The incremental value of multi-organ assessment of congestion using ultrasound in outpatients with heart failure.

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ABSTRACT

Aims. We investigated the prevalence and clinical value of assessing multi-organ congestion by ultrasound in heart failure (HF) outpatients.

Methods and results. Ultrasound congestion was defined as inferior vena cava ≥21 mm, highest tertile of lung B-lines or discontinuous renal venous flow. Associations with clinical characteristics and prognosis were explored. We enrolled 310 HF patients (median age 77 years, median NT-proBNP 1037 ng/L, 51% with a left ventricular ejection fraction [LVEF] <50%), and 101 subjects without HF. There were no clinical signs of congestion in 224 (72%) patients with HF, of whom 95 (42%) had at least one sign of congestion by ultrasound ($p<0.0001$). HF patients with ≥2 ultrasound signs were older, had greater neurohormonal activation, lower urinary sodium concentration, and larger left atria despite similar LVEF. During a median follow-up of 13 (interquartile range 6–15) months, 77 HF patients (19%) died or were hospitalized for HF. HF patients without ultrasound evidence of congestion had a similar outcome to subjects without HF (reference; HR 1.02, 95% CI 0.86 – 1.35), while those with ≥2 ultrasound signs had the worst outcome (HR 26.7, 95% CI 12.4–63.6), even after adjusting for multiple clinical variables and NT-proBNP. Adding multi-organ assessment of congestion by ultrasound to a clinical model, including NT-proBNP, provided a net reclassification improvement of 28% ($p=0.03$).

Conclusion. Simultaneous assessment of pulmonary, venous and kidney congestion by ultrasound is feasible, fast and identifies a high prevalence of sub-clinical congestion associated with poor outcomes.

Keywords: congestion; heart failure; renal venous flow; lung ultrasound; inferior vena cava; prognosis.

INTRODUCTION

Excessive renal salt and water retention increases cardiac filling pressures, leading to an expanded intravascular volume and interstitial fluid accumulation, otherwise known as congestion[1]. Congestion is a key driver of symptoms, poor quality of life, disease progression and prognosis for patients with heart failure (HF), irrespective of left ventricle ejection fraction (LVEF)[2,3]. In patients with HF, clinical signs of congestion (e.g., an elevated jugular venous pressure or presence of peripheral oedema) identify those most at risk[1]. However, clinically overt congestion is a late manifestation of HF and might often be missed unless it is severe. Indeed, the assessment of clinical congestion is subjective and highly dependent on clinical skills, experience and level of training[4,5].

Recent research has shown that quantification of venous (measuring the inferior vena cava [IVC] and/or jugular vein distention), lung (counting B-lines), and renal congestion by ultrasound is feasible and identifies patients with HF with a worse prognosis[6]. Whether a simultaneous, multi-organ evaluation of congestion by ultrasound further improves risk stratification is unknown. Therefore, in the present study, we assessed congestion by ultrasound in the great veins, lungs and kidneys in patients with HF across the LVEF spectrum to understand the prevalence of these signs, their physiopathology and prognostic relevance.

METHODS

Study population. Between September 2020 and December 2021, we prospectively enrolled 326 consecutive patients with a prior clinical diagnosis of HF, attending a routine follow-up visit at the University Hospital of Pisa, Italy. During the same period, we also enrolled 102 consecutive patients with cardiovascular risk factors, including hypertension, type II diabetes or chronic ischemic heart disease and no history of HF. They were required to have an NT-proBNP <125 ng/L, LVEF $\geq$50%, and were not taking loop diuretics[7]. All patients underwent a complete clinical assessment, blood and urine tests, 12-lead ECG, and an ultrasound evaluation. We excluded eight patients (<2%) whose quantification of ultrasound congestion was impossible due to poor quality images (IVC: n=2; lung: n=5; kidney: n=1). All the patients with a history of lung disease underwent spirometry, and those (n=9, 2%) with more than moderate airflow obstruction were excluded. The final study population (n=411) consisted of 101 subjects without HF and 310 patients with HF, who were stratified into HF with reduced (LVEF <50%, HFrEF, n=159) and preserved LVEF (≥50%, HFpEF, n=151;

Supplemental Figure 1). The study fulfilled the requirements in the Declaration of Helsinki; the protocol was approved by the local ethics committees (number 19204), and written informed consent was obtained from all patients.

Laboratory evaluation. Patients were instructed to fast overnight and not to take any medications before blood and urine sampling on the morning of the tests. Blood samples were drawn after a 30 min supine rest. Detailed laboratory protocol is provided in the supplementary appendix. After blood sampling, patients were asked to give a urine sample. We estimated the fractional excretion of sodium (FENa) as[8]:

$$\frac{\text{urine sodium x serum creatinine}}{\text{serum sodium x urine creatinine}}\%$$

We defined micro-albuminuria and macro-albuminuria as a urinary albumin-to-creatinine ratio (UACR) >30 mg/g and >300 mg/g, respectively. We evaluated the instantaneous estimated plasma volume status (ePVS) in mL/g[9] as:

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

Baseline echocardiography. All patients underwent a comprehensive transthoracic echocardiography examination with a phased array transducer (1-5 MHz, Hitachi Medical Systems LISENDO 880, Tokyo, Japan) according to the international recommendations, including 3D and speckle tracking evaluation (STE)[10]. We non-invasively estimated echo-derived pulmonary artery wedge pressure (ePAWP) and pulmonary vascular resistance using a previously validated equation[11]. A detailed echocardiographic protocol is provided in the supplementary appendix.

Renal venous flow (RVF). Doppler assessment of RVF was performed in the left lateral decubitus position, using the same phased array transducer aligned with the lowest intercostal space rendering a longitudinal view of the right kidney. The flow scale of color Doppler imaging was adjusted to low-flow velocities (<20 cm/s) to optimise the identification of the interlobar veins. The best-aligned vein was then sampled with pulsed-wave Doppler during an end-expiratory breath hold. The scale was adjusted to maximise the signal amplitude (usually around ≈20 cm/s), and the electrocardiographic signal was used to synchronise the RVF signal with the cardiac cycle. We used a semi-quantitative assessment of the effects of central venous pressure (CVP) on renal haemodynamics (Graphical abstract). In normal conditions, the interlobar RVF is continuous with a small varying amplitude during the cardiac cycle. With worsening congestion, the amplitude

variation increases with the minimal velocity gradually approaching zero, eventually leading to a discontinuous, pulsatile or even biphasic flow. In the most severe cases, RVF is only seen during diastole (monophasic)[6]. We also measured the renal venous impedance index (VII) and the venous discontinuity index (VDI). The VII is the ratio of the difference between the maximum and minimum velocity to the maximum velocity during a cardiac cycle with a number varying from 0 (no variation in velocity) to 1 (minimum velocity is zero, i.e., the flow becomes discontinuous). VDI expresses the percentage of no-flow time during a cardiac cycle[6].

Lung ultrasound (LUS). B-lines were measured with a linear transducer in parallel orientation (transverse) to the ribs at an imaging depth of ~15–18 cm using an eight-region scan[6]. In each region, B-lines were counted one by one if distinguishable; if confluent, we estimated their number by the percentage of space occupied on the screen, divided by 10 (up to a max of 10 B-lines/region). The sum of B-lines from the eight scanning regions yielded a score denoting the extent of the extravascular lung water; zero was defined as a complete absence of B-lines.

We defined congestion by ultrasound as a discontinuous RVF, a dilated IVC (≥21 mm), or B-lines above or equal to the lower boundary of the highest tertile (≥4)[6].

Clinical follow-up. The minimum follow-up period was three months for the last patient enrolled. The primary outcome was all-cause mortality or HF hospitalisation. HF hospitalisation was defined as an in-hospital stay >24 hours due to HF as the primary diagnosis on the discharge letter. When multiple events occurred, patients were censored at the time of the first event. In our department, follow-up events are regularly adjudicated by an independent trained investigator, blinded to clinical data, and entered into a dedicated database.

Detailed statistical analysis protocol is provided in the supplementary appendix.

RESULTS

Study population. Demographic and clinical characteristics of the HF population according to US signs of congestion are shown in Table 1, while the whole study population, including those without HF, is

summarised in Supplemental Table 1. Likewise, the ultrasound evaluation is summarised in Table 2 and Supplemental Table 2. The reproducibility of ultrasound markers of congestion was excellent (Supplemental Table 3). Classification of RVF patterns was highly consistent between intra-observer and inter-observer assessments ($\kappa > 0.9$). On average, the time of acquisition and interpretation for LUS required <3 minutes per patient and RVF about 5 minutes per patient. Congestion by ultrasound was nearly twice as common as clinical congestion. Around 1/3 of patients with HF had pulmonary or renal congestion, while only 1 in 5 had evidence of venous congestion; isolated venous congestion was rare (2%). Patients with HF with ≥2 ultrasound signs of congestion had higher plasma concentrations of NT-proBNP than those with less congestion by ultrasound; this was true even when only patients in sinus rhythm were considered (Figure 1).

