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Enlighten – Research publications by members of the University of Glasgow <u>http://eprints.gla.ac.uk</u> Laboratory evaluation. The estimated glomerular filtration rate (eGFR) was calculated through the Chronic Kidney Disease Epidemiology Collaboration formula¹. Plasma norepinephrine was evaluated using high-performance liquid chromatography with the electrochemical detector CLC 100 (Chromsystems, Munchen, Germany). Direct renin and aldosterone were assayed using a chemiluminescence immunoassay (LIASON, DiaSorin, Saluggia, Italy). NT-proBNP was measured with the ECLIA monoclonal assay using the Cobas e411 platform (Roche Diagnostics Italia, Monza, Italy). Plasma and urine osmolality were measured using a freezing point depression osmometer (KNAUER K-7400, Berlin, Germany). We assessed serum and urinary levels of sodium and creatinine (Cobas-8000 analyser, Roche Diagnostics, Basel, Switzerland) to estimate the fractional excretion of sodium (FENa) as²:

urine sodium x serum creatinine serum sodium x urine creatinine %

We measured urinary albumin (Cobas-8000 analyser, Roche Diagnostics, Basel, Switzerland) to estimate the urinary albumin-to-creatinine ratio (UACR); we defined micro-albuminuria and macro-albuminuria as UACR >30 mg/g and >300 mg/g, respectively. We evaluated the instantaneous estimated plasma volume status (ePVS) in mL/g³ as:

$$\frac{1-hematocrit}{hemoglobin}x\ 100$$

Baseline echocardiography protocol. All patients underwent a comprehensive transthoracic echocardiography examination (Hitachi Medical Systems LISENDO 880, Tokyo, Japan) according to the international recommendations.⁴ Stroke volume was calculated by multiplying the left ventricular (LV) outflow tract area by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler. Cardiac output was calculated by multiplying stroke volume by heart rate. With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured between 1 and 3 cm before the merger with the right atrium. The IVC collapse was visually estimated as \geq 50 or <50% following deep inspiration (a brief sniff). IVC diameter and its variations were used to estimate right atrial pressure (RAP), as recommended⁴. Systolic pulmonary artery pressure (sPAP) was measured from the peak tricuspid regurgitation velocity (TRV) with the simplified Bernoulli equation, adding the estimated RAP. Diastolic pulmonary artery pressure (dPAP) was calculated by adding RAP to the pulmonary regurgitation end-diastolic gradient (PREDG). Then mean pulmonary artery pressure (mPAP) was calculated as (sPAP + 2 · dPAP)3.

Left atrial volume index (LAVi) was estimated with the disc summation algorithm (Simpson's technique) in a biplane approach from the apical four-chamber and two-chamber view⁴. To maximise image quality and decrease the likelihood of discarding patients for poor acoustic windows, we also employed off-axis approaches, such as the right ventricle inflow tract for TRV, subcostal view for PREDG, and left lateral approach for IVC dimension and variations. We non-invasively estimated echo-derived pulmonary artery wedge pressure (ePAWP) using a previously validated equation, which includes the following variables: tricuspid regurgitation velocity (TRV), LVEF, right ventricle fractional area change, left atrial volume index (LAVi), E/e', inferior vena cava and mPAP⁵. Then, echo-derived pulmonary vascular resistance (ePVR) was calculated as (mPAP - ePAWP)/CO⁵. Valvular regurgitation was qualitatively assessed using color-Doppler, and whenever regurgitant orifice area⁶. Valvular stenosis was assessed using continuous-wave Doppler and quantified using peak transvalvular velocity and mean transvalvular pressure gradient⁷. All measurements were reported as the average of three beats for patients in normal sinus rhythm and five beats for patients with atrial fibrillation.

