, with superimposed biphasic forward velocities that peak during systole (reflecting right atrial filling during RV ejection) and diastole (reflecting RAP release after the tricuspid valve opens and RV filling occurs). With increasing RAP, intrarenal veins become less compliant, dampening the continuous flow to a discontinuous (RVSI>0) flow and increasing prominence of the superimposed biphasic forward velocities. Further increases in RAP may ultimately lead to a diastolic-only (monophasic) flow pattern, in which renal venous outflow may exclusively depend on RV filling. Of note, the increase in RAP during end-diastole (corresponding to atrial contraction) can be transmitted to the renal veins, potentially causing a reversal of vein flow, as recently described; this may have been masked by the arterial waveforms in our analysis of interlobar arteries and veins.

Deterioration of renal function in right HF appears to be mainly hemodynamic (congestive), independent of PH subtype, and associated with activation of the neurohormonal system and fluid overload. This type of congestive nephropathy can be described as a gradual decrease of renal function as RVSI worsens, with no proteinuria even at severe congestion. Interestingly, we see no significant changes in creatinine, eGFR, or cystatin C in patients with RVSI in the first tertile compared with normal RVSI (RVSI=0). This could be explained by renal lymphatic flow increasing dramatically with early congestion, consequently preventing an increase in renal interstitial pressure until full saturation, and suggests that
Table 2. Predictors of Clinical End Points Identified by the Cox Proportional Hazards Model

| Predictor | Univariate HR (95% CI) | P Value | Multiple HR (95% CI) | P Value |
|-----------|-------------------------|---------|----------------------|---------|
| **PH-related morbidity and death from any cause** | | | | |
| RVSI tertiles | 20.57 (9.03–46.87) | <0.0001 | 2.30 (0.95–5.53) | 0.064 |
| First tertile group vs RVSI 0 | 2.31 (1.06–5.05) | 0.0363 | 3.41 (1.49–7.81) | 0.0037 |
| Second tertile group vs RVSI 0 | 3.63 (1.71–7.65) | 0.0007 | 4.72 (2.10–10.59) | <0.0001 |
| Third tertile group vs RVSI 0 | 8.70 (4.33–17.48) | <0.0001 | 4.72 (2.10–10.59) | <0.0001 |
| Congestion stages | 2.00 (1.63–2.44) | <0.0001 | 2.31 (1.06–5.05) | 0.0363 |
| Stage 1 vs stage 0 | 2.65 (1.29–5.44) | 0.0078 | 2.61 (1.18–5.80) | 0.0182 |
| Stage 2 vs stage 0 | 6.35 (3.08–13.09) | <0.0001 | 4.90 (2.15–11.18) | <0.0001 |
| Stage 3 vs stage 0 | 8.45 (3.98–17.96) | <0.0001 | 4.07 (1.68–9.85) | 0.0019 |
| Uric acid | 1.25 (1.16–1.34) | <0.0001 | 1.15 (0.95–1.34) | <0.0001 |
| Atrial fibrillation | 2.56 (1.68–3.88) | <0.0001 | 1.94 (1.05–3.56) | 0.0355 |
| 6MWD | 0.997 (0.996–0.999) | 0.006 | 0.997 (0.995–0.999) | 0.0099 |
| LA diameter | 1.07 (1.04–1.10) | <0.0001 | 1.05 (1.01–1.10) | 0.0301 |
| Age | 1.02 (1.00–1.03) | 0.0439 | 0.98 (0.96–1.00) | 0.079 |
| **Unscheduled hospitalization due to fluid overload** | | | | |
| RVSI tertiles | 1.71 (1.48–1.98) | <0.0001 | 5.50 (1.09–27.85) | 0.0395 |
| First tertile group vs RVSI 0 | 6.49 (1.42–29.64) | 0.0157 | 2.65 (1.29–5.44) | 0.0078 |
| Second tertile group vs RVSI 0 | 10.98 (2.52–47.76) | 0.0014 | 6.27 (1.36–28.96) | 0.0187 |
| Third tertile group vs RVSI 0 | 35.60 (8.54–148.38) | <0.0001 | 8.84 (1.98–39.46) | 0.0043 |
| Congestion stages | 2.49 (1.94–3.20) | <0.0001 | 1.94 (1.05–3.56) | 0.0355 |
| Stage 1 vs stage 0 | 7.36 (1.71–31.72) | 0.0074 | 5.01 (1.14–22.07) | 0.0334 |
| Stage 2 vs stage 0 | 25.51 (6.05–107.67) | <0.0001 | 8.84 (1.98–39.46) | 0.0043 |
| Stage 3 vs stage 0 | 32.17 (7.44–139.09) | <0.0001 | 5.06 (1.02–25.20) | 0.0478 |
| Uric acid | 1.29 (1.19–1.41) | <0.0001 | 1.27 (1.13–1.43) | <0.0001 |
| PCWP | 1.08 (1.05–1.11) | 0.0001 | 1.04 (1.01–1.08) | 0.0159 |
| Urosecreter 1MCR | 1.01 (1.01–1.02) | <0.0001 | 1.01 (1.00–1.02) | 0.0262 |
| Atrial fibrillation | 4.05 (2.47–6.63) | <0.0001 | 1.88 (1.00–3.54) | 0.0510 |
| 6MWD | 0.996 (0.994–0.999) | 0.0006 | 0.997 (0.995–0.999) | 0.0099 |
| RA area | 1.11 (1.07–1.14) | <0.0001 | 1.05 (1.00–1.10) | 0.0477 |
| Urine feNa | 1.21 (1.07–1.36) | 0.0017 | 0.82 (0.67–1.00) | 0.0547 |
| NYHA classification | 1.81 (1.24–2.64) | 0.0022 | 0.60 (0.34–1.05) | 0.074 |
| **Escalation of PH-specific therapy** | | | | |
| Mixed venous oxygen saturation | 0.92 (0.90–0.95) | <0.0001 | 0.96 (0.93–1.00) | 0.0403 |
| Uric acid | 1.26 (1.16–1.36) | <0.0001 | 1.31 (1.02–1.62) | 0.0242 |
| RVSI tertiles | 1.43 (1.26–1.63) | <0.0001 | 1.43 (1.26–1.63) | <0.0001 |
| First tertile group vs RVSI 0 | 2.16 (0.89–5.24) | 0.087 | 1.89 (0.68–5.27) | 0.2241 |
| Second tertile group vs RVSI 0 | 3.52 (1.53–8.07) | 0.0030 | 2.91 (1.13–7.51) | 0.0271 |
| Third tertile group vs RVSI 0 | 7.03 (3.22–15.35) | <0.0001 | 4.29 (1.63–11.27) | 0.0031 |
| Congestion stages | 1.86 (1.49–2.33) | <0.0001 | 2.31 (1.06–5.05) | 0.0363 |
| Stage 1 vs stage 0 | 2.37 (1.05–5.35) | 0.0373 | 2.13 (0.84–5.37) | 0.110 |
Table 2. Continued

| Predictor                  | Univariate          | Multiple            |
|----------------------------|----------------------|---------------------|
|                            | HR (95% CI)          | P Value             | HR (95% CI)          | P Value |
| Stage 2 vs stage 0         | 6.22 (2.79–13.87)    | <0.0001             | 4.44 (1.74–11.32)    | 0.0018  |
| Stage 3 vs stage 0         | 6.39 (2.73–14.97)    | <0.0001             | 3.31 (1.13–9.70)     | 0.0293  |
| E/e’ ratio                 | 1.07 (1.03–1.12)     | 0.0006              | 1.06 (1.01–1.10)     | 0.0138  |
| 6MWD                       | 0.997 (0.995–0.999)  | 0.0013              | 0.998 (0.996–1.00)   | 0.073   |
| LVEDD                      | 0.95 (0.91–0.99)     | 0.0221              | 0.94 (0.89–0.99)     | 0.0179  |
| All-cause mortality        |                      |                     |                     |
| Mixed venous oxygen saturation | 0.92 (0.88–0.96) | <0.0001             | 0.94 (0.89–0.99)     | 0.0120  |
| RA area                    | 1.10 (1.04–1.17)     | 0.0018              | 1.07 (1.01–1.15)     | 0.0341  |
| NYHA classification        | 2.65 (1.30–5.41)     | 0.0074              | 1.97 (0.99–3.90)     | 0.0536  |

Table includes only variables that remained significant after Cox regression analysis. All available variables were included in the univariate analyses, and variables that were significant in the univariate analyses are provided in Tables S9–S12. a1MCR indicates α1-microglobulin-to-creatinine ratio; E/e’ ratio, ratio of mitral inflow velocity to lateral annular relaxation velocity; feNa, fractional excretion of sodium; HR, hazard ratio; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; RA, right atrial; RVSI, renal venous stasis index; 6MWD indicates 6-min walk distance.

an increase of RVSI from 0 to the first tertile may be a more sensitive marker to identify patients at risk for subsequent renal function decline than established biomarkers such as creatinine and cystatin C. Transmission of venous congestion to the renal veins is thought to impair GFR by increasing pressure in the efferent end of the glomerular capillary, which reduces glomerular–capillary hydrostatic pressure; this can be reversed by lowering renal venous pressure in experimental models. As an additional component, concomitant elevation of renal interstitial pressure is likely to reduce glomerular net ultrafiltration pressure by opposing glomerular–capillary hydrostatic pressure and to reduce renal blood flow, as shown by the significant increases in RRI in our population. Future studies need to determine whether therapies that reduce RAP will improve renal function and particularly which RAP range must be achieved to provide an acceptable balance of RV and renal function.

Our study has all the limitations of retrospective analyses of prospectively collected data. Limitations include its single-center design, selection bias, and moderate sample size and duration of follow-up. We assumed that the monophasic IRVF pattern reflects venous pressure release resulting from RV filling, but we did not determine end-diastolic filling pressures or RV volumes. In addition, entering RVSI and congestion stages to 1 Cox regression model was done for comparison of their prognostic value but may lead to overfitting of the model. All echocardiography data were collected 1 day before RHC. Although PH-specific therapy was not initiated or changed in the interval between these assessments, some patients received additional diuretics when fluid overload was present, which limits the interpretation of echocardiography relative to RHC data. Renal venous congestion does not necessarily indicate right HF because tricuspid insufficiency with intact RV function may also induce congestion, and discontinuous IRVF patterns have been described in obstructive nephropathy, where they are at least partly explained by increased renal interstitial pressure subsequent to ureter obstruction.

Our study confirmed the prognostic relevance of renal venous congestion, and the novel RVSI in particular showed promise as a simple, noninvasive, and objective Doppler measure. RVSI and IRVF patterns may be useful to identify patients who are likely to experience adverse outcomes. Longitudinal studies are needed to clarify their roles in the management of HF.

