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► To cite this version:

Alberto Palazzuoli, Gaetano Ruocco, Pierpaolo Pellicori, Luna Gargani, Stefano Coiro, et al.. Multi-modality assessment of congestion in acute heart failure: Associations with left ventricular ejection fraction and prognosis. *Current Problems in Cardiology*, 2024, 49 (3), pp.102374. 10.1016/j.cpcardiol.2024.102374 . hal-04390704

HAL Id: hal-04390704

<https://hal.univ-lorraine.fr/hal-04390704v1>

Submitted on 12 Jan 2024

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Multi-modality assessment of congestion in acute heart failure: associations with left ventricular ejection fraction and prognosis

Short Title: Congestion in AHF, according to LVEF

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Conflict of interests: NG received honoraria from Bayer, Boehringer, Lilly, Novartis, AstraZeneca, Vifor. AP from AstraZeneca. **Funding resources:** None.

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Word count:

Keywords: Acute heart failure; Congestion; Echocardiography; Lung ultrasound; Inferior vena cava; Natriuretic peptides; Ejection fraction

Abstract (250 words)

Background: Integrating clinical examination with ultrasound measures of congestion could improve risk stratification in patients hospitalized with acute heart failure (AHF).

Aim: To investigate the prevalence of clinical, echocardiographic and lung ultrasound (LUS) signs of congestion according to left ventricular ejection fraction (LVEF) and their association with prognosis in patients with AHF.

Methods: We pooled the data of four cohorts of patients (N=601, 74.9±10.8 years, 59% men) with AHF and analysed six features of congestion at enrolment: clinical (peripheral oedema and respiratory rales), biochemical (BNP/NT-proBNP_≥median), echocardiographic (inferior vena cava (IVC)_≥21mm, pulmonary artery systolic pressure (PASP)_≥40 mmHg, E/e'_≥15) and B-lines _≥25 (8-zones) in those with reduced (<40%, HFrEF), mildly reduced (40-49%, HFmrEF) and preserved (_≥50% HFpEF) LVEF.

Results: Compared to patients with HFmrEF (n=110) and HFpEF (n=201), those with HFrEF (N=290) had higher natriuretic peptides, but prevalence of clinical (39%), echocardiographic (IVC_≥21 mm: 56%, E/e'_≥15: 57%, PASP_≥40 mmHg: 76%) and LUS (48%) signs of congestion was similar. In multivariable analysis, clinical (HR: 3.24(2.15 - 4.86), p<0.001), echocardiographic [(IVC_≥21 mm (HR:1.91, 1.21 - 3.03, p=0.006); E/e'_≥15 (HR:1.54, 1.04 - 2.28, p=0.031)] and LUS (HR:2.08, 1.34 - 3.24, p=0.001) signs of congestion were significantly associated with all-cause mortality and/or HF re-hospitalization. Adding echocardiographic and LUS features of congestion to a model than included age, sex, systolic blood pressure, clinical congestion and natriuretic peptides, improved prediction at 90 and 180 days.

Conclusions: Clinical and ultrasound signs of congestion are highly prevalent in patients with AHF, regardless of LVEF and their combined assessment improves risk stratification.

Introduction

Most of the episodes of acute decompensated heart failure (AHF) are driven by salt and water retention, also known as congestion. [1-3] Clinical assessment alone is usually insufficient to detect a modest degree of intravascular and tissue congestion; [4] implementing routine evaluation with ultrasound and other diagnostic tools that quantify congestion with more precision might improve diagnosis and risk stratification. [5,6]

Natriuretic peptides (NP) are central to the diagnosis of heart failure (HF), but many patients hospitalized with AHF already have an established HF diagnosis, high NP levels or comorbidities such as atrial fibrillation or renal dysfunction that might confound their interpretation. [7,8] Echocardiography is a key diagnostic test to confirm the presence and severity of cardiac dysfunction and to estimate intravascular volume, by measuring the diameter of the inferior vena cava (IVC). Assessment of lung parenchyma with lung ultrasound (LUS) is also a simple, safe, rapid, and inexpensive test that can quantify pulmonary congestion at the patient's bedside and improve management of those with AHF. [9]

Whether combining clinical examination with natriuretic peptides and ultrasound measures of congestion improves risk stratification in patients with AHF and reduced (HFrEF), mildly reduced (HFmEF) or preserved (HFpEF) left ventricular ejection fraction (LVEF) remains uncertain. Therefore, to address this question, we pooled data from four international cohorts of patients with AHF and investigated the relevance of an integrated evaluation of congestion, overall and according to LVEF.