3D Transthoracic Echocardiography (**3DTE**). 3D full-volume data sets were acquired using a single-crystal matrix-array transducer. The acquisitions were obtained in full-volume mode from the 4-chamber apical view. Care was taken to include the entire LV and RV cavity within the pyramidal scan volume. To ensure a relatively high-volume rate, data sets throughout one cardiac cycle were acquired using two wedge-shaped subvolumes, acquired with electrocardiographic gating during a single 5- to 7-second breath-hold and over at least five cardiac cycles. The data were analysed offline using a vendor-independent software (TomTec Imaging Systems, Unterschleissheim, Germany). Measurements of 3D LV volumes and masses were performed offline by 4D LV analysis (TomTec Imaging Systems, Unterschleissheim, Germany). First, the software identifies the apex and mitral annulus on apical 4-, 3- and 2-chamber views. Then, it performs an automated contour-tracking process at end-diastole and end-systole. The 3D LV end-diastolic and end-systolic volumes were measured from the resulting three-dimensional volume. For 3D LV mass, an ellipse was also traced around the epicardial border in end-diastole: the endocardial volume was then subtracted from the epicardial volume and multiplied by the specific gravity of heart muscle (i.e. 1.05 g/mL)⁴. Endocardial and epicardial borders were manually re-drawn when deemed necessary. To determine the RV parameters, we used

the 4D RV analysis software (TomTec Imaging Systems, Unterschleissheim, Germany). Non-foreshortened apical 4- and 2-chamber views at the end-diastole were identified to select the LV apex and the centre of the mitral annular line, placing the largest LV long-axis dimensions. In the apical 3-chamber view, both the anterior and the posterior aortic annuli were identified. In the RV apical 4-chamber and coronal views, the point of the RV apex and the center of the tricuspid annular line were identified. In the short-axis view, both the anterior and the posterior junction between the RV free wall and interventricular septum were identified. Then, the distance between the interventricular septal and RV free wall was delineated perpendicular to the midpoint of the interventricular septum. The software automatically reconstructed the RV endocardial surface at end-diastole, and manual editing was performed when required. The endocardial surface was manually readjusted as necessary when tracking was deemed inadequate. RV volumes were computed throughout the cardiac cycle, from which the 3D RV end-diastolic volume, end-systolic volume and RVEF were automatically calculated. The same software performed STE analysis throughout the entire cardiac cycle and determined the RV free wall longitudinal strain. The whole post-processing quantification required 4±2 minutes.

Speckle tracking echocardiography (STE). We measured LV global longitudinal strain (GLS) from the apical long-axis view and two- and four-chamber views, ensuring a frame rate >50 Hz (2D strain analysis, TomTec Imaging Systems, Unterschleissheim, Germany). We reported the average LVGLS values from the three apical views at rest. We excluded poorly tracked segments, and patients were not analysed if more than one segment per view was deemed unacceptable. We measured left atrial (LA) reservoir strain using the same software as the average of six segments in the four-chamber and two-chamber views, ensuring a frame rate >50 Hz⁸. LA strain was measured using the QRS as the fiducial point. STE-derived measurements were reported as the average of three beats for patients in normal sinus rhythm and five beats for patients with atrial fibrillation. All measurements were performed offline by expert readers blinded to clinical and other instrumental data.

Statistical analysis. Categorical data are presented as percentages and were compared using Pearson's Chi-square test or the Fisher exact test. Continuous data are reported as the mean ± standard deviation or median and interquartile range (IQR) for normally or skewed distributed variables, respectively. Continuous variables from two data sets were compared using Student's t-test or Mann-Whitney U test for non-normal distributions. ANOVA or Kruskal-Wallis test was used to test the differential distribution of data among

groups, and post-hoc tests were performed with Bonferroni corrections (p-value for significance <0.01 for p-values <0.05 on ANOVA or Kruskal-Wallis). The relation between congestion markers as continuous variables and other variables was assessed using Spearman's rank correlation coefficients (Log-transformed NT-proBNP was used).