Conclusions

Our analyses of patients undergoing RHC present RVSI as a novel Doppler measurement of renal congestion that may be superior to IRVF patterns in predicting outcome in patients with PH. Further studies are needed to validate our findings and assess the utility of RVSI in PH management.

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SUPPLEMENTAL MATERIAL
Data S1.

SUPPLEMENTAL METHODS
Study design and participants

Data collection
Clinical variables were abstracted from patient medical records. All clinical and laboratory data, including patient demographics, were collected and stored in a password-protected dataset.

Right heart catheterization (RHC)
All RHC measures were derived at end-expiration, and reported values represent the average of 5 to 10 cardiac cycles. Cardiac output (average of three cycles with <10% variation in patients in sinus rhythm and five cardiac cycles in patients with atrial fibrillation) was derived by both thermodilution and the Fick method using nomograms for oxygen uptake in conjunction with the Fick method. If patients did not have supplemental oxygen therapy, the direct Fick method was performed directly after oxygen uptake assessment. When a discrepancy was present between both methods, cardiac output was reported by direct Fick; if direct Fick measurement was not possible, thermodilution was used. Pulmonary vascular resistance and cardiac index were calculated as described previously (pulmonary vascular resistance=[mean pulmonary arterial pressure−pulmonary capillary wedge pressure]/cardiac output; cardiac index=[cardiac output/body surface area]).

Bioimpedance spectroscopy
Bioimpedance is based on the principle that the body acts as a circuit with a given resistance (opposition of current flow through intracellular and extracellular solutions [Ri and Re]) and reactance (the capacitance of cells to store energy [Xc]). The volume of the body fluid component is largely reflected in the resistance, whereas reactance might represent cell membrane integrity. The impedance is composed of the sum of resistance and reactance (\(\sqrt{R^2 + Xc^2}\)). Another parameter that can be derived is the phase angle, which is the arc tangent of Xc/R. When a current passes through cells, a portion of the electrical current is stored and subsequently released in a different phase, termed “phase angle”. The phase angle is related to the ability of cells to function as capacitors, which is dependent on the integrity of the cell membrane and cellular health. Bioimpedance data from the study population are provided in Table S4.

The three-compartment model of the BCM Body Composition Monitor has been validated against standard reference methods for assessment of fluid status and body composition in patients undergoing hemodialysis and peritoneal dialysis, albeit partly against gold standard techniques in healthy controls only. BCM has been shown to be valid in different ethnicities, and measures impedance at 50 different frequencies between 5 kHz and 1 MHz. Reproducibility of BCM-derived parameters is high, with a coefficient of variation for the inter-observer variability for extracellular water and total body water around 1.2% in studies performed in patients undergoing hemodialysis. Therefore, only one BCM measurement was performed in each individual patient. BCM results are normalized by sex and patient height. According to the manufacturer’s recommendations we excluded patients if they had an unipolar pacemaker, while there were no limitations for patients with stents or bipolar pacemakers. For measurement, the skin was cleansed with alcohol, then the electrodes were attached to one hand and one foot at the ipsilateral side, after the patient had been supine for at least 5 minutes and not touching any metal objects.

Hydration status (expressed in Liters) was derived from the impedance data based on a physiologic tissue model that separates the body into three compartments: surplus water, normohydrated lean tissue, and fat tissue. Hydration status represents the difference between the measured amount of extracellular water and the amount of water expected in normohydrated tissue conditions. Patients are considered ‘dehydrated’ or ‘overhydrated’ when their absolute hydration status is below the 10th or above the 90th percentile of the normal, presumed healthy, reference population, respectively (corresponding to 1.1 L of negative or positive hydration status, respectively). Due to bio-physical reasons, bioimpedance spectroscopy does not measure sequestered fluid in the trunk, and presence of pleural effusion and ascites was documented by ultrasound. Lean tissue mass represents the body mass without adipose tissue and excess extracellular water (fluid overload). Fat represents the mass of adipose lipids in the body. Lean tissue mass and fat are provided in kilograms as well as in relation to body weight (%). Lean tissue index is calculated as the quotient of lean tissue mass/height. Fat tissue index is defined as the quotient of adipose tissue mass/height. Adipose tissue mass is the mass of the adipose tissue, including the adipose water. Body cell mass represents the cellular, metabolically active body mass, excluding the extracellular fluid in the metabolically active tissue.

Intra-abdominal pressure measurement
Intra-abdominal pressure was measured with a standard Foley catheter, which was connected to a pressure transducer placed in-line with the iliac crest at the midaxillary line. The Foley catheter was flushed with a maximal instillation volume of 50 mL sterile saline via the aspiration port of the Foley catheter with the drainage
tube clamped to allow a fluid-filled column to develop up into the bladder. A pressure transducer was then inserted in the aspiration port, and the pressure was measured. The intra-abdominal pressure was expressed in mm Hg and was measured at end-expiration in the supine position, ensuring that abdominal muscle contractions were absent.

**Laboratory methods**

Blood and urine samples were centrifuged for 10 minutes at 3000xg and 5 minutes at 500xg, respectively. Samples were processed within 30 minutes of collection.

B-type natriuretic peptide (BNP) and parathormone were measured by the chemiluminescence method on an Advia Centaur XPT analyzer (Siemens Healthcare GmbH, Erlangen, Germany). BNP >35 pg/mL was taken as the cut-off for diagnosing chronic heart failure. Copeptin was measured by the Time-Resolved Amplified Cryptate Emission method on a Brahms Kryptor Compact Plus (Thermo Fisher Scientific, MA, USA). The range of copeptin, a surrogate marker for proarginine vasopressin release and neurohormonal activation, in healthy individuals has been recently described as 4.2 [9.5] pmol/L. Serum aldosterone was measured by the radioimmunological method on a Multi Crystal LB 2111 Gamma Counter (Berthold Technologies, Bad Wildbich, Germany). Urine sodium-to-potassium ratio <2 was considered as a marker of hyperaldosteronism. Urine fractional excretion of sodium <1% was considered as a marker of sodium retention. Cystatin C was measured by the immunonephelometric method on an AU5800 Chemistry Analyzer (Beckman Coulter, California, USA) with reference material ERM-DA471/IFCC (distributed by the European Joint Research Institute for Reference Materials and Measurements, Geil, Belgium). Creatinine was measured by the photometric-enzymatic method on an Advia Centaur XPT analyzer, with calibration to isotope dilution mass spectrometry reference measurements. Blood urea nitrogen-to-creatinine ratio >20 was considered as a marker of neurohormonally mediated disproportionate reabsorption of urea compared with that of creatinine. Creatinine clearance was calculated as: urine creatinine (mg/dL) x urine volume (mL) x1.73 (m²)/1440 min x serum creatinine (mg/dL) x body surface area (m²). For calculation of urea clearance, creatinine was substituted with urea.

Proteinuria was measured using a colorimetric method with pyrogallol red on an AU5800 Chemistry Analyzer. Albuminuria was measured by the immunoturbidimetric method on an Advia Centaur XPT, and alpha 1-microglobulin was measured by the immuno nephelometric method on an AU5800 Chemistry Analyzer (Siemens Healthcare GmbH, Erlangen, Germany). Protein-to-creatinine ratio, albumin-to-creatinine ratio, and alpha 1-microglobulin-to-creatinine ratio (all reported in units of mg/g creatinine) were then calculated. Microalbuminuria and increased tubular proteinuria (alpha 1 microglobulin) were defined as values ≥30mg/g and ≥20mg/g creatinine, respectively. Positive acanthocyturia, a diagnostic criterion of glomerulonephritis, was defined as >5% acanthocytes in centrifuged urinary sediment detected with a phase-contrast microscope Eclipse Ci-L (Nikon, Tokyo, Japan). Sterile leukocyturia, associated with interstitial nephritis, nephrolithiasis, uroepithelial tumors, and infection with atypical organisms, was defined as a positive urinary dip stick test for leukocyte esterase in combination with a negative urine culture.

Renal replacement therapy (RRT)

Patients with fluid overload received a stepped pharmacological diuretic therapy including adjustable doses of intravenous loop diuretic agents, thiazide diuretic agents, and aldosterone antagonists. Patients who fulfilled the criteria for diuretic resistance despite the stepped pharmacological therapy were transferred to RRT, as were patients who developed stage 3 acute kidney injury with fluid overload or a life-threatening complication (eg, pulmonary edema). Modality of RRT was based on illness acuteness, patient preference, and co-morbidities (eg, presence of ascites). In general, peritoneal dialysis (conventional surgical technique; peritoneal dialysis catheter type Orecoulovs-Zellermann) was the preferred modality for patients with HF, except patients with life-threatening indications or cardiovascular instability, for whom slow extended daily hemodialysis with the GENIUS® dialysis system (Fresenius Medical Care, Bad Homburg, Germany) was preferred.
Table S1. ICC for RVSI measured by two independent nephrologists.

|                      | Intraclass correlation* | 95% confidence interval | F test with true value 0 |
|----------------------|--------------------------|--------------------------|--------------------------|
|                      |                          | Lower bound              | Upper bound              | Value | df1 | df2 | Significance |
| **Inter-observer reliability** |                          |                          |                          |       |     |     |              |
| Single measures      | 0.978†                   | 0.973                    | 0.982                    | 178.709 | 204 | 612 | 0.000        |
| Average measures     | 0.994‡                   | 0.993                    | 0.996                    | 178.709 | 204 | 612 | 0.000        |
| **Intra-observer reliability** |                          |                          |                          |       |     |     |              |
| TS – single measures | 1.000†                   | 1.000                    | 1.000                    |       |     |     |              |
| TS – average measures| 1.000‡                   | 1.000                    | 1.000                    |       |     |     |              |
| FH-S – single measures| 1.000†                   | 1.000                    | 1.000                    | 5302.258 | 204 | 204 | 0.000        |
| FH-S – average measures| 1.000‡                   | 1.000                    | 1.000                    | 5302.258 | 204 | 204 | 0.000        |

Two-way mixed effects model where people effects are random and measures effects are fixed.