Of the 224 (72%) patients with HF free of clinical congestion, 95 (42%) had at least one ultrasound marker of congestion, which was associated with higher plasma concentrations of NT-proBNP (1525, interquartile range [IQR] 810 - 2205 pg/mL vs 409, IQR: 308 - 862 pg/mL in those without ultrasound evidence of congestion; $p<0.0001$). Of the 161 (52%) patients with HF having at least one sign of congestion, a similar percentage had one (n=82, 51%) or ≥2 (n=79, 49%) ultrasound signs of congestion (Figure 1). Although patients without HF had no clinical signs of congestion and normal NT-proBNP, ultrasound assessment revealed the presence of mild congestion in 9 cases (9%), mostly B-lines ≥4 (n=7).

Patients with one or more ultrasound markers of congestion were older and more likely to have clinical congestion. They had lower urine osmolality, spot urinary sodium and FENa, with a higher prevalence of micro- and macro-albuminuria; they also showed greater ePVS and neurohormonal activation. Pharmacological therapy was similar, apart from greater use of anticoagulants in those with more signs of congestion, reflecting a higher prevalence of AF. LVEF, measured by 2D or 3D echocardiography, was also similar, regardless of the presence of congestion. However, LV global longitudinal strain (LVGLS) was higher (less negative), while LV diastolic function, left atrial function, right ventricular systolic function, and pulmonary hemodynamics were worse for those with more severe congestion by ultrasound (Table 2). The distribution of the characteristics of HF patients by each ultrasound measure of congestion is shown in Supplemental Table 4.

Patients with HFpEF were older than those with HFrEF and more likely to be women and to have hypertension and AF. Clinical and ultrasound signs of congestion were similarly common in patients with

HFrEF or HFpEF (Supplemental Tables 1 and 2). However, patients with HFrEF had higher NT-proBNP and were more likely to be treated with and receive a higher dose of loop diuretics.

Ultrasound markers of congestion correlated modestly with ePAWP and Log(NT-proBNP), but correlations amongst different ultrasound measures of congestion were generally much weaker, except for IVC and renal VII (Figure 2). The latter also showed positive correlations with serum urea and norepinephrine and an inverse correlation with FENa, LVGLS and 3D-RVEF.

Survival analysis. During a median follow-up of 13 months (interquartile range 6–15), 23 HF patients died, and 49 were hospitalised with worsening HF; 5 subjects without HF at the enrolment developed HF requiring hospitalisation (all of them had at least one ultrasound sign of congestion at baseline assessment). No patients were hospitalised immediately after the enrolment visit because of findings at the clinic visit.

Clinical and ultrasound signs of congestion were associated with adverse events (Figure 3). Patients with HF with ≥2 ultrasound signs had the worst outcome, while those free of congestion by ultrasound had a prognosis similar to subjects without HF at enrolment (Graphical abstract). In models adjusted for age, sex, AF, clinical congestion, eGFR, UACR, LVEF, and left atrial volume, only increasing Log(NT-proBNP) and worsening congestion by ultrasound were associated with an adverse outcome. HF patients with ≥2 ultrasound markers of congestion were 14 times more likely to experience the composite endpoint than those without ultrasound signs of congestion, and no interaction was noted with LVEF (Table 3).

For the entire cohort of HF patients, the base clinical model yielded a C-index of 0.75, which did not increase significantly when Log(NT-proBNP) or ultrasound signs of congestion were added singly. In contrast, adding Log(NT-proBNP) with discontinuous RVF and another measure of congestion by ultrasound significantly improved prediction. The highest C-index was observed when Log(NT-proBNP) and all ultrasound measures of congestion were added simultaneously to the base model (0.86, $p<0.001$; Supplemental Table 5). Adding Log(NT-proBNP) or ultrasound measures of congestion to the base model improved reclassification, increasing the integrated discrimination improvement (IDI) and continuous net reclassification improvement (cNRI; Supplemental Table 5). Adding discontinuous RVF pattern alone or combined with other ultrasound signs of congestion to a model that included Log(NT-proBNP) further improved reclassification, primarily by IDI. The greatest improvement by IDI was when all the ultrasound measures were simultaneously

added (p=0.004) to this model. Adding a multi-organ assessment of congestion by ultrasound to a clinical model that included Log(NT-proBNP) provided a cNRI of 28% (p=0.03; Supplemental Table 5).

DISCUSSION

In this prospective study, we performed an integrated evaluation of venous, pulmonary and renal congestion in outpatients with HF, together with a detailed clinical, echocardiographic and biomarker assessment. Previous reports focusing prevalently on one district showed that ultrasound signs of congestion are associated with higher plasma concentrations of NT-proBNP and a greater risk of an adverse outcome in patients with or at risk of HF, regardless of LVEF[2,3,6,12–14]. The present study confirms and expands those findings by demonstrating the clinical and prognostic utility of a multi-organ assessment of congestion by ultrasound in patients with chronic HF, independently of indices of cardiac contractility – including LVEF – and renal function.

Under normal conditions, hydrostatic and oncotic pressures in the capillaries and interstitium are in equilibrium. In HF patients, sympathetic activation due to elevated filling pressures and ventricular dysfunction promotes renal sodium and water retention, with subsequent intravascular volume expansion and decline in oncotic pressure[15]. When the capacity of lymphatics to drain interstitial fluids is exceeded, tissue oedema develops[1,16], which is rarely clinically evident unless severe. During months or even years, circulatory congestion may worsen, ventricular and atrial stretch increases silently, left and right ventricle longitudinal systolic function deteriorate, and arrhythmias (e.g., AF) may develop, eventually leading to pulmonary and systemic venous hypertension. For many patients, the diagnosis is delayed until symptoms and signs are so severe that they require hospitalisation and intensive diuretic therapy[17,18]; more than 20% of these patients will die within a year[19,20]. Earlier identification of congestion before the onset of symptoms and signs might allow intervention to prevent clinically overt congestion and potentially improve outcomes[21,22].

Currently, the gold standard for assessing congestion is to measure atrial pressures invasively, which incurs substantial cost, requires specialised equipment and expertise, and carries small risks[7]; therefore, it is neither attractive nor practical for routine clinical use. Ultrasound is widely available and affordable, does not expose patients to radiation, and images can be interpreted in real-time to assess congestion and identify its cardiac origin and recorded for later discussion at team meetings[6]. Pellicori et al. showed that half of the

patients attending an HF outpatient clinic who did not have clinical signs of congestion had ultrasound evidence of pulmonary or intravascular congestion and greater clinical risk[14]. Many patients with risk factors for HF but who do not fulfil the current guideline definition of HF probably have pre-clinical congestion when investigated adequately, and there is clear evidence that this is associated with a worse prognosis[23–26]. Our results are consistent with these observations and show that the absence of congestion by ultrasound is associated with an excellent prognosis.

Renal venous flow (RVF) is a novel tool to help HF specialists manage congestion[6]. We assessed RVF with the same transducer used for echocardiography within about 5 minutes, with good reproducibility and without dedicated training in renal Doppler ultrasound[6]. The shift from a continuous to a discontinuous RVF pattern in patients with HF has been associated with higher right atrial pressure and a poorer prognosis in acute and chronic settings[13]. Conversely, the normalisation of RVF is associated with an excellent response to treatments for congestion[27,28]. Interestingly, the transition from euvolemic status to volume overload is accompanied by a worsening RVF pattern (i.e. from a continuous to a discontinuous pattern) without any significant changes in CVP estimated from the analysis of the IVC[28]. Changes in the RVF pattern could be an early marker of congestion, salt-avid state and neurohormonal activation.

In the present study, we observed a moderate relation between ultrasound markers of congestion and plasma concentrations of NT-proBNP. NT-proBNP is a robust marker of cardio-renal dysfunction and congestion and is one of the most reliable prognosticators in patients with or at risk of HF[7]. However, NT-proBNP concentrations are influenced by several other clinical factors (e.g., age, sex, body mass index, and AF)[7] and are lower in patients with HFpEF than HFrEF for the same LV end-diastolic pressure[29]. Notably, the results of blood tests are not immediately available, and natriuretic peptide-guided treatment has not been convincingly shown to improve outcomes in HF patients[30]. Conversely, ultrasound is widely available, and our experience indicates that this proposed protocol is easy to implement in a heart failure clinic for the real-time assessment of congestion. Whether the initial measurement of NT-proBNP followed by serial ultrasound evaluation with a particular focus on multi-organ congestion improves HF diagnosis and management is a concept that requires further investigation, particularly now that miniaturised devices are available. Indeed, there are no guideline recommendations for ultrasound markers of congestion to guide HF treatment. Three small randomised clinical trials suggest that LUS-guided treatment significantly reduces HF rehospitalisations

and/or the number of urgent visits for worsening HF both in acute and chronic setting[31–33]. These data have been pooled in a meta-analysis, supporting the role of LUS in evaluating the risk of adverse outcomes in patients with HF regardless of the clinical setting, and supporting the presence of a beneficial effect of LUS-guided management, particularly in HF outpatients[34]. The existing evidence, the present findings, and a robust pathophysiological background support the concept that to master HF we need to identify and master congestion efficiently and with more precision, irrespective of LVEF[35]. Hopefully, this concept will pave the way for designing a large randomised clinical trial to demonstrate if and how addressing congestion more precisely with ultrasound can improve the prognosis of patients with HF.