Associations between variables and prognosis were evaluated using Cox proportional-hazards models. To determine the predictive value of ultrasound markers of congestion compared with other variables, we selected, a priori, a limited list of variables of interest with potential prognostic significance based on clinical experience and prior publications⁹. We used forward stepwise selection (entry and removal value of p<0.01 and p<0.10, respectively) to prevent overfitting. Assumptions of the models were tested, such as multicollinearity and proportional hazards. Kaplan–Meier analyses with log-rank statistics were used to illustrate the outcome.

To estimate the predictive value of the different variables of interest, we constructed a baseline a priori model including variables of clinical interest based on clinical experience and prior publications⁹ and then tested the added value of each measure (and combinations of measures) of congestion, in turn. The incremental value of the variables (the model's cumulative discrimination) was measured using Harrell's C statistic. We assessed the reclassification of patients who experienced an event at one year of follow-up by adding ultrasound congestion measurements to the baseline model with the continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI).

In a random sample of 50 patients (including ten subjects with atrial fibrillation [AF]), two observers independently assessed ultrasound measures of congestion. To test intra-observer variability, a single observer analysed the data twice at a 1-month interval. We tested the reproducibility of continuous variables with the intra-class correlation coefficient and Bland-Altman plot. We used Cohen's kappa coefficient (κ) to measure the intra-rater and inter-rater reliability of RVF patterns.

Missing data were not included in the models. All tests were two-sided, with a p-value of <0.05 considered significant. Data were analysed with SPSS version 25.0 (IBM Corp., Armonk, NY) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Supplemental Table 1. Population characteristics.

Variable	Patients w/o HF	HFpEF	HFrEF	p-value
	(n=101)	(n=151)	(n=159)	
Demographics (0 missing)				
Age, years	70 (62 - 76)	79 (73 – 85)*	74 (63 – 81)*†	<0.0001
Men	62 (61)	74 (49)	127 (80)*†	<0.0001
BMI, Kg/m ²	26.7±4.5	29.6±5.1*	27.4±5.5†	<0.0001
BSA, m ²	1.8±0.2	1.9±0.3	1.9±0.2	0.2
Smoker	14 (14)	23 (15)	38 (24)	0.1
NYHA class				<0.0001
Ι	59 (58)	24 (16)*	23 (14)*	
II	42 (46)	89 (59)	91 (57)	
III	0	38 (25)*	45 (29)*	
KCCQ score	65±22	51±20*	48±24*	<0.0001
Arterial hypertension	86 (85)	137 (91)	97 (61)	<0.0001
Stroke/TIA	5 (5)	15 (10)	19 (12)	0.1
Diabetes mellitus	26 (26)	42 (28)	51 (32)	0.2
COPD	14 (14)	30 (20)	25 (16)	0.2
CAD	15 (15)	27 (18)	76 (48)*†	<0.0001
Previous MI	4 (4)	11 (7)	62 (39)*†	<0.0001
Previous PCI/CABG	14 (14)	24 (16)	65 (41)*†	<0.0001
Pacemaker	0	24 (16)*	43 (27)*†	<0.0001
ICD	0	6 (4)	46 (29)*†	<0.0001
CRT	0	3 (2)	29 (18)*†	<0.0001
Atrial fibrillation	3 (3)	68 (45)*	54 (34)*†	<0.0001
Clinical evaluation (0 missing)				
Brachial systolic BP, mmHg	131±20	135±23	123±20†	0.001
Brachial diastolic BP, mmHg	77±13	78±12	75±10	0.3
Heart rate, beats/min	75±12	73±14	72±13	0.5
No clinical signs of congestion	101 (100)	106 (70)*	118 (74)*	<0.0001
Pitting oedema (any degree)	-	41 (27)	38 (24)	0.3
Lung crackles (any degree)	-	15 (10)	19 (12)	0.5
Jugular vein distension (any degree)	-	9 (6)	11 (7)	0.5
Blood tests (0 missing)				
Haemoglobin, g/dL (men)	13.5±1.8	13.6±1.7	13.4±1.9	0.1
Haemoglobin, g/dL (women)	12.9±1.7	12.8 ± 1.8	12.7 ± 2.1	0.1
Na ⁺ , mEq/L	140±2	141±3	141±5	0.1
K ⁺ , mEq/L	4.2±0.5	4.3±0.5	4.3±0.5	0.1
Total cholesterol, mg/dL	165±35	161±38	164±39	0.1
Fasting glucose, mg/dL	96±27	101±29	99±31	0.4
HbA1c, mmol/mol	41±9	42±10	41±7	0.6
Uric acid, mg/dL	$5.9{\pm}1.8$	8.6±2.7*	6.9±1.9*†	<0.0001
hs-CRP, mg/dL	0.32 (0.14 – 0.44)	0.49 (0.29 - 0.68)*	0.41 (0.24 – 0.64)*†	<0.0001
Creatinine, mg/dL	0.94 (0.77 – 1.09)	1.04 (0.89 – 1.35)*	0.99 (0.83 - 1.20)	<0.0001
eGFR, mL/min/1.73 m ²	77 (61 – 89)	63 (51 – 81)*	64 (50 - 75)*	<0.0001
Urea, mg/dL	40 (33 – 50)	50 (41 - 68)*	49 (37 – 62)*	<0.0001
ePVS, mL/g	4.5 (4.0 – 5.1)	4.9 (4.3 – 5.8)*	5.1 (4.4 – 6.1)*	<0.0001
Osmolality, mOsm/kg	291 (289 - 295)	295 (291 - 300)	296 (292 - 301)*	<0.0001
Norepinephrine, pg/mL	228 (168 - 363)	330 (242 - 498)*	354 (255 - 523)*	<0.0001
Renin, mIU/L	12.7 (5.7 – 31.2)	18.6 (7.9 – 72.1)	30.1 (9.9 – 142.6)*	0.001
Aldosterone, ng/dL	9.2 (6.5 – 12.4)	10.8 (7.5 – 17.4)*	11.2 (7.9 – 16.2)*	0.008
NT-proBNP, pg/mL	65 (25 - 100)	897 (426 – 1027)*	1294 (486 – 2728)*†	<0.0001
NT-proBNP, pg/mL (SR only)	65 (25 - 90)	364 (162 - 549)*	1101 (401 – 2334)*†	<0.0001