*Type A ICCs using an absolute agreement definition for inter-observer reliability; Type C ICCs using a consistency definition for intra-observer reliability.
†The estimator is the same, whether the interaction effect is present or not.
‡This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.
df=degrees of freedom; ICC=intraclass correlation coefficient; RVSI=renal venous stasis index.
Table S2. Classification of the RHC Cohort According to PH Subcategories.

| Category                                                                 | n (%)     |
|-------------------------------------------------------------------------|-----------|
| No PH                                                                   | 40 (100)  |
| Disease control                                                         | 27 (67.5) |
| HF with preserved ejection fraction                                      | 13 (32.5) |
| Group 1 (PAH)                                                           | 46 (100)  |
| Idiopathic PAH                                                          | 27 (58.7) |
| Connective tissue disease                                               | 8 (17.4)  |
| Congenital systemic-to-pulmonary shunts                                  | 6 (13.0)  |
| Porto-pulmonary PH                                                      | 5 (10.9)  |
| Group 2 (PH due to left heart disease)                                   | 30 (100)  |
| PH-HF with preserved ejection fraction                                  | 30 (100)  |
| Group 3 (PH due to lung disease and/or hypoxemia)                       | 41 (100)  |
| Chronic obstructive pulmonary disease                                   | 22 (53.7) |
| Interstitial lung disease                                               | 15 (36.6) |
| Sleep-disordered breathing                                              | 4 (9.8)   |
| Group 4 (chronic thromboembolic PH)                                     | 34 (100)  |
| Group 5 (PH with unclear multifactorial mechanisms)                     | 14 (100)  |
| Sarcoidosis                                                             | 9 (64.3)  |
| Churg-Strauss syndrome                                                  | 1 (1.6)   |
| Unknown mechanisms                                                      | 4 (28.6)  |

HF denotes heart failure, PAH pulmonary arterial hypertension, PH pulmonary hypertension, and RHC right heart catheterization.
Table S3. Clinical characteristics, invasive hemodynamics, echocardiographic data, renal function, and neurohormonal and hydration status stratified according to congestion stages as determined by intravenous venous flow patterns.

| Clinical characteristic | All patients (n=205) | No congestion (n=59) | Stage 1 congestion (n=77) | Stage 2 congestion (n=44) | Stage 3 congestion (n=25) | p value† |
|-------------------------|----------------------|----------------------|---------------------------|--------------------------|--------------------------|---------|
| **Baseline clinical data** |                      |                      |                           |                          |                          |         |
| LVEF, %                 | 60.0 [60.0–65.0]      | 60 [60.0–65.0]       | 60 [60.0–65.0]            | 60 [55.0–65.0]           | 60 [52.5–60.5]           | 0.0552  |
| eSWD, m                 | 277.2±136.05         | 309.7±118.16        | 296.8±142.92              | 224.5±127.15             | 232.8±137.57             | 0.0022  |
| NYHA classification, n (%) |                      |                      |                           |                          |                          |         |
| 1–2                     | 44 (21.5)            | 15 (25.4)           | 22 (28.6)                 | 4 (9.1)                  | 3 (12)                   | 0.078   |
| 3–4                     | 161 (78.5)           | 44 (74.6)           | 45 (71.4)                 | 40 (90.9)                | 22 (88)                  |         |
| Oxygen supply, n (%)    | 118 (57.6)           | 28 (47.5)           | 45 (58.4)                 | 33 (75.0)                | 12 (48.0)                | 0.0306  |
| **Maintenance therapy** |                      |                      |                           |                          |                          |         |
| AECr or ARB, n (%)      | 83 (40.5)            | 23 (39.0)           | 33 (42.9)                 | 13 (29.5)                | 14 (56.0)                | 0.178   |
| Loop diuretic dose, mg/day | 40.0 [0.0–60.0]     | 20.0 [0.0–40.0]     | 20.0 [0.0–45.0]           | 40.0 [0.0–80.0]          | 80.0 [40.0–200.0]        | <0.0001 |
| Thiazide diuretic, n (%) | 72 (35.1)            | 18 (30.5)           | 27 (35.1)                 | 17 (38.6)                | 10 (40.0)                | 0.789   |
| Aldosterone antagonist, n (%) | 76 (37.1)         | 16 (27.1)           | 30 (39.0)                 | 17 (38.6)                | 13 (52.0)                | 0.168   |
| Triamterene, n (%)      | 5 (2.4)              | 0 (0.0)             | 3 (2.9)                   | 2 (4.5)                  | 0 (0.0)                  | 0.307   |
| **PH-specific therapy, n (%)** |                      |                      |                           |                          |                          | 0.433   |
| Treatment-naive         | 116 (56.6)           | 42 (71.2)           | 36 (46.8)                 | 24 (54.5)                | 14 (56.0)                |         |
| Monotherapy             | 49 (23.9)            | 8 (13.6)            | 23 (29.9)                 | 11 (25.0)                | 7 (28.0)                 |         |
| Dual therapy            | 28 (13.7)            | 6 (10.2)            | 13 (16.9)                 | 6 (13.6)                 | 3 (12.0)                 |         |
| Triple therapy          | 12 (5.9)             | 3 (5.1)             | 5 (6.5)                   | 3 (6.8)                  | 1 (4.0)                  |         |
| **Hemodynamics**        |                      |                      |                           |                          |                          |         |
| Mean PAP, mm Hg         | 34.8±14.63           | 24.10±9.62          | 37.14±15.02               | 42.84±12.33              | 39.0±13.11               | <0.0001 |
| PVR, dyn.s/cm²          | 394 [214–604]        | 229 [110–420]       | 440 [277–600]             | 558 [293–829]            | 428 [245–750]            | <0.0001 |
| RAP, mm Hg              | 5.76±5.63            | 2.46±3.66           | 4.44±4.75                 | 9.00±5.04                | 11.88±7.54               | <0.0001 |
| Cardiac index, L/min/m² | 2.73±0.98            | 2.98±1.01           | 2.76±1.00                 | 2.47±0.70                | 2.48±1.13                | 0.0332  |
| PCWP, mm Hg             | 9.0 [5.0–13.0]       | 7.0 [4.0–10.0]      | 9.0 [6.0–13.0]            | 10.5 [6.0–15.0]          | 12.0 [8.5–18.5]          | <0.0001 |
| Mixed venous oxygen saturation, % | 63.7±8.35               | 66.7±6.42          | 65.1±6.59                 | 59.8±9.70                | 59.6±10.63               | <0.0001 |
| Heart rate, beats/min   | 71.6±13.23           | 72.00±11.32         | 70.34±12.55               | 72.23±13.49              | 73.60±18.51              | 0.703   |
| MAP, mm Hg†             | 84.25±11.57          | 85.22±10.28        | 83.71±12.18               | 85.69±13.06              | 81.09±9.48               | 0.375   |
| **Echocardiographic parameters** |                      |                      |                           |                          |                          |         |
| Right heart             |                      |                      |                           |                          |                          |         |
| TAPSE, mm               | 19.89±4.41           | 21.88±3.82          | 20.87±4.01                | 18.18±3.80               | 15.20±3.46               | <0.0001 |
| RV myocardial performance index (Tei index) | 0.49±0.22        | 0.46±0.20           | 0.47±0.23                 | 0.59±0.23                | 0.48±0.22                | 0.323   |
| SV, cm³/s              | 11.60±3.52           | 12.95±3.31          | 12.18±3.20                | 10.17±3.23               | 9.08±3.43                | <0.0001 |
| TAPSE/Systolic PAP ratio | 0.39±0.21           | 0.56±0.27           | 0.35±0.15                 | 0.30±0.11                | 0.30±0.13                | <0.0001 |
| Tricuspid insufficiency, n (%) |                    |                    |                            |                           |                          | 0.0007  |
| Mild                    | 66 (32.2)            | 34 (57.6)           | 15 (19.5)                 | 12 (27.3)                | 5 (20)                   |         |
| Moderate                | 112 (54.6)           | 23 (39.0)           | 51 (66.2)                 | 25 (56.8)                | 13 (52)                  |         |
| Severe                  | 25 (12.2)            | 1 (17.7)            | 10 (13.0)                 | 7 (15.9)                 | 7 (28)                   |         |
| RA area, cm²            | 18.89±6.72           | 14.14±6.30          | 18.87±5.70                | 20.99±6.24               | 24.16±6.60               | <0.0001 |
| RV diameter, mm         | 40.78±8.08           | 37.93±7.58          | 40.43±6.68                | 43.40±8.86               | 44.04±9.86               | 0.0009  |
| IVC, cm                 | 2.27±0.49            | 2.01±0.52           | 2.30±0.44                 | 2.45±0.31                | 2.51±0.54                | <0.0001 |
| Left heart              |                      |                      |                           |                          |                          |         |
| LVEF, %                 | 60.0 [60.0–65.0]     | 60 [60.0–65.0]      | 60 [60.0–65.0]            | 60 [55.0–65.0]           | 60 [52.5–60.5]           | 0.0552  |
| LA diameter, mm | 41.98±6.86 | 39.78±6.35 | 40.65±6.51 | 43.17±6.12 | 48.56±5.85 | <0.0001 |
|-----------------|-------------|-------------|-------------|-------------|-------------|---------|
| LVEDD, mm       | 46.03±5.59  | 46.28±4.73  | 45.10±5.45  | 46.24±7.01  | 47.84±4.85  | 0.184   |
| E/e’ ratio      | 12.98±4.34  | 11.07±3.52  | 12.96±4.12  | 13.80±4.52  | 16.42±8.07  | 0.0007  |

### Renal function

| Serum creatinine, mg/dL | 1.01±0.45 |
|-------------------------|-----------|
| Cystatin C, mg/L        | 1.10 [0.91–1.52] |
| Urea, mg/dL             | 47.44±35.85 |
| eGFR (CKD-EPI creatinine equation), mL/min/1.73 m² | 74.45±26.12 |
| eGFR (CKD-EPI creatinine-cystatin C equation), mL/min/1.73 m² | 68.58±26.86 |

### Renal filtration gradient, mm Hg**

| Urine PCR, mg/g creatinine | 58.8 [40.2–114.2] |
|----------------------------|-------------------|
| Urine ACR, %               | 11.4 [6.3–29.7]   |
| Urine o1MCr, mg/g creatinine | 10.9 [6.0–19.1] |
| Acanthocyturia, n (%)      | 7 (3.4)            |
| Sterile leukocyturia, n (%) | 2 (1.0)           |

### Renal Doppler ultrasonography

| RVSI                        | 0.11 [0.00–0.32] |
| Venous impedance index      | 0.84±0.26        |
| RRI                         | 0.71±0.07        |

### Neurohormonal status

| BNP, pg/mL                  | 138.0 [50.0–321.0] |
|-----------------------------|-------------------|
| Copeptin, pmol/L            | 11.1 [5.8–23.3]   |
| Sodium, mmol/L              | 13.96±3.07        |
| Urine FeNo %                | 0.6 [0.4–1.3]     |
| BUN-to-creatinine ratio      | 21.15±7.53        |
| Aldosterone, ng/dL          | 5.60 [3.1–11.8]   |
| Potassium, mmol/L           | 3.67±0.42         |
| Urine Na/K ratio             | 3.23±2.24         |

### Hydration status

| Asites, n (%)               | 7 (3.4)           |
| Pleural effusion, n (%)      | 17 (3.8)          |
| Peripheral edema, n (%)      | 60 (29.3)         |
| Hydration status (as measured by bioimpedance), L | 0.71±2.12 |
| Total body water, L          | 37.78±7.47        |
| ECW, L                      | 23.48±3.60        |