Limitations. This is a single-centre study from a tertiary referral centre: it has inherent flaws related to selection and referral bias and the absence of a validation cohort. As an observational study, causality cannot be deduced based on these data. We classified all patients with LVEF <50% as HFrEF because only 50 cases had mildly reduced LVEF (41-49%). A sensitivity analysis revealed a similar distribution of signs of congestion by ultrasound for patients with LVEF ≤40%. We used spot samples to assess urinary sodium, as 24-h urine collection was impractical; spot samples are easy to obtain and clinically valid[36]. Different protocols have been proposed for performing LUS[37], and our findings may have been different if we had used another method. Some patient characteristics, such as a high body mass index, might decrease the number of identifiable B-lines[37] and make RVF and IVC assessment difficult[6]. B-lines are not specific for pulmonary congestion and may also reflect parenchymal lung disease, albeit we excluded moderate-to-severe lung disease with spirometry. The study could not determine how concomitant factors such as intrinsic renal pathology contributed to RVF patterns; however, we adjusted the models for UACR. Guidelines make no recommendation to guide treatment according to markers of congestion on ultrasound, but it is possible that knowledge of the results influenced subsequent management for our patients. We did not study additional ultrasound measurements of congestion, e.g., jugular, portal and hepatic vein ultrasound[6].

CONCLUSIONS

Simultaneous assessment of pulmonary, venous and kidney congestion by ultrasound is feasible and identifies a high prevalence of sub-clinical congestion associated with poor outcomes, irrespective of LVEF.

The feasibility and speed of investigation, along with the widespread availability and relatively low cost of ultrasound, make the proposed protocol easy to implement in an HF clinic for the real-time assessment of congestion, especially when point-of-care testing (e.g., NT-proBNP) is not readily available. Whether treatment of congestion guided by ultrasound improves outcomes requires further investigation.

Data available on request.

References

1. Boorsma EM, Maaten JM ter, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. Nat. Rev. Cardiol. 2020. p. 641–655.
2. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. *Eur Heart J* Narnia; 2016;**37**:1244–1251.
3. Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, et al. IVC diameter in patients with chronic heart failure: Relationships and prognostic significance. *JACC Cardiovasc Imaging* Elsevier; 2013;**6**:16–28.
4. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, et al. Assessing and grading congestion in acute heart failure: A scientific statement from the acute heart failure committee of the heart failure association of the European society of cardiology and endorsed by the European society of intensive care medicine. *Eur J Heart Fail* John Wiley & Sons, Ltd; 2010;**12**:423–433.
5. Narang N, Chung B, Nguyen A, Kalathiya RJ, Laffin LJ, Holzhauser L, et al. Discordance Between Clinical Assessment and Invasive Hemodynamics in Patients With Advanced Heart Failure. *J Card Fail* Churchill Livingstone; 2020;**26**:128–135.
6. Pellicori P, Platz E, Dauw J, Maaten JM ter, Martens P, Pivetta E, et al. Ultrasound imaging of congestion in heart failure: examinations beyond the heart. *Eur J Heart Fail* 2021;**23**:703–712.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart J. Oxford Academic; 2021. p. 3599–3726.
8. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
9. Kobayashi M, Huttin O, Donal E, Duarte K, Hubert A, Breton H Le, et al. Association of estimated plasma volume status with hemodynamic and echocardiographic parameters. *Clin Res Cardiol*

Springer Berlin Heidelberg; 2020;**109**:1060–1069.

10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–271.
11. Chubuchny V, Pugliese NR, Taddei C, Poggianti E, Spini V, Barison A, et al. A novel echocardiographic method for estimation of pulmonary artery wedge pressure and pulmonary vascular resistance. *ESC Hear Fail* ESC Heart Fail; 2021;**8**:1216–1229.
12. Goonewardena SN, Gemignani A, Ronan A, Vasaiwala S, Blair J, Brennan JM, et al. Comparison of Hand-Carried Ultrasound Assessment of the Inferior Vena Cava and N-Terminal Pro-Brain Natriuretic Peptide for Predicting Readmission After Hospitalization for Acute Decompensated Heart Failure. *JACC Cardiovasc Imaging* 2008;**1**:595–601.
13. Iida N, Seo Y, Sai S, Machino-Ohtsuka T, Yamamoto M, Ishizu T, et al. Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure. *JACC Hear Fail* Elsevier; 2016;**4**:674–682.
14. Pellicori P, Shah P, Cuthbert J, Urbinati A, Zhang J, Kallvikbacka-Bennett A, et al. Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. *Eur J Heart Fail* John Wiley & Sons, Ltd; 2019;**21**:904–916.
15. Pugliese NR, Masi S, Taddei S. The renin-angiotensin-aldosterone system: a crossroad from arterial hypertension to heart failure. Heart Fail. Rev. Springer US; 2020. p. 31–42.
16. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WHW, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J. Am. Coll. Cardiol. 2013. p. 485–495.
17. Mullens W, Verbrugge FH, Nijst P, Tang WHW. Renal sodium avidity in heart failure: From pathophysiology to treatment strategies. Eur. Heart J. 2017. p. 1872–1882.
18. Cleland JGF, Pfeffer MA, Clark AL, Januzzi JL, McMurray JJV, Mueller C, et al. The struggle towards a Universal Definition of Heart Failure-how to proceed? *Eur Heart J* Oxford Academic; 2021;**42**:2331–2343.

19. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ* British Medical Journal Publishing Group; 2019;**364**:223.

20. Parizo JT, Kohsaka S, Sandhu AT, Patel J, Heidenreich PA. Trends in Readmission and Mortality Rates Following Heart Failure Hospitalization in the Veterans Affairs Health Care System From 2007 to 2017. *JAMA Cardiol* American Medical Association; 2020;**5**:1042–1047.

21. Lindenfeld JA, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet* Elsevier B.V.; 2021;**398**:991–1001.

22. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, et al. Integrative Assessment of Congestion in Heart Failure Throughout the Patient Journey. JACC Hear. Fail. Elsevier Inc.; 2018. p. 273–285.

23. Cuthbert JJ, Pellicori P, Flockton R, Kallvikbacka-Bennett A, Khan J, Rigby AS, et al. The prevalence and clinical associations of ultrasound measures of congestion in patients at risk of developing heart failure. *Eur J Heart Fail* John Wiley & Sons, Ltd; 2021;**23**:1831–1840.

24. Gargani L, Pugliese NR, Frassi F, Frumento P, Poggianti E, Mazzola M, et al. Prognostic value of lung ultrasound in patients hospitalized for heart disease irrespective of symptoms and ejection fraction. *ESC Hear Fail* 2021;ehf2.13206.

25. Pugliese NR, Biase N De, Gargani L, Mazzola M, Conte L, Fabiani I, et al. Predicting the transition to and progression of heart failure with preserved ejection fraction: a weighted risk score using bio-humoural, cardiopulmonary, and echocardiographic stress testing. *Eur J Prev Cardiol* 2021;**28**:1650–1661.

26. Kobayashi M, Gargani L, Palazzuoli A, Ambrosio G, Bayés-Genis A, Lupon J, et al. Association between right-sided cardiac function and ultrasound-based pulmonary congestion on acutely decompensated heart failure: findings from a pooled analysis of four cohort studies. *Clin Res Cardiol* Springer; 2020;1–12.

27. Maaten JM Ter, Dauw J, Martens P, Somers F, Damman K, Metalidis C, et al. The Effect of Decongestion on Intrarenal Venous Flow Patterns in Patients With Acute Heart Failure. *J Card Fail*

2021;**27**:29–34.

28. Nijst P, Martens P, Dupont M, Tang WHW, Mullens W. Intrarenal Flow Alterations During Transition From Euvolemia to Intravascular Volume Expansion in Heart Failure Patients. *JACC Hear Fail* 2017;**5**:672–681.

29. Tanase DM, Radu S, Shurbaji S Al, Baroi GL, Costea CF, Turliuc MD, et al. Natriuretic peptides in heart failure with preserved left ventricular ejection fraction: From molecular evidences to clinical implications. Int. J. Mol. Sci. MDPI AG; 2019.

30. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide–guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA - J Am Med Assoc* American Medical Association; 2017;**318**:713–720.

31. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, Maestro A, López-López L, Solé-González E, et al. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). *Eur J Heart Fail* John Wiley and Sons Ltd; 2019;**21**:1605–1613.

32. Marini C, Fragasso G, Italia L, Sisakian H, Tufaro V, Ingallina G, et al. Lung ultrasound-guided therapy reduces acute decompensation events in chronic heart failure. *Heart* BMJ Publishing Group Ltd and British Cardiovascular Society; 2020;**106**:1934–1939.

33. Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, Cabello-López A, Alanis-Estrada G, Luna-Herbert A, et al. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). *Am Heart J* Mosby Inc.; 2020;**227**:31–39.

34. Rastogi T, Bozec E, Pellicori P, Bayes-Genis A, Coiro S, Domingo M, et al. Prognostic Value and Therapeutic Utility of Lung Ultrasound in Acute and Chronic Heart Failure: A Meta-Analysis. JACC Cardiovasc. Imaging. Elsevier; 2022. p. 950–952.

35. Cleland JGF, Pellicori P. To master heart failure, first master congestion. Lancet. Lancet; 2021. p. 935–936.

36. Martens P, Dupont M, Verbrugge FH, Damman K, Degryse N, Nijst P, et al. Urinary Sodium Profiling in Chronic Heart Failure to Detect Development of Acute Decompensated Heart Failure.

JACC Hear Fail Elsevier; 2019;**7**:404–414.

37. Platz E, Jhund PS, Girerd N, Pivetta E, McMurray JJV, Peacock WF, et al. Expert consensus document: Reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. *Eur J Heart Fail* John Wiley and Sons Ltd; 2019;**21**:844–851.

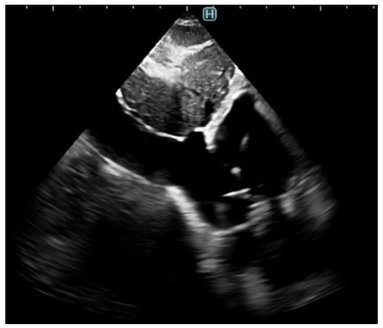
Figure legend.

Graphical abstract. A) Congestion assessment by ultrasound (US): increasing B-lines (≥4), discontinuous renal venous flow (RVF) and dilated inferior vena cava (IVC≥21 mm). **B)** The value of measuring congestion by US: Kaplan–Meier for the primary outcome of all-cause death (ACM) and heart failure hospitalisations (HFH) in HF patients (black lines) and subjects without HF (red line). HF patients with ≥2 US signs had the worst outcome, while those free of congestion at US had a prognosis similar to subjects without HF.

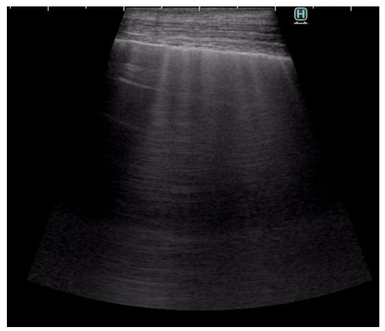
Figure 1. Distribution of patients with heart failure (HF) according to the presence of congestion by ultrasound (US). HF patients with ≥2 US signs of congestion had the highest levels of NT-proBNP (bottom left), also when considering HF patients with sinus rhythm only (bottom centre) or HF patients without sinus rhythm (i.e., n=122 having atrial fibrillation and n=8 with atrial pacing; bottom right). IVC: inferior vena cava; RVF: renal venous flow.

Figure 2. Univariate correlation matrix for different markers of congestion using Spearman's Rank correlation. *p<0.05, **p<0.001, ***p<0.0001. Red shading indicates positive correlations, and blue shading indicates inverse correlations. White boxes are non-significant (p>0.05). Aldo: aldosterone; ePAWP: echo-derived pulmonary artery wedge pressure; ePVS: estimated plasma volume status; FENa: fractional excretion of sodium; hs-CRP: high sensitive C-reactive protein; IVC: inferior vena cava; LVGLS: left ventricle global longitudinal strain; LVEF: left ventricle ejection fraction; Nora: norepinephrine; RVEF: right ventricle ejection fraction; U_{Na+}: urinary sodium; VII: venous impedance index.

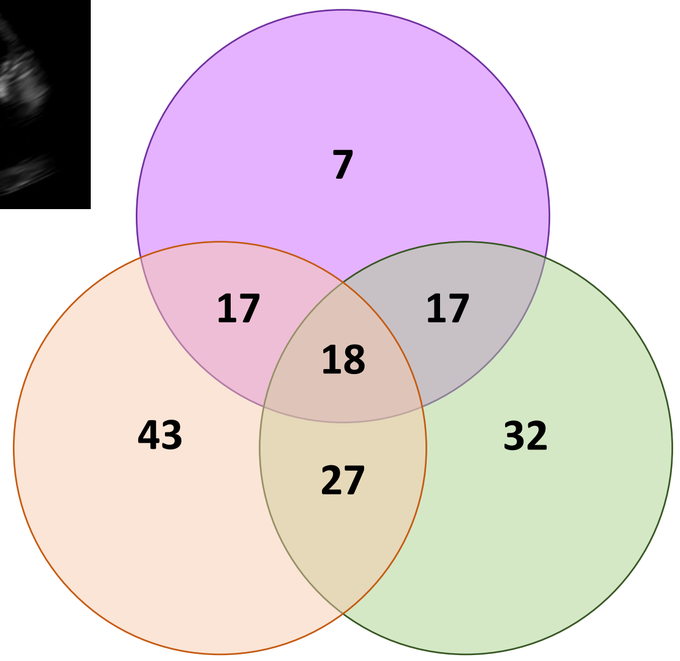
Figure 3. Multi-panel Kaplan–Meier for the primary outcome of all-cause death (ACM) and heart failure hospitalisations (HFH) in patients with heart failure (n=310) according to clinical or ultrasound signs of congestion. A) Signs of clinical congestion (pitting oedema, lung crackles, jugular vein distension). **B)** Inferior vena cava (IVC) diameter. **C)** B-lines (tertile 1: <1 B-line, tertile 2: 1–3 B-lines, tertile 3: ≥4 B-lines). **D)** Renal venous flow (RVF) patterns.



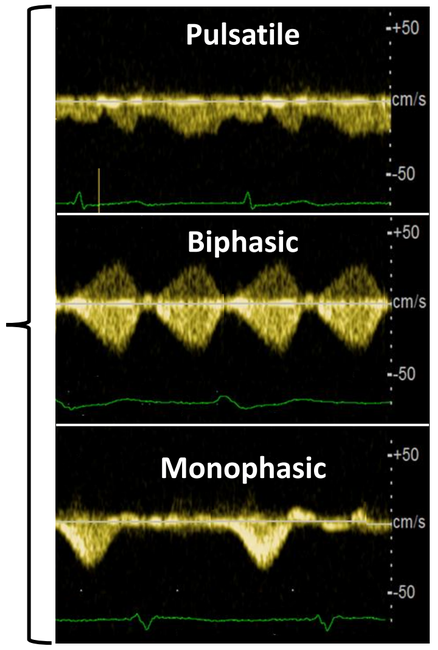
IVC ≥21 mm (n=59, 19%)]



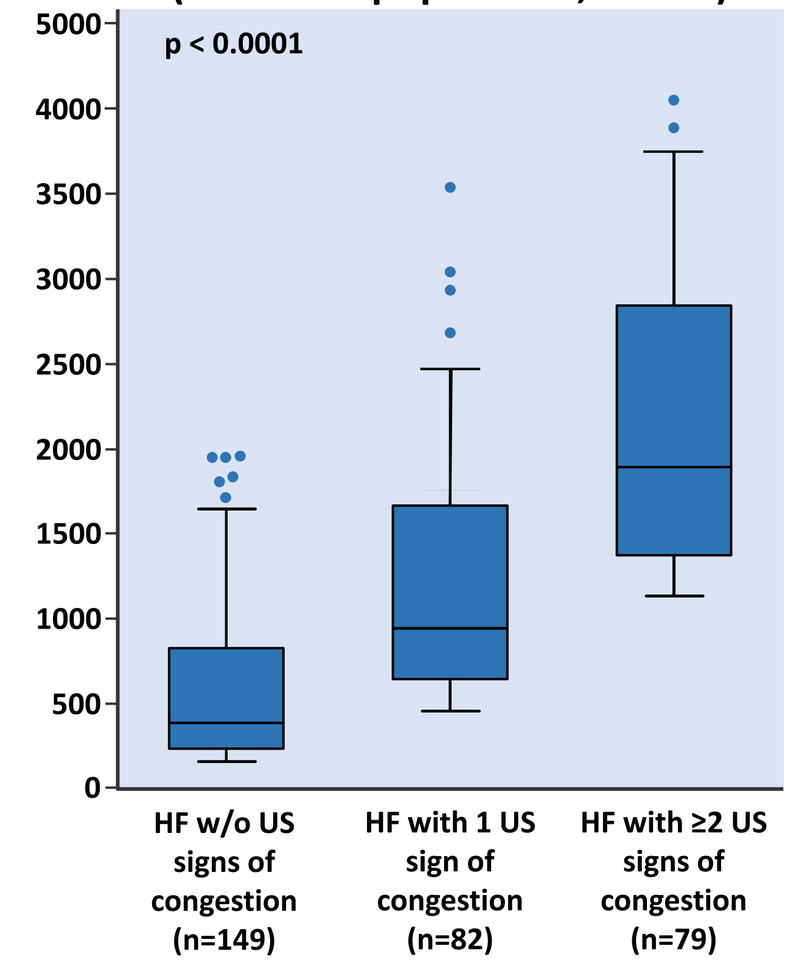
B-lines ≥4
(n=105, 34%)