hs-Troponin T, pg/mL	8 (5 – 12)	19 (11 – 32)*	21 (13 – 34)*	<0.0001
Urine test (12 missing)				
Osmolality, mOsm/kg	595 (505 - 708)	518 (400 - 676)*	480 (389 - 632)*	<0.0001
UACR, mg/g	12 (5 – 29)	24 (9 - 83)*	21 (8-63)*	<0.0001
Micro-albuminuria§	9 (9)	59 (39)	56 (35)	<0.0001
Macro-albuminuria§	0	12 (8)	11 (7)	0.02
Spot urinary sodium, mEq/L	101 (76 – 130)	65 (42 - 107)*	62 (40 - 103)*	< 0.0001
FENa, %	0.65 (0.39 - 1.02)	0.52 (0.37 - 0.97)*	$0.46 (0.26 - 0.71)^*$	<0.0001
Therapy (0 missing)				
Beta-Blocker	44 (44)	110 (73)*	138 (87)*†	<0.0001
DHP CCB	31 (31)	39 (26)	22 (14)	0.01
Non-DHP CCB	2 (2)	3 (2)	0	0.2
ACEi or ARB	67 (67)	104 (69)	92 (58)	0.1
MRA	12 (12)	54 (36)*	103 (65)*†	<0.0001
ARNI	0	7 (5)	59 (37)*†	<0.0001
ASA	33 (33)	57 (38)	81 (51)*†	<0.0001
Statins	51 (51)	80 (53)	86 (54)	0.6
Thiazides/thiazide-like diuretics	24 (24)	22 (15)	10 (6)*†	<0.0001
Loop diuretics	-	101 (67)	129 (81)	<0.0001
Furosemide equivalent dose				0.01
1-50 mg	-	34 (22)	20 (13)	
51 - 100 mg	-	63 (42)	88 (55)	
>100 mg	-	4 (3)	21 (13)	
SGLT2i	3 (3)	12 (8)	24 (15)	0.2
Insulin	10 (10)	18 (12)	8 (5)	0.1
Oral anticoagulants	3 (3)	69 (46)*	56 (35)*†	<0.0001

Values are mean \pm standard deviation, n (%), or median (25th quartile, 75th quartile).