### Intra-abdominal pressure measurement

| Intra-abdominal pressure, mm Hg†† | 7.0 [6.0–9.0] |
| Abdominal perfusion pressure, mm Hg†† | 76.78±11.81 |

Values are mean±SD, median [interquartile range], or n (%).
After application of the Bonferroni correction, p<0.0008 was considered significant. †MAP was calculated as (systolic blood pressure+2x diastolic pressure)/3. ‡To convert the values for serum creatinine to μmol/L, multiply by 88.4. §eGFR was calculated with the CKD-EPI equation based on serum creatinine. **The renal filtration gradient was calculated as: MAP–2x intra-abdominal pressure. 6MWD=6-min walk distance; ACEi=angiotensin-converting enzyme inhibitor; ACR=albumin-to-creatinine ratio; α1MCR=α1-microglobulin-to-creatinine ratio; ARB=angiotensin receptor blocker; BUN=blood urea nitrogen; BNP=b-type natriuretic peptide; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ECW=extracellular water; E/e’ ratio=mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; ICW=intracellular water; IVC=inferior vena cava; LA=left atrial; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; Na/K=sodium/potassium; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PCR=protein-to-creatinine ratio; PCWP=pulmonary capillary wedge pressure; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrial; RAP=right atrial pressure; RRI=renal resistive index; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S4. Additional data on clinical characteristics, invasive hemodynamics, echocardiographic data, renal function, neurohormonal and hydration status according to congestion stages as determined by renal venous stasis index.

| Maintenance therapy, n (%) | All patients (n=205) | RVSI=0 (n=59) | First >0<RVSI≤0.12 (n=49) | Second >0.12<RVSI≤0.32 (n=48) | Third RVSI>0.32 (n=49) | p value* |
|----------------------------|---------------------|---------------|---------------------------|-------------------------------|-----------------------|----------|
| Calcium channel blocker    | 46 (22.4)           | 10 (16.9)     | 11 (22.4)                 | 14 (29.2)                     | 11 (22.4)             | 0.518    |
| Thiazide diuretic          | 72 (35.1)           | 18 (30.5)     | 18 (36.7)                 | 17 (35.4)                     | 19 (38.8)             | 0.826    |
| Aldosterone antagonist     | 76 (37.1)           | 16 (27.1)     | 24 (49.0)                 | 12 (25.0)                     | 24 (49.0)             | 0.0095   |
| Triamterene                | 5 (2.4)             | 0 (0)         | 2 (4.1)                   | 3 (6.3)                       | 0 (0)                 | 0.103    |
| Renal function, n (%)      |                     |               |                           |                               |                       |          |
| Acanthocyturia             | 7 (3.4)             | 2 (3.4)       | 2 (4.1)                   | 1 (2.1)                       | 2 (4.1)               | 0.942    |
| Sterile leukocyturia       | 2 (1.0)             | 1 (1.7)       | 0 (0)                     | 0 (0)                         | 1 (2.0)               | 0.605    |
| Neurohormonal status       |                     |               |                           |                               |                       |          |
| BUN-to-creatinine ratio    | 21.15±7.53          | 20.48±7.14    | 20.38±6.60                | 20.78±6.93                    | 23.06±9.14            | 0.236    |
| Aldosterone, ng/dL         | 5.60 [3.1–11.8]     | 4.9 [3.0–8.6] | 5.9 [3.0–13.5]            | 4.7 [3.0–11.8]                | 7.2 [4.1–16.7]        | 0.0292   |
| Urine Na/K ratio           | 3.23±2.24           | 3.84±2.58     | 3.34±2.35                 | 2.87±1.76                    | 2.76±1.98             | 0.0470   |
| Hydration status, n (%)    | Total body water, L | 37.78±7.47    | 37.93±8.71                | 36.50±7.30                   | 37.82±6.19            | 38.92±7.11 | 0.495 |
| Extracellular water, L     | 17.55±3.30          | 17.36±3.79    | 16.62±2.95                | 17.80±3.17                   | 18.54±2.87            | 0.0450   |
| Intracellular water, L     | 20.28±4.53          | 20.56±5.24    | 19.88±4.66                | 20.03±3.64                   | 20.62±4.27            | 0.812    |

Values are mean±SD, median [interquartile range], or n (%).
* After application of the Bonferroni correction, p<0.004 was considered significant.
BUN=blood urea nitrogen; Na/K=sodium/potassium; PH=pulmonary hypertension; RVSI=renal venous stasis index.
| Demographics | RVSI Correlation coefficient | p value† |
|--------------|-------------------------------|----------|
| Age          | 0.238                         | 0.0006   |
| Body mass index | −0.025                      | 0.720    |
| Clinical variables |                         |          |
| 6MWD        | −0.279                      | 0.0006   |
| Loop diuretic dose | 0.369                      | <0.0001  |
| Hemodynamics |                              |          |
| Mean PAP     | 0.472                        | <0.0001  |
| PVR          | 0.321                        | <0.0001  |
| RAP          | 0.584                        | <0.0001  |
| Cardiac index | −0.321                     | <0.0001  |
| PCWP         | 0.404                        | <0.0001  |
| Mixed venous oxygen saturation | −0.391       | <0.0001  |
| Echocardiographic parameters |                |          |
| Right heart  |                              |          |
| TAPSE        | −0.456                      | <0.0001  |
| RV myocardial performance index (Tei index) | 0.037   | 0.672    |
| RV S’        | −0.357                      | <0.0001  |
| TAPSE/Systolic PAP ratio | −0.332                  | <0.0001  |
| RA area      | 0.471                        | <0.0001  |
| RV diameter  | 0.272                        | <0.0001  |
| IVC          | 0.355                        | <0.0001  |
| Left heart   |                              |          |
| LVEF         | −0.163                      | 0.0201   |
| LA diameter  | 0.404                        | <0.0001  |
| E/e’ ratio   | 0.250                        | 0.0006   |
| Renal function |                            |          |
| Serum creatinine | 0.394                     | <0.0001  |
| Urea         | 0.427                        | <0.0001  |
| Cystatin C   | 0.462                        | <0.0001  |
| eGFR (MDRD equation) | −0.365     | <0.0001  |
| eGFR (CKD-EPI creatinine equation)§ | −0.365 | <0.0001  |
| eGFR (CKD-EPI creatinine-cystatin C equation)| −0.433   | <0.0001  |
| Renal filtration gradient# | −0.327   | <0.0001  |
| Urine PCR    | 0.315                        | <0.0001  |
| Urine ACR    | 0.341                        | <0.0001  |
| Urine aMCR   | 0.233                        | 0.0008   |
| RRI          | 0.323                        | <0.0001  |
| Neurohormonal status |                  |          |
| BNP          | 0.623                        | <0.0001  |
| Copeptin     | 0.350                        | <0.0001  |
| Hydration status |                           |          |
| Hydration status (as measured by bioimpedance) | 0.301   | <0.0001  |
| ECW/ICW ratio | 0.178                          | 0.0141   |
| Intra-abdominal pressure measurement |                  |          |
| Intra-abdominal pressure | 0.772                     | <0.0001  |
| Abdominal perfusion pressure** | −0.214           | 0.0021   |

Pearson or Spearman correlation was considered as appropriate. *Relevant parameters were chosen based on their clinical role; in addition, parameters that showed a significant difference across RVSI tertiles (table 2) were included. †After application of the Bonferroni correction, p<0.0014 was considered significant. ‡eGFR was calculated with the MDRD equation based on serum creatinine. §eGFR was calculated with the CKD-EPI equation based on serum creatinine. ¤eGFR was calculated with the CKD-EPI equation based on serum creatinine and cystatin C. 22 #The renal filtration gradient was calculated as: MAP−2x intra-abdominal pressure. 24 **The abdominal perfusion pressure was calculated using the equation: MAP−intra-abdominal pressure. 24

6MWD=6-min walk distance; ACR=albumin-to-creatinine ratio; α1MCR=α1-microglobulin-to-creatinine ratio; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; BNP=b-type natriuretic peptide; ECW=extracellular water; E/e’ ratio=ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; ICW=intracellular water; IVC=inferior vena cava; LA=left atrial; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; MDRD=Modification of Diet in Renal Disease; PAP=pulmonary arterial pressure; PCR=protein-to-creatinine ratio; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrial; RAP=right atrial pressure; RRI=renal resistive index; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S6. Correlation of renal function with relevant parameters*.

| Demographics | Serum creatinine | p value† | eGFR (CKD-EPI creatinine-cystatin C equation) | p value† |
|--------------|------------------|----------|---------------------------------------------|----------|
|              | Correlation coefficient |          | Correlation coefficient |          |
| Age, yrs     | 0.342             | <0.0001  | –0.542                                      | <0.0001  |
| Baseline clinical data |              |          |                                             |          |
| PaO₂‡       | –0.021            | 0.764    | 0.028                                       | 0.685    |
| PaCO₂‡      | 0.005             | 0.944    | 0.053                                       | 0.451    |
| 6MWD        | –0.211            | 0.0023   | 0.350                                       | <0.0001  |
| Laboratory data |              |          |                                             |          |
| Hemoglobin  | –0.166            | 0.0173   | 0.258                                       | 0.0002   |
| Uric acid   | 0.479             | <0.0001  | –0.510                                      | <0.0001  |
| C-reactive protein | 0.213    | 0.0022   | –0.282                                      | <0.0001  |
| Maintenance therapy |       |          |                                             |          |
| Loop diuretic dose | 0.482  | <0.0001  | –0.389                                      | <0.0001  |
| Hemodynamics |              |          |                                             |          |
| RAP         | 0.293             | <0.0001  | –0.323                                      | <0.0001  |
| PCWP        | 0.265             | <0.0001  | –0.270                                      | <0.0001  |
| Mixed venous oxygen saturation | –0.249 | <0.0001  | 0.312                                       | <0.0001  |
| Echocardiographic parameters |     |          |                                             |          |
| TAPSE       | –0.315            | <0.0001  | 0.300                                       | <0.0001  |
| RV myocardial performance index (Tei index) | –0.011 | 0.901   | 0.062                                       | 0.092    |
| RV S'        | –0.176            | 0.012    | 0.126                                       | 0.073    |
| TAPSE/Systolic PAP ratio | –0.168 | 0.016   | 0.258                                       | <0.0001  |
| RA area     | 0.342             | <0.0001  | –0.333                                      | <0.0001  |
| LA diameter | 0.310             | <0.0001  | 0.310                                       | <0.0001  |
| Renal function |              |          |                                             |          |
| Renal filtration gradient | –0.279 | <0.0001  | 0.283                                       | <0.0001  |
| Urine PCR   | 0.180             | 0.0099   | –0.240                                      | 0.0005   |
| Urine ACR   | 0.179             | 0.0104   | –0.238                                      | 0.0006   |
| Urine α1MCR | 0.397             | <0.0001  | –0.523                                      | <0.0001  |
| Renal Doppler Ultrasonography |       |          |                                             |          |
| RRI         | 0.237             | <0.0001  | –0.430                                      | <0.0001  |
| RVSI        | 0.486             | <0.0001  | –0.433                                      | <0.0001  |
| Neurohormonal status |       |          |                                             |          |
| BNP         | 0.343             | <0.0001  | –0.416                                      | <0.0001  |
| Copeptin    | 0.554             | <0.0001  | –0.599                                      | <0.0001  |
| Urine FeNa  | 0.447             | <0.0001  | –0.492                                      | <0.0001  |
| Hydration status |       |          |                                             |          |
| ECW/ICW ratio | 0.085  | 0.246   | –0.261                                      | 0.0003   |
| Intra-abdominal pressure measurement |       |          |                                             |          |
| Intra-abdominal pressure | 0.333  | <0.0001  | –0.327                                      | <0.0001  |

Pearson or Spearman correlation was considered as appropriate. *All available study variables were included in the analysis, but only variables that were significant in the analysis are presented here; in addition, PaO₂ and PaCO₂ are presented based on their clinical role. †After application of the Bonferroni correction, p<0.0006 was considered significant. ‡Blood gas measurements were taken from arterialized capillary ear lobe blood during right heart catheterization. In patients with long-term oxygen treatment, oxygen was applied via nasal cannula at the previously prescribed flow rate.