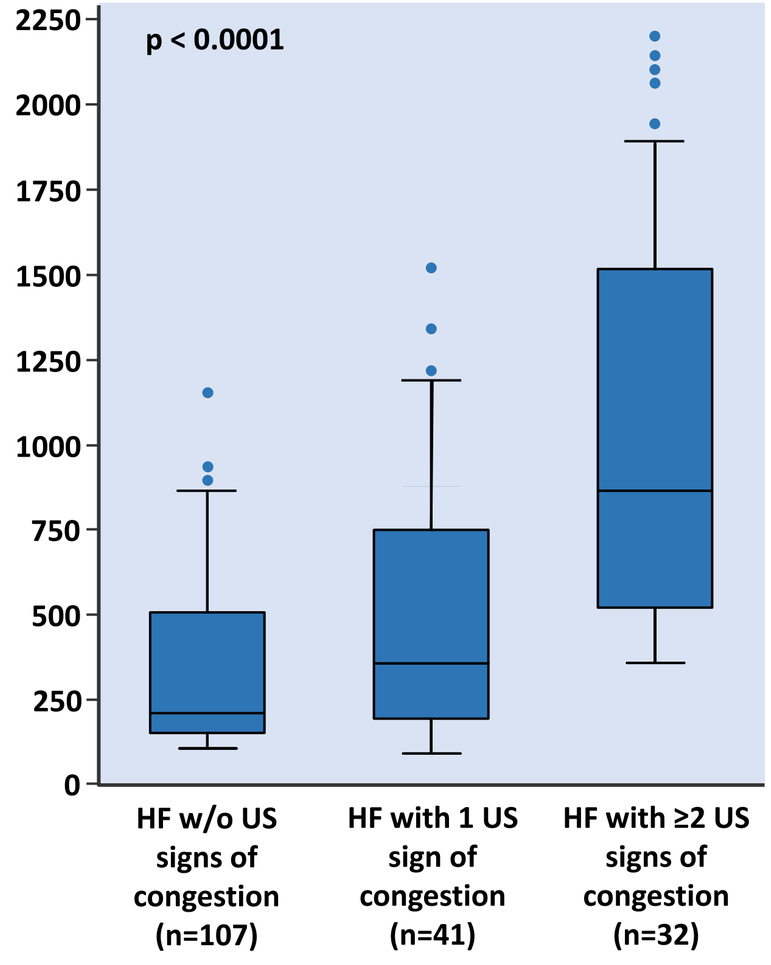
Discontinuous RVF
(n=94, 30%)



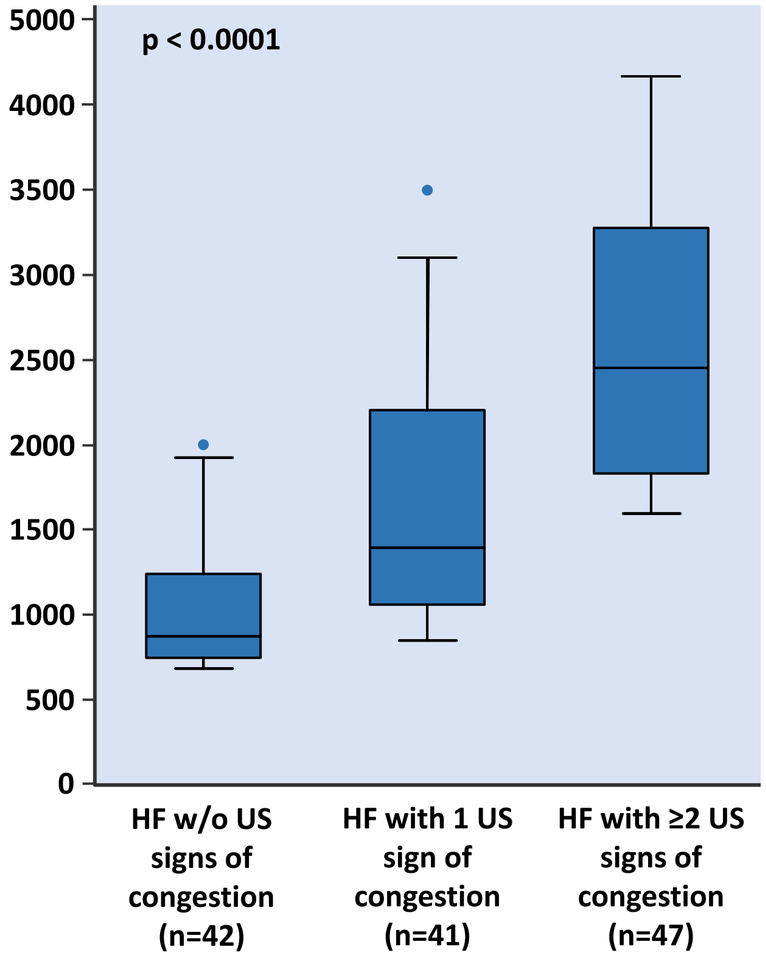
Median NT-proBNP, pg/mL (whole HF population, n=310)



Median NT-proBNP, pg/mL (HF with sinus rhythm only, n=180)



Median NT-proBNP, pg/mL (HF without sinus rhythm, n=130)