*p<0.01 vs No HF; †p<0.01 vs HFpEF.

#p<0.01 vs No US congestion; ^p<0.01 vs 1 US sign of congestion.

Micro-albuminuria and macro-albuminuria were defined as UACR >30 mg/g and >300 mg/g, respectively

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; ASA: acetylsalicylic acid; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; DHP CCB: dihydropyridine calcium channel blocker; eGFR: estimated glomerular filtration rate; ePVS: estimated plasma volume status; FENa: fractional excretion of sodium; HbA1c: glycated haemoglobin (available only in patients with diabetes mellitus); HFpEF: heart failure with preserved ejection fraction; hS-CRP: high sensitivity C-reactive protein; ICD: implantable cardioverter defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCI: percutaneous coronary intervention; SR: sinus rhythm; SGLT2i: sodium glucose co-transporter 2 inhibitors; TIA: transient ischemic attack; UACR: albumin-to-creatinine ratio.

Variable	Mis	Patients w/o HF	HFpEF	HFrEF	p-value
	sing	(n=101)	(n=151)	(n=159)	-
Left ventricle size and function					
LVMi, g/m ²	0	115±31	117 ± 28	158±36*†	<0.0001
RWT	0	0.40 ± 0.09	0.42 ± 0.08	0.30±0.09*†	<0.0001
LVEDV, mL	0	133±41	127±37	209±39*†	<0.0001
LV Ejection fraction, %	0	59±7	58±5	37±8*†	<0.0001
3D-LV Ejection fraction, %	15	56±5	55±4	35±7*†	<0.0001
LVGLS, %	5	-17.5±3.4	-15.4±3.3*	-9.2±3.5*†	<0.0001
Stroke volume, mL/beat	0	64±17	60±19	56±18*	0.001
Cardiac output, L/min	0	4.8 ± 0.9	4.4 ± 0.7	4.1±0.5*	0.001
Mitral E wave, cm/s	0	82±28	116±26*	91±33†	<0.0001
Average e', cm/s	0	8.6±2.1	7.3±2.2*	6.7±2.1*†	<0.0001
Average E/e'	0	10.3±4.1	15.6±4.1*	14.3±3.8*	<0.0001
Mitral regurgitation (\geq moderate)	0	1 (1)	18 (12)*	21 (13)*	0.003
Left atrium size and function					
LAVi, mL/m ²	0	34±10	49±13*	49±17*	<0.0001
LA reservoir strain, %	0	-28±11	-19±9*	-15±8*†	<0.0001
Right ventricle and pulmonary circulation					
TAPSE, mm	0	21±3	20±4	18±3*†	<0.0001
RVFAC, %	0	55±9	51±9*	46±12*†	<0.0001
RV free wall longitudinal strain, %	19	-30±6	-29±5	-25±6*†	<0.0001
3D-RVEDV	19	136±39	135±38	160±47*†	<0.0001
3D-RV Ejection fraction, %	19	61±9	54±10*	46±11*†	<0.0001
Tricuspid regurgitation (\geq moderate)	0	2 (2)	17 (11)	14 (9)	0.03
Systolic PAP, mmHg	8	31±8	45±15*	38±14*†	<0.0001
Diastolic PAP, mmHg	10	7±4	11±6*	11±7*	<0.0001
Mean PAP, mmHg	10	16±4	23±6*	21±6*†	<0.0001
ePVR, WU	10	1.5 ± 0.9	$1.9\pm0.9*$	$2.0\pm0.6*$	<0.0001
ePAWP, mmHg	10	9±3	15±5*	16±7*	<0.0001
Congestion assessment	0				
IVC, mm		15 (12 – 17)	18 (15 – 20)*	18 (15 – 20)*	<0.0001
IVC ≥21 mm		2 (2)	26 (17)*	33 (21)*	<0.0001
IVC collapse <50%		0	13 (11)*	23 (16)*	<0.0001
B-lines		0 (0 – 2)	3 (1 – 11)*	3 (1 – 10)*	<0.0001
B-lines ≥4		7 (7)	59 (39)*	56 (35)*	<0.0001
RVF pattern					<0.0001
Continuous		99 (98)	113 (75)*	103 (65)*	
Discontinuous: pulsatile		2 (2)	21 (14)*	19 (12)*	
Discontinuous: biphasic		0	11 (7)	24 (15)*	
Discontinuous: monophasic		0	6 (4)	13 (8)*	
Renal venous impedance index		0.2 (0.1 – 0.3)	0.6 (0.2 – 0.9)*	0.7 (0.2 – 1)*	<0.0001
Renal venous discontinuity index, %‡		-	16 (11 – 39)	23 (14 - 58)	0.4