6MWD=6-min walk distance; ACR=albumin-to-creatinine ratio; α1MCR=α1-microglobulin-to-creatinine ratio; BNP=b-type natriuretic peptide; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ECW=extracellular water; E/e' ratio=ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; ICW=intracellular water; LA=left atrial; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; PaCO₂=arterial carbon dioxide pressure; PaO₂=arterial oxygen pressure; PAP=pulmonary arterial pressure; PCR=protein-to-creatinine ratio; RAP=right atrial pressure; RRI=refractoriness index; RVEF=right ventricular ejection fraction; RV S’=ratio of mitral inflow velocity to lateral annular relaxation velocity; TAPSE=tricuspid annular plane excursion; TVICW=tricuspid valvular intracardiac capacitance.
ratio; PCWP=pulmonary capillary wedge pressure; RA=right atrial; RAP=right atrial pressure; RV=right ventricular; RV S' =systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S7. Clinical characteristics, invasive hemodynamics, echocardiographic data, renal function, and neurohormonal and hydration status according to PH groups

|                                      | No PH (n=40) | Group 1 PH (pulmonary arterial hypertension) (n=46) | Group 2 PH (PH due to left heart disease) (n=30) | Group 3 PH (PH due to lung disease and/or hypoxemia) (n=41) | Group 4 PH (chronic thromboembolic PH) (n=34) | Group 5 PH (PH with unclear multifactorial mechanisms) (n=14) | p value* |
|--------------------------------------|-------------|-----------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------|-------------------------------------------------|----------|
| **Baseline clinical data**           |             |                                                     |                                                 |                                                 |                                             |                                                 |          |
| Oxygen supply, n (%)                 |             |                                                     |                                                 |                                                 |                                             |                                                 | <0.0001 |
| 6MWd, m                              | 313.15±126.56 | 309.07±153.40                                       | 269.60±115.46                                  | 199.12±105.30                                  | 308.38±174.46                              | 239.43±104.40                                  |          |
| NYHA classification, n (%)           |              |                                                     |                                                 |                                                 |                                             |                                                 | 0.0054   |
| 1–2                                  | 10 (25)      | 17 (37.0)                                           | 5 (16.7)                                       | 3 (7.3)                                        | 8 (23.5)                                   | 1 (7.1)                                        |          |
| 3–4                                  | 30 (75)      | 29 (63.0)                                           | 25 (83.3)                                      | 38 (92.7)                                      | 26 (76.5)                                  | 13 (92.9)                                      |          |
| **Comorbidities, n (%)**             |              |                                                     |                                                 |                                                 |                                             |                                                 |          |
| Hypertension                         | 23 (57.5)    | 21 (45.7)                                           | 27 (90.0)                                      | 32 (78.0)                                      | 18 (52.9)                                  | 7 (50.0)                                       | <0.0001 |
| Diabetes mellitus                    | 8 (20.0)     | 8 (17.4)                                            | 11 (36.7)                                      | 11 (26.8)                                      | 6 (17.6)                                   | 4 (28.6)                                       | 0.388    |
| Atrial fibrillation                  | 10 (25.0)    | 7 (15.2)                                            | 24 (80.0)                                      | 6 (14.6)                                       | 7 (20.6)                                   | 2 (14.3)                                       | <0.0001 |
| **Maintenance therapy**              |              |                                                     |                                                 |                                                 |                                             |                                                 |          |
| ACEI or ARB, n (%)                   | 18 (45.0)    | 12 (26.1)                                           | 21 (70.0)                                      | 18 (43.9)                                      | 9 (26.5)                                   | 5 (35.7)                                       | 0.0027   |
| Loop diuretic dose, mg/day           | 0.0 [0.0-35.0] | 40.0 [0.0-65.0]                                     | 50.0 [20.0-90.0]                               | 40.0 [0.0-50.0]                                | 40.0 [0.0-80.0]                            | 40.0 [0.0-80.0]                                | 0.0017   |
| Thiazide diuretic, n (%)             | 9 (22.5)     | 18 (39.1)                                           | 11 (36.7)                                      | 17 (41.5)                                      | 13 (35.3)                                  | 5 (35.7)                                       | 0.567    |
| Aldosterone antagonist, n (%)        | 8 (20.0)     | 22 (47.8)                                           | 12 (40.0)                                      | 13 (31.7)                                      | 17 (50.0)                                  | 4 (28.6)                                       | 0.0562   |
| Triamterene, n (%)                   | 0 (0)        | 3 (6.5)                                             | 0 (0)                                          | 1 (2.9)                                        | 1 (7.1)                                    | 0.197                                           |          |
| **PH-specific therapy, n (%)**       |              |                                                     |                                                 |                                                 |                                             |                                                 | <0.0001 |
| Treatment-naive                     | 40 (100)     | 10 (21.7)                                           | 21 (70.0)                                      | 22 (53.7)                                      | 18 (52.9)                                  | 5 (35.7)                                       |          |
| Monotherapy                          | 0 (0)        | 14 (30.4)                                           | 9 (30)                                         | 11 (26.8)                                      | 10 (29.4)                                  | 5 (35.7)                                       |          |
| Dual therapy                         | 0 (0)        | 14 (30.4)                                           | 0 (0)                                          | 6 (14.6)                                       | 4 (11.7)                                   | 4 (28.6)                                       |          |
| >Triple therapy                      | 0 (0)        | 8 (17.4)                                            | 0 (0)                                          | 2 (4.9)                                        | 2 (5.9)                                    | 0 (0)                                           |          |
| **Hemodynamics**                     |              |                                                     |                                                 |                                                 |                                             |                                                 |          |
| Mean PAP, mm Hg                      | 17.68±4.60   | 42.13±18.07                                         | 37.90±12.03                                    | 35.63±9.31                                     | 36.91±8.25                                | 46.00±11.75                                    | <0.0001 |
| PVR, dyn.s/cm²                       | 151.5 [89.5-223.8] | 547.5 [343.8-786.5]       | 315.5 [166.3-478.5]                           | 486.0 [344.5-707.5]                            | 454.5 [334.0-632.5]                        | 519.5 [475.0-613.5]                            | <0.0001 |
| RAP, mm Hg                           | 2.75±4.74    | 5.24±5.61                                           | 9.97±6.08                                      | 5.29±5.55                                      | 5.53±5.05                                 | 8.93±4.44                                      | <0.0001 |
| Cardiac index, L/min/m²              | 3.10±1.41    | 2.69±0.80                                           | 2.68±0.92                                      | 2.47±0.67                                      | 2.56±0.64                                 | 2.99±1.31                                      | 0.0533   |
| PCWP, mm Hg                          | 7.0 [4.0-10.0] | 8.5 [5.0-11.3]                                     | 19.0 [12.8-24.3]                               | 7.0 [4.5-10.0]                                 | 8.0 [5.0-11.3]                             | 12.0 [8.5-15.3]                                | <0.0001 |
| Mixed venous oxygen saturation, %   | 67.65±7.01   | 64.69±8.81                                          | 61.91±8.81                                     | 62.69±7.05                                     | 60.73±8.72                                | 64.05±8.51                                     | 0.0083   |
| Heart rate, beats/min               | 71.45±11.11  | 70.39±11.46                                         | 66.13±12.01                                    | 73.98±12.91                                    | 72.15±13.56                               | 97.71±21.30                                    | 0.0306   |
| MAP, mm Hg‡                         | 86.28±10.54  | 81.28±10.42                                         | 82.94±10.16                                    | 84.91±13.16                                    | 82.58±13.07                               | 84.52±10.88                                    | 0.191    |
| Parameters                        | Right heart                                                                 |
|----------------------------------|-------------------------------------------------------------------------------|
| TAPSE, mm                        | 21.45±4.83                                                                  |
| RV myocardial performance index  | 0.40±0.19                                                                   |
| RV S\(^{'}\), cm/s               | 12.40±3.88                                                                  |
| TAPSE/Systolic PAP ratio          | 0.67±0.24                                                                   |
| Tricuspid insufficiency           | Mild: 23 (57.5)                                                             |
|                                  | Moderate: 12 (30.0)                                                         |
|                                  | Severe: 5 (12.5)                                                            |
| RA area, m\(^{2}\)               | 15.15±6.47                                                                  |
| RV diameter, mm                  | 36.43±7.88                                                                  |
| IVC, cm                          | 2.15±0.47                                                                   |
| Left heart                       | LVEF, % 60.0 [58.1-65.0]                                                    |
|                                 | LA diameter, mm 40.87±7.60                                                  |
|                                 | LVEDD, mm 47.78±5.09                                                        |
|                                 | E/e' ratio 11.69±4.64                                                       |
| Renal function                   | Serum creatinine, mg/dL\(\uparrow\) 0.91±0.45                              |
|                                 | Cystatin C, mg/L 0.97 [0.76-1.21]                                            |
|                                 | Urea, mg/dL\(\downarrow\) 39.98±29.56                                        |
|                                 | eGFR (CKD-EPI creatinine equation), mL/min/1.73 m\(^{2}\) 83.28±23.76      |
|                                 | eGFR (CKD-EPI creatinine-Cystatin C equation), mL/min/1.73 m\(^{2}\) 80.60±27.39 |
|                                 | Renal filtration gradient, mm Hg\(\uparrow\) 73.88±10.66                   |
|                                 | Urine PCR, mg/g creatinine 54.3 [44.9-82.9]                                  |
|                                 | Urine ACR, mg/g creatinine 11.6 [6.1-17.0]                                   |
|                                 | Urine α1MC, mg/g creatinine 9.8 [15.9-18.6]                                  |
| Acanthocyturia, n (%)            | 1 (2.5)                                                                     |
| Sterile leukocyturia, n (%)       | 0 (0)                                                                        |
| Intra-renal Doppler Ultrasonography |        |        |        |        |
|-----------------------------------|--------|--------|--------|--------|
| Congestion stage                  |        |        |        |        |
| 0                                 | 27 (67.5) | 10 (21.7) | 1 (3.3) | 1 (24.4) | 9 (26.5) | 2 (14.3) |
| 1                                 | 13 (32.5) | 20 (43.5) | 12 (40) | 16 (39.0) | 14 (41.2) | 6 (42.9) |
| 2                                 | 0 (0) | 11 (23.9) | 7 (23.3) | 10 (24.4) | 9 (26.5) | 4 (28.6) |
| 3                                 | 0 (0) | 5 (10.9) | 10 (33.3) | 5 (12.2) | 2 (5.9) | 2 (14.3) |
| Venous impedance index of 1.0     | 13 (32.5) | 36 (78.3) | 29 (96.7) | 31 (75.6) | 25 (73.5) | 12 (85.7) | 0.482 |
| RVSI                              | 0.0 [0.00-0.09] | 0.13 [0.04-0.34] | 0.27 [0.11-0.46] | 0.09 [0.02-0.29] | 0.12 [0.00-0.29] | 0.15 [0.06-0.36] | <0.0001 |
| RRI                               | 0.67±0.05 | 0.71±0.07 | 0.76±0.06 | 0.71±0.08 | 0.73±0.07 | 0.71±0.07 | <0.0001 |
| Neurohormonal status              |        |        |        |        |
| BNP, pg/mL                        | 51.00 [22.5-175.5] | 134.00 [375.5-324.8] | 232.50 [157.5-590.0] | 114.00 [55.0-538.5] | 160.00 [98.5-314.5] | 196.00 [45.8-531.0] | <0.0001 |
| Copeptin, pmol/L                  | 6.95 [4.2-13.5] | 7.95 [5.2-18.9] | 15.45 [6.4-39.2] | 14.15 [8.0-27.7] | 16.30 [6.8-23.1] | 11.35 [6.1-20.1] | 0.0063 |
| Urine FeNa, %                      | 0.60 [0.4-1.1] | 0.65 [0.3-1.4] | 1.20 [0.6-1.9] | 0.80 [0.4-1.3] | 0.50 [0.3-1.4] | 0.4 [0.3-0.5] | 0.0162 |
| Sodium, mmol/L                    | 139.33±3.24 | 139.24±3.14 | 139.90±2.90 | 139.66±3.03 | 139.47±3.52 | 140.50±1.51 | 0.783 |
| BUN-to-creatinine ratio            | 20.28±8.18 | 19.09±6.80 | 23.05±7.86 | 22.58±7.22 | 21.47±7.84 | 21.29±6.46 | 0.189 |
| Aldosterone, ng/dL                | 4.70 [3.00-8.45] | 8.85 [3.90-19.88] | 5.75 [3.00-10.90] | 5.70 [3.00-12.30] | 6.30 [3.00-11.83] | 4.65 [3.00-6.95] | 0.079 |
| Potassium, mmol/L                 | 3.75±0.45 | 3.61±0.39 | 3.78±0.45 | 3.60±0.43 | 3.62±0.40 | 3.67±0.25 | 0.271 |
| Urine Na/K ratio                   | 3.52±3.31 | 2.80±1.70 | 3.61±2.65 | 3.45±2.54 | 3.04±2.16 | 2.90±1.94 | 0.53 |
| Hydration status                  |        |        |        |        |
| Ascites, n (%)                    | 0 (0) | 2 (4.3) | 3 (10.0) | 1 (2.4) | 1 (2.9) | 0 (0) | 0.588 |
| Peripheral edema, n (%)           | 9 (22.5) | 14 (30.4) | 9 (30.0) | 12 (29.3) | 11 (32.4) | 5 (35.7) | 0.929 |
| Pleural effusion, n (%)            | 0 (0) | 5 (10.9) | 3 (10.0) | 3 (7.3) | 2 (5.9) | 4 (28.6) | 0.0346 |
| Hydration status (as measured by bioimpedance), L | 0.11±1.64 | 0.97±2.02 | 1.05±2.53 | 0.54±2.21 | 0.71±2.28 | 1.35±1.91 | 0.282 |
| Total body water, L               | 38.46±7.26 | 36.13±7.81 | 37.73±6.31 | 38.85±8.35 | 37.76±7.91 | 38.16±5.58 | 0.679 |
| ECW, L                            | 17.57±3.30 | 16.88±3.28 | 17.74±2.84 | 17.82±3.75 | 17.54±3.45 | 18.39±2.68 | 0.710 |
| ICW, L                            | 20.88±4.31 | 19.51±4.53 | 19.97±4.01 | 20.03±5.12 | 20.22±4.93 | 19.76±3.37 | 0.669 |
| ECW/ICW ratio                     | 0.85±0.09 | 0.87±0.12 | 0.90±0.12 | 0.86±0.13 | 0.88±0.13 | 0.94±0.11 | 0.132 |
| Intra-abdominal pressure measurement |        |        |        |        |
| Intra-abdominal pressure, mmHg    | 6.0 [5.0-7.0] | 7.0 [6.0-9.0] | 8.5 [7.0-10.0] | 7.0 [6.0-9.0] | 7.0 [6.0-8.3] | 8.0 [6.8-10.3] | <0.0001 |
| Abdominal perfusion pressure, mmHg | 80.08±10.50 | 73.73±10.11 | 75.99±10.66 | 79.47±13.70 | 75.31±13.35 | 74.74±10.95 | 0.092 |