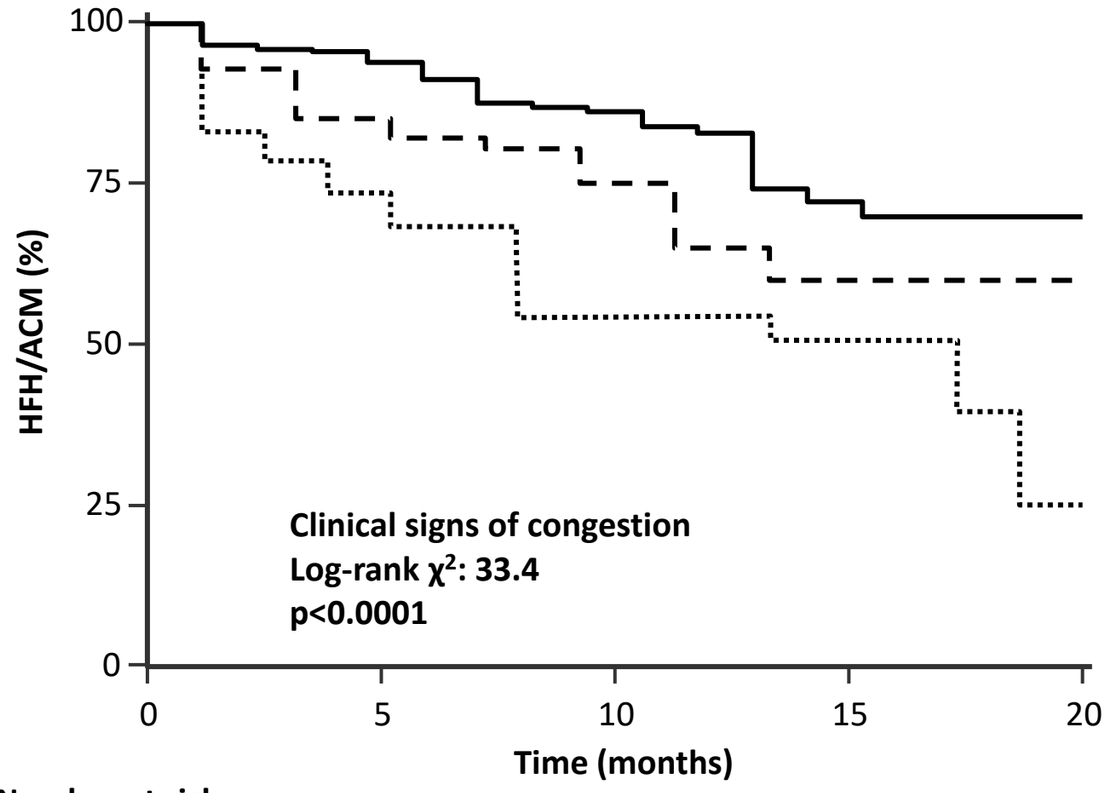


Spearman's rank correlation coefficient

-1 +1

	IVC (mm)	B-lines	Renal VII	Age (years)	Uric acid (mg/dL)	hs-CRP (mg/dL)	Crea (mg/dL)	Urea (mg/dL)	ePVS (mL/g)	Nora (pg/mL)	Renin (mIU/L)	Aldo (ng/dL)	Log[NT-proBNP]	U_{Na+} (mEq/L)	FENa (%)	LVEF (%)	LVGLS (%)	3D-RVEF (%)
B-lines	0.284**																	
Renal VII	0.463**	0.340***																
Age (years)	0.107	0.102	0.040															
Uric acid (mg/dL)	0.141*	0.218**	0.306**	0.048														
hs-CRP (mg/dL)	-0.019	0.100	-0.113	0.130*	0.049													
Crea (mg/dL)	0.073	0.135*	0.133*	0.261**	0.296**	0.072												
Urea (mg/dL)	0.129*	0.360**	0.407***	0.282**	0.453***	0.118*	0.636***											
ePVS (mL/g)	0.022	0.123	0.155*	0.181*	0.016	0.081	0.077	0.163*										
Nora (pg/mL)	0.177*	0.299**	0.402***	0.205**	0.149*	0.058	0.159*	0.200*	0.241**									
Renin (mIU/L)	0.102	0.056	0.081	0.077	0.058	0.049	0.052	0.134*	0.012	0.071								
Aldo (ng/dL)	0.169*	0.212**	0.285**	0.108	0.129*	0.033	0.182*	0.155*	0.220**	0.170*	0.085							
Log[NT-proBNP]	0.434***	0.466***	0.483***	0.303**	0.227**	0.092	0.408***	0.414***	0.418***	0.250**	0.068	0.164*						
U_{Na+} (mEq/L)	-0.185*	-0.201**	-0.401***	-0.125*	-0.279**	-0.024	-0.249**	-0.214**	-0.232**	-0.180*	-0.166**	-0.206**	-0.246**					
FENa (%)	0.094	0.071	-0.439***	0.106	-0.022	0.035	0.334**	0.448***	-0.135*	-0.156*	-0.039	-0.137*	-0.187*	0.330**				
LVEF (%)	-0.146*	-0.122*	-0.294**	0.067	-0.260**	-0.039	-0.141*	-0.159*	-0.121*	-0.042	-0.217**	-0.115*	-0.346**	0.171*	0.030			
LVGLS (%)	0.231**	0.309**	0.460***	-0.053	0.230**	0.067	0.143*	0.160*	0.272*	0.175*	0.283**	0.192*	0.415***	-0.164*	-0.051	-0.651***		
3D-RVEF (%)	-0.307**	-0.205**	-0.458***	0.025	-0.236**	-0.060	-0.140*	-0.150*	-0.189*	-0.161*	-0.182**	-0.124*	-0.301**	0.139*	-0.045	0.531***	-0.463***	
ePAWP (mmHg)	0.565***	0.526***	0.545***	0.103	0.259**	0.016	0.145*	0.261**	0.149*	0.282**	0.104	0.164*	0.541***	-0.325**	-0.275**	-0.153*	0.406***	-0.415***

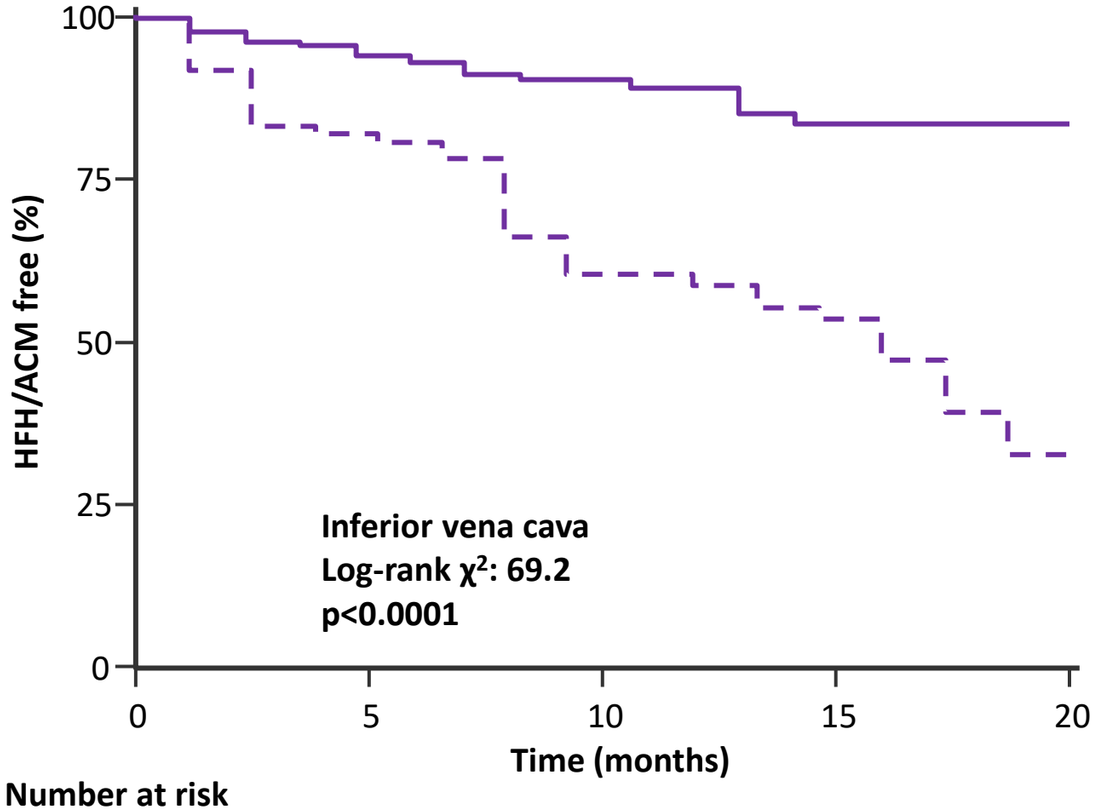
A



Number at risk

No signs of clinical congestion	224	192	147	94	80
1 sign of clinical congestion	70	51	42	30	15
≥2 signs of clinical congestion	16	9	7	6	3