Values are mean±standard deviation, n (%), or median (25th quartile, 75th quartile).

*p<0.01 vs No HF; †p<0.01 vs HFpEF.

#p<0.01 vs No US congestion; ^p<0.01 vs 1 US sign of congestion.

‡measured only in patients with discontinuous renal venous flow (n=94).

EDV: end-diastolic volume; ePAWP: echo-derived pulmonary artery wedge pressure; ePVR: echo-derived pulmonary vascular resistance; GLS: global longitudinal strain; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; IVC: inferior vena cava; LA: left atrium; LAVi: left atrial volume; LV: left ventricle; LVMi: left ventricle mass index; PAP: pulmonary artery pressure; RVF: renal venous flow; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion.

Su	pplemental	Table	3. Re	producibility	analysis.
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Variable	Intra-observ	er variability	Inter-observer variability		
	ICC	MD (LoA)	ICC	MD (LoA)	
Inferior vena cava, mm	0.98 (0.95 - 0.99)	-0.03 (-1.51, 1.59)	0.94 (0.85 - 0.96)	-0.05 (-2.55, 2.58)	
B-lines	$0.89\ (0.77 - 0.94)$	0.1 (-1.5, 1.6)	$0.81 \ (0.70 - 0.88)$	0.3 (-2.1, 1.7)	
Renal venous impedance index	$0.95\;(0.84-0.98)$	-0.05 (-0.14, 0.10)	0.86(0.77 - 0.91)	-0.06 (-0.18, 0.15)	
Renal venous discontinuity index, %	0.93 (0.82 - 0.97)	0.08 (-1.62, 1.88)	0.85(0.75 - 0.88)	0.09 (-1.96, 1.99)	

ICC: intra-class correlation coefficient (single measurements) and 95% confidence interval; LoA: 95% limits of agreement; MD: mean difference. Legend as in the previous tables.

Supplemental Table 4. Characteristics of HF patients by US measures of congestion.