Values are mean±SD, median [interquartile range], or n (%).
After application of the Bonferroni correction, $p<0.0008$ was considered significant. †MAP was calculated as (systolic blood pressure+2x diastolic pressure)/3. ‡To convert the values for serum creatinine to μmol/L, multiply by 88.4. §To convert the values for urea to BUN, multiply by 0.467. ¶eGFR was calculated with the CKD-EPI equation based on serum creatinine. ExtGFR was calculated with the CKD-EPI equation based on serum creatinine and cystatin C. **The renal filtration gradient was calculated as: MAP–2x intra-abdominal pressure. ††The abdominal perfusion pressure was calculated using the equation: MAP–intra-abdominal pressure. 6MWD=6-min walk distance; ACEi=angiotensin-converting enzyme inhibitor; ACR=albumin-to-creatinine ratio; α1MCR=α1-microglobulin-to-creatinine ratio; ARB=angiotensin receptor blocker; BNP=b-type natriuretic peptide; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ECW=extracellular water; E/e’ ratio=ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; ICW=intracellular water; IVC=inferior vena cava; LA=left atrial; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; Na/K=sodium/potassium; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PCR=protein-to-creatinine ratio; PCWP=pulmonary capillary wedge pressure; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrial; RAP=right atrial pressure; RRI=renal resistive index; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S8. Outcomes in the RHC cohort.

| Outcome                                              | RHC cohort (n=205) |
|------------------------------------------------------|--------------------|
| PH-related morbidity and death from any cause        | 91 (44.4%)         |
| Unscheduled hospitalizations for fluid overload      | 64 (31.2%)         |
| Escalations of PH-specific therapy                   | 71 (34.6%)         |
| Death from any cause                                 | 21 (10.2%)         |

Five patients underwent pulmonary thrombendarterectomy, and one patient underwent lung transplantation.

RHC=right heart catheterization; PH=pulmonary hypertension.
Table S9. Predictors of morbidity and mortality by the univariate Cox proportional hazard model.

| Predictor                                      | Univariate | p value |
|------------------------------------------------|------------|---------|
| **Baseline clinical data**                     |            |         |
| Age                                            | 1.02 (1.00–1.03) | 0.0439  |
| Sex                                            | 0.63 (0.42–0.95) | 0.0265  |
| 6MWd                                           | 0.997 (0.996–0.999) | 0.0096  |
| NYHA classification                            | 1.62 (1.19–2.20) | 0.0024  |
| Pulmonary hypertension group                   | 0.81 (0.72–0.91) | <0.0001 |
| Diabetes mellitus                              | 1.88 (1.21–2.91) | 0.0048  |
| Atrial fibrillation                            | 2.56 (1.68–3.88) | <0.0001 |
| Uric acid                                      | 1.25 (1.16–1.34) | <0.0001 |
| **Hemodynamics**                               |            |         |
| Mean PAP                                       | 1.03 (1.02–1.04) | <0.0001 |
| PVR                                            | 1.00 (1.00–1.00) | <0.0001 |
| RAP                                            | 1.12 (1.07–1.14) | <0.0001 |
| Cardiac index                                  | 0.54 (0.39–0.74) | <0.0001 |
| PCWP                                           | 1.06 (1.03–1.09) | <0.0001 |
| Mixed venous oxygen saturation                 | 0.93 (0.91–0.96) | <0.0001 |
| **Echocardiographic parameters**               |            |         |
| TAPSE                                          | 0.90 (0.86–0.94) | <0.0001 |
| RV S0                                          | 0.86 (0.80–0.93) | <0.0001 |
| TAPSE/Systolic PAP ratio                       | 0.05 (0.01–0.19) | <0.0001 |
| Tricuspid insufficiency                        | 1.76 (1.32–2.35) | <0.0001 |
| RA area                                        | 1.07 (1.04–1.09) | <0.0001 |
| RV diameter                                    | 1.05 (1.02–1.07) | <0.0001 |
| LV cavity                                      | 2.08 (1.38–3.13) | <0.0001 |
| LVEF                                           | 0.98 (0.95–1.00) | 0.0477  |
| LA diameter                                    | 1.07 (1.04–1.10) | <0.0001 |
| E/e’ ratio                                     | 1.07 (1.03–1.11) | <0.0001 |
| **Renal function**                             |            |         |
| Serum creatinine                               | 2.59 (1.83–3.66) | <0.0001 |
| Cystatin C                                     | 2.18 (1.69–2.82) | <0.0001 |
| Urea                                           | 1.01 (1.01–1.02) | <0.0001 |
| eGFR (MDRD equation)*                          | 0.99 (0.98–0.99) | <0.0001 |
| eGFR (CKD-EPI creatinine equation) ‡           | 0.98 (0.97–0.98) | <0.0001 |
| eGFR (CKD-EPI creatinine-cystatin C equation) †| 0.98 (0.97–0.99) | <0.0001 |
| Renal filtration gradient                      | 0.97 (0.95–0.99) | 0.0007  |
| Urine α1MCR                                    | 1.01 (1.01–1.02) | <0.0001 |
| Urine FeNa                                     | 1.21 (1.09–1.34) | <0.0001 |
| **Renal Doppler ultrasonography**              |            |         |
| RVSI tertiles                                  | 20.57 (9.03–46.87) | <0.0001 |
| 1st tertile RVSI vs RVSI=0                     | 2.31 (1.06–5.05) | 0.0363  |
| 2nd tertile RVSI vs RVSI=0                     | 3.63 (1.71–7.65) | 0.0007  |
| 3rd tertile RVSI vs RVSI=0                     | 8.70 (4.33–17.48) | <0.0001 |
| Congestion stages                              | 2.00 (1.63–2.44) | <0.0001 |
| Stage 1 congestion vs stage 0                  | 2.65 (1.29–5.44) | 0.0078  |
| Stage 2 congestion vs stage 0                  | 6.35 (3.98–13.09) | <0.0001 |
| Stage 3 congestion vs stage 0                  | 8.45 (5.98–17.96) | <0.0001 |
| Venous impedance index                         | 14.61 (4.31–49.55) | <0.0001 |
| **Neurohormonal status**                       |            |         |
| BNP                                            | 1.00 (1.00–1.00) | <0.0001 |
| Copeptin                                       | 1.02 (1.02–1.03) | <0.0001 |
| Aldosterone                                    | 1.01 (1.00–1.02) | 0.0184  |
| **Hydration status**                           |            |         |
| Hydration status (as measured by bioimpedance) | 1.14 (1.03–1.25) | 0.0081  |
| Extracellular/intracellular water              | 8.42 (3.15–54.25) | 0.0251  |
| Ascites                                        | 2.85 (1.30–6.23) | 0.0089  |
| Pleural effusion                               | 2.27 (1.26–4.10) | 0.0064  |
| **Intra-abdominal pressure measurement**       |            |         |
| Intra-abdominal pressure                       | 1.25 (1.17–1.34) | <0.0001 |
| Abdominal perfusion pressure§                  | 0.98 (0.96–1.00) | 0.0226  |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here. *eGFR was calculated with the MDRD equation based on serum creatinine. ‡eGFR was calculated with the CKD-EPI equation based on serum creatinine. §The abdominal perfusion pressure was calculated using the equation: MAP—abdominal pressure, while MAP was calculated as (systolic blood pressure+2x diastolic pressure)/3.  