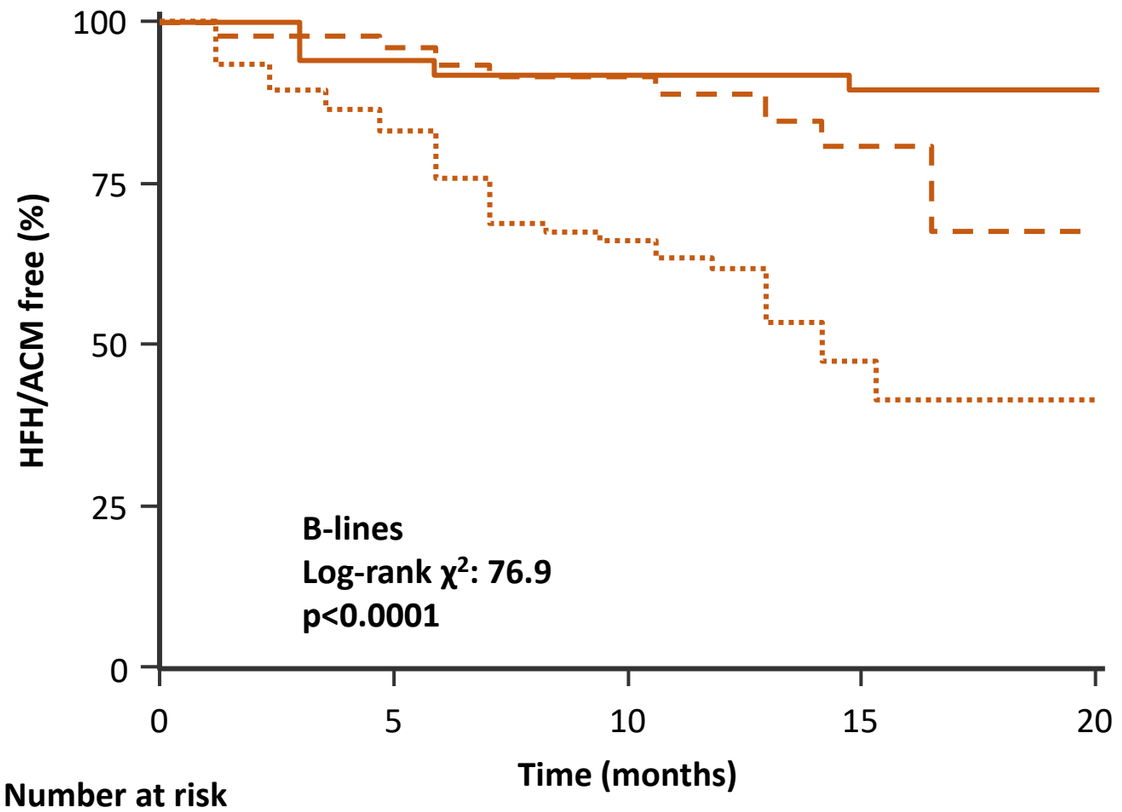
B



Number at risk

IVC <21 mm	251	209	167	116	88
IVC ≥21 mm	59	43	29	20	10

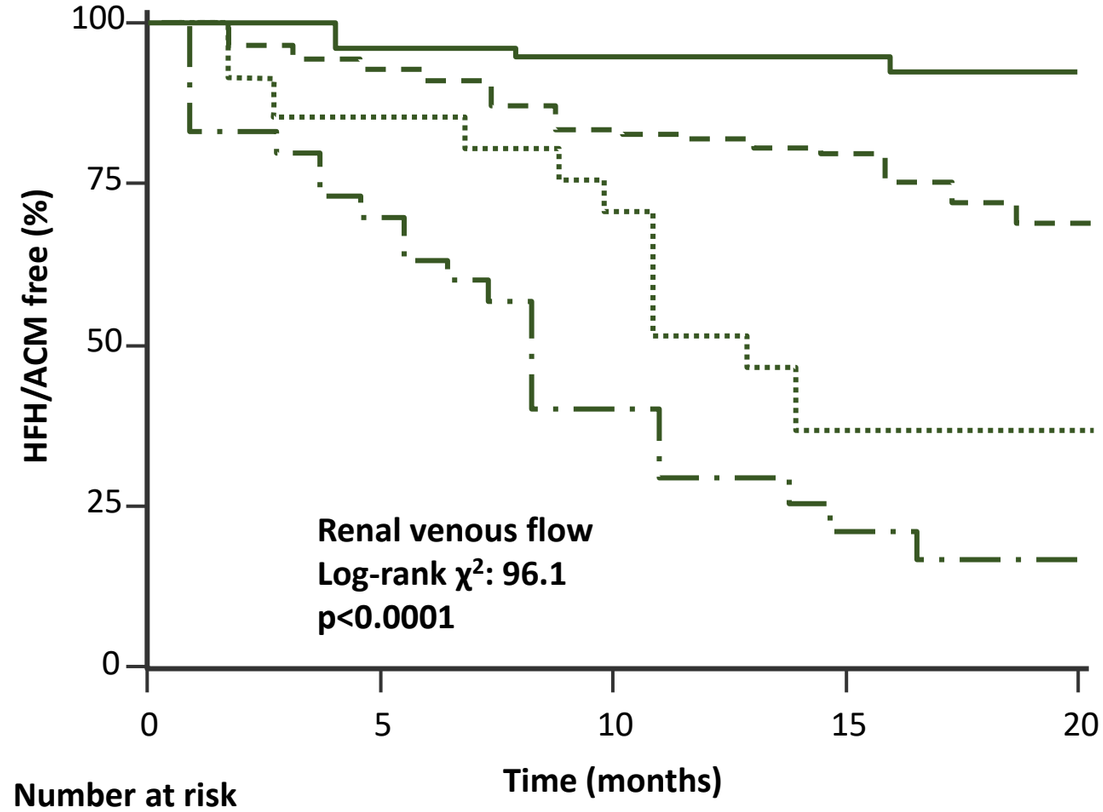
C



Number at risk

B-lines Tertile 1	102	88	85	66	55
B-lines Tertile 2	103	89	72	49	32
B-lines Tertile 3	105	75	43	21	11

D



Number at risk

RVF pattern: continuous	216	187	152	102	75
RVF pattern: discontinuous pulsatile	40	30	27	21	16
RVF pattern: discontinuous biphasic	35	25	16	10	5
RVF pattern: discontinuous monophasic	19	10	5	3	2

Table 1. Population characteristics.

Variable	HF w/o US signs of congestion (n=149)	HF with 1 US sign of congestion (n=82)	HF with ≥2 US signs of congestion (n=79)	p-value
Demographics (0 missing)				
Age, years	73 (64 – 81)	75 (69 – 82)#	78 (72 – 85)#	**0.001**
Men	89 (60)	56 (68)	56 (71)	0.2
BMI, Kg/m^2	27.5±4.7	28.4±5.1	28.6±5.6	0.2
BSA, m^2	1.9±0.2	1.9±0.3	1.9±0.3	0.9
Smoker	27 (18)	16 (20)	18 (23)	0.3
NYHA class				**0.001**
I	28 (19)	12 (15)	7 (9)	
II	97 (65)	46 (56)	37 (47)	
III	24 (16)	24 (29)	35 (44)	
KCCQ score	53±22	50±27	48±29	0.1
Arterial hypertension	112 (75)	65 (79)	57 (72)	0.4
Stroke/TIA	18 (12)	8 (10)	8 (10)	0.5
Diabetes mellitus	43 (29)	25 (30)	25 (32)	0.2
COPD	24 (16)	16 (20)	15 (19)	0.3
CAD	48 (32)	29 (35)	26 (33)	0.3
Previous MI	34 (23)	21 (26)	18 (23)	0.2
Previous PCI/CABG	42 (28)	25 (30)	22 (28)	0.5
Pacemaker	31 (21)	18 (22)	18 (23)	0.3
ICD	26 (17)	12 (15)	14 (18)	0.6
CRT	19 (13)	9 (11)	4 (5)	0.1
Atrial fibrillation	39 (26)	38 (46)#	45 (57)#^	**0.01**
Clinical evaluation (0 missing)				
Brachial systolic BP, mmHg	131±22	130±22	121±19#^	**0.001**
Brachial diastolic BP, mmHg	77±14	76±14	76±13	0.8
Heart rate, beats/min	72±12	73±16	73±15	0.9
No clinical signs of congestion	129 (87)	61 (74)#	34 (43)#^	**<0.0001**
Pitting oedema (any degree)	23 (15)	21 (25)	35 (44)#^	**0.001**
Lung crackles (any degree)	4 (3)	7 (9)	23 (28)#^	**<0.0001**
Jugular vein distension (any degree)	0	6 (7)	14 (18)#^	**<0.0001**
Blood tests (0 missing)				
Haemoglobin, g/dL (men)	13.5±1.7	13.5±1.9	13.4±1.6	0.1
Haemoglobin, g/dL (women)	12.9±1.8	12.8±1.8	12.7±2.1	0.1
Na^+, mEq/L	140±3	141±3	142±3#	**0.005**
K^+, mEq/L	4.3±0.5	4.3±0.4	4.3±0.5	0.9
Total cholesterol, mg/dL	163±41	163±39	164±40	0.3
Fasting glucose, mg/dL	98±31	99±28	102±26	0.6
HbA1c, mmol/mol	41±10	41±10	41±9	0.9
Uric acid, mg/dL	7.3±1.9	7.7±2.4	8.3±2.9#^	**<0.0001**
hs-CRP, mg/dL	0.42 (0.24 – 0.60)	0.44 (0.25 – 0.63)	0.48 (0.27 – 0.69)#	**0.006**
Creatinine, mg/dL	1.01 (0.82 – 1.23)	1.05 (0.91 – 1.30)	1.08 (0.95 – 1.32)	0.1
eGFR, mL/min/1.73 m^2	65 (54 – 82)	64 (52 – 77)	61 (50 – 72)	0.1
Urea, mg/dL	47 (36 – 57)	48 (37 – 58)	54 (43 – 72)#^	**0.001**
ePVS, mL/g	4.7 (4.1 – 5.3)	4.8 (4.3 – 5.5)	5.3 (4.7 – 6.2)#^	**<0.0001**
Osmolality, mOsm/kg	294 (289 – 298)	294 (290 – 299)	298 (292 – 301)#^	**<0.0001**
Norepinephrine, pg/mL	318 (232 – 384)	332 (287 – 483)	398 (313 – 592)#^	**<0.0001**
Renin, mIU/L	21.1 (6.1 – 51.4)	23.7 (8.2 – 75.4)	28.3 (9.1 – 123.1)	0.1
Aldosterone, ng/dL	9.5 (6.5 – 12.7)	10.3 (7.1 – 13.8)	15.1 (9.8 – 23.1)#^	**<0.0001**
NT-proBNP, pg/mL	409 (308 – 862)	936 (627 – 1671)#	1862 (1379 – 2886)#^	**<0.0001**
NT-proBNP, pg/mL (SR only)	211 (160 – 543)	336 (185 – 749)	847 (561 – 1590)#^	**<0.0001**
hs-Troponin T, pg/mL	15 (11 – 24)	18 (12 – 27)	25 (15 – 46)#^	**<0.0001**
Urine test (12 missing)				
Osmolality, mOsm/kg	540 (417 – 680)	507 (408 – 630)	456 (334 – 571)#	**0.001**
UACR, mg/g	21 (8 – 63)	23 (9 – 65)	57 (21 – 99)#^	**<0.0001**
Micro-albuminuria§	38 (25)	26 (32)	51 (65)	**<0.0001**