Variable	IVC <21 mm	IVC ≥21 mm	B-lines <4	B-lines ≥4	cRVF	dRVF
	(n=251)	(n=59)	(n=205)	(n=105)	(n=216)	(n=94)
Demographics						
Age, years	76 (67-83)	80 (75-85)*	77 (69-83)	78 (70-85)	78 (70-84)	81 (74-86)
Male	159 (63)	42 (71)	132 (64)	69 (66)	134 (62)	68 (72)
KCCQ score	55±27	48 ± 24	53±25	49±27	53±25	50±27
Atrial fibrillation	82 (33)	40 (68)**	69 (34)	53 (50)*	63 (29)	59 (63)**
Blood tests						
Na ⁺ , mEq/L	140±3	141±4	140±3	141±3	140±3	142±3**
K ⁺ , mEq/L	4.3±0.5	4.2±0.5	4.3±0.5	4.2 ± 0.5	4.3±0.5	4.3±0.5
Fasting glucose, mg/dL	97±23	101±32	99±23	106±37	99±32	102±27
Uric acid, mg/dL	7.3±1.7	8.2±2.1**	$7.6{\pm}1.8$	8.1±2.0*	7.2±1.8	8.4±1.9**
hs-CRP, mg/dL	0.43 (0.22-0.60)	0.47 (0.25-0.65)	0.42 (0.23-0.59)	0.47 (0. 26-0.65)*	0.41 (0.23-0.58)	0.48 (0. 28-0.68)*
Creatinine, mg/dL	1.00 (0.84-1.26)	1.05 (0.90-1.35)	0.99 (0.85-1.36)	1.02 (0.86-1.24)	0.97 (0.83-1.17)	1.10 (0.96-1.26)
Urea, mg/dL	48 (38-62)	53 (41-73)	49 (38-63)	50 (38-66)	47 (37-62)	53 (44-67)**
ePVS, mL/g	4.9 (4.1-5.2)	5.2 (4.3-5.9)	4.8 (4.1-5.2)	5.2 (4.2-6.1)	4.7 (4.1-5.1)	5.3 (4.5-5.9)**
Osmolality, mOsm/kg	294 (290-300)	297 (291-301)	295 (290-300)	297 (291-301)	294 (290-299)	300 (298-301)**
Norepinephrine, pg/mL	270 (157-407)	392 (208-560)**	280 (157-443)	377 (198-561)*	251 (153-392)	395 (336-597)**
Aldosterone, ng/dL	10.7 (7.4-15.9)	14.3 (8.8-20.7)*	10.6 (7.7-15.5)	14.1 (9.7-21.6)*	10.1 (7.2-13.5)	15.4 (11.1-24.0)**
NT-proBNP, pg/mL	766 (306-1744)	1890 (1114-3181)**	808 (390-1860)	1786 (790-2965)*	752 (245-1679)	1912 (1181-3256)**
NT-proBNP, pg/mL (SR only)	301 (133-885)	872 (512-2092)*	322 (173-991)	808 (490-2065)*	296 (133-857)	915 (543-2174)**
Urine test						
Osmolality, mOsm/kg	543 (423-695)	426 (368-616)*	531 (438-680)	492 (386-665)	542 (455-692)	435 (377-630)*
UACR, mg/g	19 (6-61)	45 (21-99)**	24 (8-63)	43 (20-87)*	17 (6-36)	59 (24-108)**
Micro-albuminuria	69 (27)	46 (78)**	58 (28)	57 (54)**	54 (25)	61 (65)**
Macro-albuminuria	16 (6)	7 (12)	14 (7)	9 (9)	14 (6)	9 (10)
Spot urine sodium, mEq/L	70 (45-111)	57 (43-90)*	67 (47-116)	62 (43-99)	75 (53-1280	41 (29-88)**
FENa, %	0.56 (0.36-0.90)	0.51 (0.29-0.78)	0.58 (0.38-0.87)	0.51 (0.32-0.83)	0.59 (0.41-0.92)	0.38 (0.20-0.65)**
Echocardiography						
LV Ejection fraction, %	48±12	47±12	48±12	47±12	49±12	46±13
LVGLS, %	-13.8±4.6	-11.9±4.5*	-13.9±4.2	-11.7±4.4**	-14.7±4.1	-11.2±4.5**

Average E/e'	14.9±6.5	16.6±7.9	14.1±6.7	16.9±7.2**	13.8±5.9	17.6±7.4**
LAVi, mL/m ²	46±19	59±19**	48±21	55±18*	44±15	63±17**
LA reservoir strain, %	-19±9	-13±7**	-19±9	-16±9*	-21±9	-13±6**
3D-RV Ejection fraction, %	56±10	47±14**	55±12	49±13**	58±11	46±14**
Systolic PAP, mmHg	38±15	52±15**	39±14	50±15**	39±14	52±15**
ePVR, WU	1.7±0.9	2.1±0.8**	1.6±0.7	2.0±0.9**	1.7±0.9	2.0±0.8**
ePAWP, mmHg	13±4	19±6**	13±5	18±5**	12±4	19±6**

*p<0.01; **<0.001.

cRVF: continuous renal venous flow; dRVF: discontinuous renal venous flow. Other acronyms as in the main tables.