6MWd=6-min walk distance; α1MCR=α1-microglobulin-to-creatinine ratio; BNP=b-type natriuretic peptide; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; E/e’ ratio=ratio of
mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; HR=hazard ratio; IVC=inferior vena cava; LA=left atrial; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; MDRD=Modification of Diet in Renal Disease; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrial; RAP=right atrial pressure; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S10. Predictors of unscheduled hospitalization due to fluid overload by the univariate Cox proportional hazard model.

| Predictor                                      | Univariate |
|------------------------------------------------|------------|
| **Baseline clinical data**                     |            |
| Age                                            | 1.04 (1.01–1.06) | 0.0013 |
| Sex                                            | 0.48 (0.29–0.79) | 0.0039 |
| 6MWMD                                          | 0.996 (0.994–0.998) | <0.0001 |
| NYHA classification                            | 1.81 (1.24–2.64) | 0.0022 |
| Pulmonary hypertension group                   | 0.83 (0.72–0.95) | 0.0083 |
| Diabetes mellitus                              | 2.58 (1.56–4.27) | <0.0001 |
| Atrial fibrillation                            | 4.05 (2.47–6.63) | <0.0001 |
| Sodium                                         | 0.93 (0.86–0.99) | 0.0286 |
| Uric acid                                      | 1.29 (1.19–1.41) | <0.0001 |
| **Hemodynamics**                               |            |
| Mean PAP                                       | 1.02 (1.01–1.04) | 0.0008 |
| PVR                                            | 1.00 (1.00–1.00) | 0.0246 |
| Cardiac index                                  | 1.15 (1.11–1.20) | <0.0001 |
| PCWP                                           | 0.46 (0.31–0.68) | <0.0001 |
| Mixed venous oxygen saturation                 | 1.08 (1.05–1.11) | <0.0001 |
| **Echocardiographic parameters**               |            |
| TAPSE                                          | 0.86 (0.81–0.91) | <0.0001 |
| RV S′                                          | 0.77 (0.70–0.85) | <0.0001 |
| TAPSE/Systolic PAP ratio                       | 0.02 (0.00–0.18) | <0.0001 |
| Tricuspid insufficiency                         | 2.22 (1.55–3.18) | <0.0001 |
| RA area                                        | 1.11 (1.07–1.14) | <0.0001 |
| RV diameter                                    | 1.06 (1.03–1.10) | <0.0001 |
| JVC diameter                                   | 2.60 (1.59–4.16) | <0.0001 |
| LVEF                                           | 0.96 (0.94–0.99) | 0.0037 |
| LA diameter                                     | 1.07 (1.04–1.11) | <0.0001 |
| E/e’ ratio                                     | 1.08 (1.03–1.12) | <0.0001 |
| **Renal function**                             |            |
| Serum creatinine                               | 3.40 (2.33–4.94) | <0.0001 |
| Cystatin C                                     | 2.62 (1.99–3.45) | <0.0001 |
| Urea                                           | 1.01 (1.01–1.02) | <0.0001 |
| eGFR (MDRD equation)*                          | 0.98 (0.97–0.99) | <0.0001 |
| eGFR (CKD-EPI creatinine equation) †           | 0.97 (0.96–0.98) | <0.0001 |
| eGFR (CKD-EPI creatinine-cystatin C equation)‡ | 0.97 (0.96–0.98) | <0.0001 |
| BUN-to-creatinine ratio                        | 1.04 (1.01–1.07) | 0.0117 |
| Renal filtration gradient                      | 0.96 (0.94–0.98) | <0.0001 |
| Urine α1MCR                                     | 1.01 (1.01–1.02) | <0.0001 |
| Urine FeNa                                      | 1.21 (1.07–1.36) | 0.0017 |
| **Renal Doppler ultrasonography**              |            |
| RVSI tertiles                                  | 1.71 (1.48–1.98) | <0.0001 |
| 1st tertile RVSI group vs RVSI=0               | 6.49 (1.42–29.64) | 0.0157 |
| 2nd tertile RVSI group vs RVSI=0               | 10.98 (2.52–47.76) | 0.0014 |
| 3rd tertile RVSI group vs RVSI=0               | 35.60 (8.54–148.38) | <0.0001 |
| Congestion stages                              | 2.49 (1.94–3.20) | <0.0001 |
| Stage 1 congestion vs stage 0                  | 7.36 (1.71–31.72) | 0.0074 |
| Stage 2 congestion vs stage 0                  | 25.51 (6.05–107.67) | <0.0001 |
| Stage 3 congestion vs stage 0                  | 32.17 (7.44–139.09) | <0.0001 |
| Venous impedance index                         | 121.10 (9.45–1552.61) | <0.0001 |
| **Neurohormonal status**                       |            |
| BNP                                            | 1.00 (1.00–1.00) | <0.0001 |
| Copoetin                                       | 1.03 (1.02–1.04) | <0.0001 |
| Aldosterone                                    | 1.02 (1.00–1.03) | 0.0122 |
| **Hydration status**                           |            |
| Hydration status (as measured by bioimpedance) | 1.16 (1.04–1.29) | 0.0089 |
| Extracellular/intracellular water              | 14.97 (1.66–135.09) | 0.0159 |
| Extracellular water                            | 1.09 (1.01–1.18) | 0.0280 |
| Ascites                                        | 3.11 (1.24–7.77) | 0.0153 |
| Pleural effusion                               | 2.42 (1.19–4.90) | 0.0142 |
| Peripheral edema                               | 2.09 (1.28–3.44) | 0.0034 |
| **Intra-abdominal pressure measurement**       |            |
| Intra-abdominal pressure                       | 1.36 (1.26–1.47) | <0.0001 |
| Abdominal perfusion pressure§                  | 0.97 (0.95–1.00) | 0.0210 |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here. eGFR was calculated with the MDRD equation based on serum creatinine. eGFR was calculated with the CKD-EPI equation based on serum creatinine. eGFR was calculated with the CKD-EPI equation based on serum creatinine and cystatin C. §The abdominal perfusion pressure was calculated with the EPI creatinine equation.
pressure was calculated using the equation: MAP–intra-abdominal pressure, while MAP was calculated as (systolic blood pressure+2x diastolic pressure)/3.\textsuperscript{24}

6MWD=6-min walk distance; α1MCR=α1-microglobulin-to-creatinine ratio; BNP=b-type natriuretic peptide; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; E/e’ ratio=ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; IVC=inferior vena cava; HR=hazard ratio; LA=left atrial; LVEF=left ventricular ejection fraction; MAP=mean arterial pressure; MDRD=Modification of Diet in Renal Disease; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PCR=protein-to-creatinine ratio; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance; RA=right atrial; RAP = right atrial pressure; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S11. Predictors of escalation of PH-specific therapy by the univariate Cox proportional hazard model.