Macro-albuminuria§	7 (5)	5 (6)	11 (14)	**0.04**
Spot urinary sodium, mEq/L	69 (48 – 118)	63 (44 – 117)	45 (30 – 76)#^	**<0.0001**
FENa, %	0.58 (0.40 – 0.91)	0.53 (0.37 – 0.89)	0.40 (0.20 – 0.66)#^	**<0.0001**
Therapy (0 missing)				
Beta-Blocker	118 (79)	66 (80)	64 (81)	0.5
DHP CCB	34 (23)	18 (22)	9 (11)	0.1
Non-DHP CCB	0	2 (2)	0	0.2
ACEi or ARB	94 (63)	50 (61)	52 (66)	0.3
MRA	69 (46)	43 (52)	45 (57)	0.2
ARNI	37 (25)	14 (17)	15 (19)	0.3
ASA	67 (45)	34 (41)	37 (47)	0.7
Statins	83 (56)	42 (51)	41 (52)	0.3
Thiazides/thiazide-like diuretics	16 (11)	11 (13)	5 (6)	0.4
Loop diuretics	106 (71)	62 (75)	62 (78)	0.1
Furosemide equivalent dose				0.4
1 – 50 mg	28 (19)	14 (17)	12 (15)	
51 – 100 mg	70 (47)	39 (48)	42 (53)	
>100 mg	8 (6)	7 (8)	10 (13)	
SGLT2i	19 (13)	9 (11)	8 (10)	0.3
Insulin	15 (10)	6 (7)	5 (6)	0.2
Oral anticoagulants	40 (27)	39 (48)#	46 (58)#	**0.01**

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.

§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 resynchronization 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; HFrEF: heart failure with reduced 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.

Table 2. Ultrasound evaluation.

Variable	Missing	HF w/o US signs of congestion (n=149)	HF with 1 US sign of congestion (n=82)	HF with ≥2 US signs of congestion (n=79)	p-value
Left ventricle size and function					
LVMi, g/m^2	0	131±38	137±35	140±40	0.3
RWT	0	0.36±0.10	0.36±0.10	0.38±0.13	0.5
LVEDV, mL	0	171±58	174±53	182±61	0.6
LVEF, %	0	50±14	52±14	47±14	0.2
3D-LVEF, %	15	48±11	49±13	44±12	0.1
LVGLS, %	5	-14.1±4.2	-13.9±4.9	-11.6±4.7$^{\#\wedge}$	**0.001**
Stroke volume, mL/beat	0	61±32	59±28	54±19	0.4
Cardiac output, L/min	0	4.6±2.2	4.4±1.6	3.9±1.3	0.1
Mitral E wave, cm/s	0	93±44	111±48	127±43$^{\#}$	**<0.0001**
Average e', cm/s	0	7.3±2.3	7.3±2.2	8.9±3.1$^{\#\wedge}$	**0.002**
Average E/e'	0	13.6±5.6	16.1±6.2	16.9±6.6$^{\#}$	**0.004**
Mitral regurgitation (≥ moderate)	0	14 (9)	8 (10)	10 (13)	0.2
Left atrium size and function					
LAVi, mL/m^2	0	45±21	49±18	62±18$^{\#\wedge}$	**<0.0001**
LA reservoir strain, %	0	-20±8	-17±10	-12±6$^{\#\wedge}$	**<0.0001**
Right ventricle and pulmonary circulation					
TAPSE, mm	0	19±4	19±4	18±4	0.1
RVFAC, %	0	50±10	49±11	42±9$^{\#\wedge}$	**<0.0001**
RV free wall longitudinal strain, %	19	-28±6	-27±6	-24±6	**0.03**
3D-RVEDV	19	137±34	151±39	165±50$^{\#\wedge}$	**0.001**
3D-RVEF, %	19	56±10	55±13	46±10$^{\#\wedge}$	**<0.0001**
Tricuspid regurgitation (≥ moderate)	0	11 (7)	8 (10)	8 (10)	0.3
Systolic PAP, mmHg	8	37±13	45±15$^{\#}$	53±14$^{\#\wedge}$	**<0.0001**
Diastolic PAP, mmHg	10	9±4	12±7$^{\#}$	17±7$^{\#\wedge}$	**<0.0001**
Mean PAP, mmHg	10	19±6	24±8$^{\#}$	30±9$^{\#\wedge}$	**<0.0001**
ePVR, WU	10	1.5±0.7	1.9±0.9$^{\#}$	2.1±0.7$^{\#}$	**<0.0001**
ePAWP, mmHg	10	12±4	15±6$^{\#}$	20±5$^{\#\wedge}$	**<0.0001**
Congestion assessment	0				
IVC, mm		17 (15 – 18)	18 (15 – 21)$^{\#}$	23 (21 – 27)$^{\#\wedge}$	**<0.0001**
IVC ≥21 mm		0	7 (8)	52 (66)$^{\#\wedge}$	**<0.0001**
IVC collapse <50%		3 (2)	15 (18)$^{\#}$	21 (27)$^{\#\wedge}$	**<0.0001**
B-lines		0 (0 – 2)	7 (4 – 14)$^{\#}$	13 (8 – 28)$^{\#\wedge}$	**<0.0001**
B-lines ≥4		0	43 (52)$^{\#}$	62 (78)$^{\#\wedge}$	**<0.0001**
RVF pattern					**<0.0001**
Continuous		149 (100)	50 (61)$^{\#}$	17 (21)$^{\#\wedge}$	
Discontinuous: pulsatile		0	29 (35)$^{\#}$	11 (14)$^{\#\wedge}$	
Discontinuous: biphasic		0	3 (4)	32 (41)$^{\#\wedge}$	
Discontinuous: monophasic		0	0	19 (24)$^{\#\wedge}$	
Renal venous impedance index		0.2 (0.1 – 0.3)	0.3 (0.2 – 1)$^{\#}$	1 (1 – 1)$^{\#\wedge}$	**<0.0001**
Renal venous discontinuity index, %‡		-	12 (10 – 25)	29 (14 – 66)	**0.01**

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; LVEF: left ventricle ejection fraction; LVMi: left ventricle mass index; PAP: pulmonary artery pressure; RVEF: right ventricle ejection fraction; RVF: renal venous flow; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion.

Table 3. Cox proportional-hazards multivariable regression analysis for predicting the composite endpoint (all-cause death and hospitalization for heart failure) in the HF population (n=310).

Variable	HR (95% CI)	p-value
Model 1		
Log(NT-proBNP)	5.73 (1.67 – 19.64)	**0.006**
US signs of congestion		
None	Reference	
1 US signs of congestion	1.45 (0.52 – 4.33)	0.4
1 US signs of congestion*LVEF	1.02 (0.89 – 1.22)	0.3
≥2 US signs of congestion	13.9 (4.9 – 39.3)	**<0.0001**
≥2 US signs of congestion*LVEF	1.97 (0.77 – 2.45)	0.4
Model 2		
Log(NT-proBNP)	3.94 (2.38 – 6.05)	**<0.0001**
IVC, mm		
<21 mm	Reference	
≥21 mm	3.35 (1.67 – 6.75)	**0.001**
B-lines		
Tertile 1: <1	Reference	
Tertile 2: 1 – 3	0.99 (0.39 – 2.52)	0.9
Tertile 3: ≥4	1.66 (1.15 – 2.88)	**0.01**
RVF pattern		
Continuous	Reference	
Discontinuous: pulsatile	1.83 (0.62 – 5.39)	0.2
Discontinuous: biphasic	8.14 (3.37 – 19.67)	**<0.0001**
Discontinuous: monophasic	10.12 (2.84 – 26.16)	**<0.0001**
Model 3		
Log(NT-proBNP)	3.85 (2.13 – 6.95)	**<0.0001**
IVC, mm	1.13 (1.06 – 1.21)	**<0.0001**
B-lines	1.03 (1.01 – 1.08)	**0.03**
Log(Renal venous impedance index)	5.23 (2.24 – 22.31)	**<0.0001**

All the models were adjusted for age (years), sex (male), atrial fibrillation, any signs of clinical congestion, eGFR (mL/min/1.73 m^2), UACR (mg/g), LVEF (%), LAVi (mL/m^2).
Legend as in the previous tables.