Supplemental Table 5. Discrimination and reclassification of prediction models for predicting the composite endpoint (all-cause death and hospitalisation for heart failure) in the HF population (n=310).

Model	Discrimination				Reclassification			
no.								
	Model	C-statistics	Difference vs	Difference vs	cNRI	p-value	IDI	p-value
		(95% CI)	model 1 (p-value)	model 2a (p-value)	(95% CI)		(95% CI)	
1	Base model*	0.75 (0.70-0.81)	_	_	-	_	_	_
2a	1 + Log(NT - proBNP)	0.78 (0.73-0.85)	0.1	_	0.74 (0.40-1.05)	<0.0001	0.14 (0.08-0.20)	<0.0001
2b	$1 + B - lines \ge 4$	0.77 (0.71–0.83)	0.4	_	0.47 (0.12-0.77)	0.02	0.07 (0.04-0.11)	0.01
2c	1 + IVC ≥21 mm	0.76 (0.71–0.82)	0.5	_	0.51 (0.29–0.86)	0.01	0.08 (0.03-0.12)	0.01
2d	1 + dRVF pattern	0.78 (0.73-0.84)	0.2	_	0.77 (0.44-1.01)	0.001	0.12 (0.07-0.15)	0.001
3	2a + clinical congestion°	0.79 (0.73–0.87)	0.4	0.9	0.05 (-0.28, 0.47)	0.8	0.00 (-0.03, 0.02)	0.9
4	$2a + B - lines \ge 4$	0.80 (0.74–0.87)	0.4	0.7	0.18 (-0.03, 0.34)	0.2	0.03 (-0.01, 0.06)	0.3
5	$2a + IVC \ge 21 mm$	0.79 (0.73–0.86)	0.5	0.8	0.13 (-0.29-0.44)	0.6	0.02 (-0.09, 0.05)	0.5
6	2a + dRVF pattern	0.81 (0.76-0.87)	0.2	0.5	0.15 (-0.21, 0.53)	0.4	0.05 (0.01-0.08)	0.03
7	$2a + B$ -lines $\geq 4 + IVC \geq 21 mm$	0.82 (0.77-0.87)	0.1	0.4	0.19 (-0.08, 0.66)	0.2	0.04 (-0.01, 0.04)	0.1
8	$2a + B$ -lines $\geq 4 + dRVF$ pattern	0.83 (0.78-0.89)	0.02	0.1	0.22 (-0.05, 0.44)	0.1	0.06 (0.02-0.10)	0.02
9	$2a + IVC \ge 21 mm + dRVF$ pattern	0.84 (0.80-0.90)	0.001	0.03	0.23 (-0.01, 0.59)	0.1	0.07 (0.03-0.11)	0.01
10	$2a + B$ -lines $\geq 4 + IVC \geq 21 mm +$	0.86 (0.81-0.91)	<0.0001	0.01	0.28 (0.11-0.68)	0.03	0.10 (0.05-0.14)	0.004
	dRVF pattern							

* Base model: age (years), sex (male), atrial fibrillation, eGFR (mL/min/1.73 m²), UACR (mg/g), LV ejection fraction (%), LAVi (mL/m²).

° any signs of clinical congestion vs no signs.

CI: confidence interval; cNRI: continuous net reclassification improvement; dRVF: discontinuous renal venous flow; IDI: integrated discrimination improvement; IVC: inferior vena cava; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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Figure legend.

Supplemental Figure 1. The enrolment flowchart. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction.



Patients analysed in the current study (n=411)

- 151 HFpEF
- 159 HFrEF
- 101 without HF