| Predictor                                      | Univariate |         |
|-----------------------------------------------|------------|---------|
| **Baseline clinical data**                    |            |         |
| 6MWD                                          | 0.997 (0.995–0.999) | 0.0013  |
| NYHA classification                            | 1.59 (1.11–2.27)  | 0.0110  |
| Pulmonary hypertension group                   | 0.79 (0.69–0.91)  | 0.008   |
| Diabetes mellitus                              | 1.90 (1.16–3.12)  | 0.0105  |
| Atrial fibrillation                            | 1.79 (1.11–2.89)  | 0.0177  |
| Potassium                                      | 0.49 (0.28–0.88)  | 0.0162  |
| Uric acid                                      | 1.26 (1.16–1.36)  | <0.0001 |
| **Hemodynamics**                               |            |         |
| Mean PAP                                       | 1.03 (1.02–1.04)  | <0.0001 |
| PVR                                           | 1.00 (1.00–1.00)  | <0.0001 |
| RAP                                           | 1.08 (1.04–1.12)  | <0.0001 |
| Cardiac index                                  | 0.41 (0.28–0.60)  | <0.0001 |
| PCWP                                          | 1.04 (1.01–1.07)  | 0.0072  |
| Mixed venous oxygen saturation                 | 0.92 (0.90–0.95)  | <0.0001 |
| **Echocardiographic parameters**               |            |         |
| TAPSE                                         | 0.89 (0.85–0.94)  | <0.0001 |
| RV S'                                         | 0.84 (0.77–0.91)  | <0.0001 |
| TAPSE/Systolic PAP ratio                       | 0.04 (0.01–0.21)  | <0.0001 |
| Tricuspid insufficiency                        | 1.54 (1.12–2.12)  | 0.0079  |
| RA area                                       | 1.05 (1.02–1.09)  | 0.0013  |
| RV diameter                                    | 1.05 (1.02–1.08)  | 0.0005  |
| IVC diameter                                   | 2.00 (1.25–3.19)  | 0.0037  |
| LA diameter                                    | 1.05 (1.01–1.08)  | 0.0072  |
| LVEDD                                         | 0.95 (0.91–0.99)  | 0.0271  |
| E/e' ratio                                     | 1.07 (1.03–1.12)  | 0.0006  |
| **Renal function**                             |            |         |
| Serum creatinine                               | 2.55 (1.74–3.73)  | <0.0001 |
| Urea                                          | 1.01 (1.00–1.01)  | <0.0001 |
| Cystatin C                                     | 1.95 (1.30–2.55)  | <0.0001 |
| eGFR (MDRD equation)*                         | 0.99 (0.98–0.99)  | <0.0001 |
| eGFR (CKD-EPI creatinine equation) †          | 0.98 (0.97–0.99)  | <0.0001 |
| eGFR (CKD-EPI creatinine-cystatin C equation) ‡| 0.98 (0.97–0.99)  | <0.0001 |
| Renal filtration gradient                     | 0.96 (0.94–0.99)  | 0.0007  |
| Urine α1MCR                                    | 1.01 (1.01–1.02)  | <0.0001 |
| Urine FeNa                                     | 1.24 (1.10–1.39)  | <0.0001 |
| **Renal Doppler ultrasonography**              |            |         |
| RVSI tertiles                                  | 1.43 (1.26–1.63)  | <0.0001 |
| 1st tertile RVSI group vs RVSI=0               | 2.16 (0.89–5.24)  | 0.0872  |
| 2nd tertile RVSI group vs RVSI=0               | 3.52 (1.53–8.07)  | 0.0030  |
| 3rd tertile RVSI group vs RVSI=0               | 7.03 (3.22–15.55) | <0.0001 |
| Congestion stages                              | 1.86 (1.49–2.33)  | <0.0001 |
| Stage 1 congestion vs stage 0                  | 2.37 (1.05–5.35)  | 0.0373  |
| Stage 2 congestion vs stage 0                  | 6.22 (2.79–13.87) | <0.0001 |
| Stage 3 congestion vs stage 0                  | 6.39 (2.73–14.97) | <0.0001 |
| Venous impedance index                         | 12.59 (3.20–49.45)| <0.0001 |
| **Neurohormonal status**                      |            |         |
| BNP                                           | 1.00 (1.00–1.00)  | <0.0001 |
| Copeptin                                       | 1.03 (1.02–1.04)  | <0.0001 |
| **Hydration status**                           |            |         |
| Pleural effusion                               | 2.15 (1.10–4.21)  | 0.0256  |
| **Intra-abdominal pressure measurement**       |            |         |
| Intra-abdominal pressure                       | 1.22 (1.13–1.32)  | <0.0001 |
| Abdominal perfusion pressure§                  | 0.97 (0.95–0.99)  | 0.0098  |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here. *eGFR was calculated with the MDRD equation based on serum creatinine.25 †eGFR was calculated with the CKD-EPI equation based on serum creatinine.23 ‡eGFR was calculated with the CKD-EPI equation based on serum creatinine and cystatin C.22 §The abdominal perfusion pressure was calculated using the equation: MAP−intra-abdominal pressure, while MAP was calculated as (systolic blood pressure+2x diastolic pressure)/3.24

6MWD=6-min walk distance; α1MCR=α1-microglobulin-to-creatinine ratio; BNP=b-type natriuretic peptide; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; E/e' ratio=ratio of mitral inflow velocity to lateral annular relaxation velocity; eGFR=estimated glomerular filtration rate; FeNa=fractional excretion of sodium; HR=hazard ratio; IVC=inferior vena cava; LA=left atrial; LVEDD=left ventricular end-diastolic diameter; MAP=mean arterial pressure; MDRD=Modification of Diet in Renal Disease;
NYHA=New York Heart Association; PAP=pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; RA=right atrial; RAP=right atrial pressure; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S12. Predictors of death from any cause by the univariate Cox proportional hazard model.

| Predictor                                | Univariate | p value |
|------------------------------------------|------------|---------|
| **Baseline clinical data**               |            |         |
| Sex                                      | 0.30 (0.12–0.77) | 0.0127  |
| 6MWD                                     | 1.0 (0.99–1.00)  | 0.0239  |
| NYHA classification                       | 2.65 (1.30–5.41) | 0.0074  |
| Uric acid                                | 1.25 (1.09–1.43) | 0.0018  |
| **Hemodynamics**                         |            |         |
| RAP                                      | 1.08 (1.02–1.15) | 0.0149  |
| Mixed venous oxygen saturation           | 0.92 (0.88–0.96)  | <0.0001 |
| **Echocardiographic parameters**         |            |         |
| TAPSE                                    | 0.88 (0.80–0.96)  | 0.0045  |
| RV S’                                    | 0.74 (0.64–0.87)  | <0.0001 |
| TAPSE/Systolic PAP ratio                 | 0.01 (0.00–0.17)  | 0.011   |
| RA area                                  | 1.10 (1.04–1.17)  | 0.0018  |
| RV diameter                              | 1.07 (1.02–1.12)  | 0.0076  |
| **Renal function**                       |            |         |
| Serum creatinine                         | 2.14 (1.05–4.40)  | 0.0376  |
| Urea                                     | 1.01 (1.00–1.02)  | 0.0262  |
| **Renal Doppler ultrasonography**        |            |         |
| RVSI tertiles                            | 0.065      |         |
| 1<sup>st</sup>tertile RVSI group vs RVSI=0 | 2.00 (0.48–8.38) | 0.342   |
| 2<sup>nd</sup>tertile RVSI group vs RVSI=0 | 1.25 (0.25–6.17) | 0.788   |
| 3<sup>rd</sup>tertile RVSI group vs RVSI=0 | 4.33 (1.19–15.72) | 0.026   |
| Congestion stages                        | 1.39 (1.10–1.77)  | 0.0066  |
| Stage 1 congestion vs stage 0            | 1.29 (0.31–5.38)  | 0.732   |
| Stage 2 congestion vs stage 0            | 3.84 (1.02–14.48) | 0.0469  |
| Stage 3 congestion vs stage 0            | 4.03 (0.96–16.86) | 0.0564  |
| **Neurohormonal status**                 |            |         |
| BNP                                      | 1.00 (1.00–1.00)  | 0.0012  |
| Copeptin                                 | 1.02 (1.00–1.04)  | 0.0193  |
| **Intra-abdominal pressure measurement** |            |         |
| Intra-abdominal pressure                 | 1.22 (1.06–1.41)  | 0.0069  |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here.

6MWD=6-min walk distance; BNP=b-type natriuretic peptide; CI=confidence interval; HR=hazard ratio; NYHA=New York Heart Association; PAP=pulmonary arterial pressure; RA=right atrial; RAP=right atrial pressure; RV=right ventricular; RV S’=systolic annular tissue velocity of the lateral tricuspid annulus; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Table S13. Performance of RVSI versus IRVF patterns in models including both variables for prediction of secondary endpoints.

| Secondary endpoint                  | Wald statistic          |            |            |            |
|-------------------------------------|-------------------------|------------|------------|------------|
|                                     | RVSI                    | IRVF patterns | RVSI | IRVF patterns |
|                                     | Unplanned hospitalization due to fluid overload | Escalation of PH-specific therapy | All-cause mortality |
| RVSI                                | 6.163                   | 0.996      | 0.721      | 2.675      | 0.611      | 0.204      |

Higher Wald statistic indicates superiority for prediction of endpoint. RVSI was superior to IRVF patterns in models including both RVSI and IRVF patterns as predictor variables for all component endpoints except need for escalation of PH-specific therapy.

IRVF=intrarenal venous flow; PH=pulmonary hypertension; RVSI=renal venous stasis index.
Severity of renal congestion can be evaluated by identifying four distinct IRVF patterns using renal Doppler ultrasonography. The figure illustrates the associations of these IRVF patterns with RAP and renal function (a), right ventricular systolic function and right atrial area (b), neurohormonal (c), and hydration status (d). Fluid overload as measured by bioimpedance is likely to occur as a result of hemodynamic alterations and neurohormonal activation leading to a deterioration of renal function and fluid retention.

BNP=b-type natriuretic peptide; D=diastole; eGFR=estimated glomerular filtration rate (based on Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation\(^2\)); IRVF=intrarenal venous flow; RA=right atrial; RAP=right atrial pressure; S=systole; TAPSE=tricuspid annular plane systolic excursion; VII=venous impedance index.
Figure S2. Correlation of RVSI with RAP (a), TAPSE (b), eGFR (c), and intra-abdominal pressure (d).

eGFR=estimated glomerular filtration rate (based on Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation\textsuperscript{22}); RAP=right atrial pressure; RVSI=renal venous stasis index; TAPSE=tricuspid annular plane systolic excursion.
Patients in the 3rd tertile RVSI group had a significantly higher probability than other patients of the following individual components of the composite endpoint: unscheduled hospitalization for fluid overload (p<0.0001) (a) and escalation of PH-specific therapy (p<0.0001) (b). After Bonferroni correction, death from any cause did not show a significant difference between patients in the 3rd tertile RVSI group and other patients (p=0.0412) (c).

PH=pulmonary hypertension; RVSI = renal venous stasis index.
Patients in the highest IRVF pattern group had a significantly higher probability than other patients of the composite endpoint of PH-related morbidity or death from any cause (p<0.0001) (a) and the following individual components of the composite endpoint: unscheduled hospitalization for fluid overload (p<0.0001) (b) and escalation of PH-specific therapy (p<0.0001) (c). After Bonferroni correction, death from any cause did not show a significant difference between patients in the highest IRVF pattern group and other patients (p=0.0387) (d).

IRVF=intrarenal venous flow; PH=pulmonary hypertension.
Figure S5. Comparison of RVSI and IRVF patterns as predictors of the primary and secondary clinical endpoints.

Receiver operating characteristic analyses indicate that RVSI was superior to the four IRVF patterns as a predictor of the composite primary endpoint (AUC: 0.789 and 0.761, respectively; p=0.038) (a), and for the prediction of unplanned hospitalization due to fluid overload (AUC: 0.843 and 0.813, respectively; p=0.045) (b) but not escalation of pulmonary hypertension-specific therapy (AUC: 0.737 and 0.724, respectively; p=0.36) (c), nor all-cause mortality (AUC: 0.650 and 0.668, respectively; p=0.37) (d). Diagonal segments are produced by ties.

AUC=area under the curve; IRVF=intrarenal venous flow; RVSI=renal venous stasis index.
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