Methods

Pooled Patient Population

The current pooled study was performed as a patient-level meta-analysis combining datasets from four independent cohort studies conducted in Europe. Apart than those enrolled in Nancy, all patients included gave their written consent for data storage and evaluation. For the Nancy cohort, data were acquired as part of usual clinical management and collected retrospectively; collection of patient data was approved by the Commission Nationale Informatique et Libertés (CNIL), in keeping with French law. The final database was constructed and maintained by the collaborative group by integrating anonymized data. The database is password protected, held securely on a server, and only accessible by authorized researchers; it

will not be used in any publication without the permission of the investigators who have contributed their data. The Nancy cohort study included patients who were hospitalized for AHF in the Institute Lorrain du Coeur et des Vaisseaux in France from April 2014 to August 2015; [10]; The Pisa cohort study included patients who were hospitalized for AHF in the Cardiology Department in Pisa from October 2004 to October 2008; [11] the Siena cohort study included patients with AHF and with sinus rhythm enrolled between 2017 and 2020. [12] Additionally, we included the first patients recruited in the AHF-CORE study, an ongoing cohort study (NCT03327532) that enrolls patients hospitalised for AHF in two university hospitals of the Grand-Est region of France. All patients underwent clinical, echocardiography, laboratory, and lung ultrasound assessment during the initial phases of the hospitalization (12 to 24 hours from admission, and up to 72 hours in the AHF-CORE study).

We excluded patients with conditions that might affect assessment of B-lines in AHF, or make their evaluation too difficult, and those patients who were unable to tolerate prolonged and detailed examinations including those with: (i) a poor acoustic window, (ii) pulmonary fibrosis, significant pleural effusion (ie, effusions causing a lung collapse), or other severe respiratory conditions; (iii) breast prosthesis; (iv) acute myocardial infarction, (v) cardiogenic shock and (vi) severe sepsis.

Assessment of congestion

1) Clinical

Patients were evaluated at enrolment to identify the presence of pulmonary congestion (respiratory rales on lung auscultation) or peripheral oedema (any degree). We defined clinical congestion as the presence of both respiratory rales and peripheral oedema.

2) By echocardiography

LVEF was measured using the modified biplane Simpson's method. Patients were classified according to LVEF as those with reduced (HFrEF, LVEF<40%), mildly reduced (HFmrEF, LVEF 40-49 %) and preserved LVEF (HFpEF, LVEF≥50%). Mitral early diastolic velocities (e') were assessed at the septal and lateral annulus using tissue Doppler imaging and their average value was used to calculate the E/e' ratio. Pulmonary artery systolic pressure was derived from the tricuspid regurgitation velocity (TRV) by adding an approximation of right atrial pressure and IVC diameter was measured in the subcostal view, according to interna-

tional recommendations [13]. Echocardiographic signs of congestion were defined as E/e' ≥ 15 , PASP ≥ 40 mmHg, IVC ≥ 21 mm [1, 13].

3) By lung ultrasound

Two protocols were used to assess lung B-lines. In Siena, it was used an eight thoracic zones protocol. The maximum number B-lines counted in each zone was summed up to obtain the total number of B-lines. In other cohorts (Nancy, Pisa, AHF-Core) where the 28-zone scanning protocol was used, we derived the corresponding total number of B-lines on 8 zones, as previously reported, by grouping zones as it follows: [14]

- I) parasternal and midclavicular zones, 2nd and 3rd intercostal space on right side (4 zones grouped in 1 zone).
- II) parasternal and midclavicular zones, 2nd and 3rd intercostal space on left side (4 zones grouped in 1 zone).
- III) anterior and mid-axillary zones, 2nd and 3rd intercostal space on right side (4 zones grouped in 1 zone).
- IV) anterior and mid-axillary zones, 2nd and 3rd intercostal space on left side (4 zones grouped in 1 zone).
- V) para-sternal and midclavicular zones, 4th and 5th intercostal space on right side (4 zones grouped in 1 zone).
- VI) anterior and mid-axillary zones, 4th and 5th intercostal space on right side (4 zones grouped in 1 zone).
- VII) para-sternal and midclavicular zones, 4th intercostal space on left side (2 zones grouped in 1 zone).
- VIII) anterior and mid-axillary zones, 4th intercostal space on left side (2 zones grouped in 1 zone).

We added up the highest number of B-lines seen within one of the 4 or 2 zones to derive the total number of B-lines in zones I-VIII.

Congestion on LUS was considered when the total number of B-lines was \geq median (25) [15]

4) Natriuretic peptides

We defined congested patients with natriuretic peptides above the median value in each cohort (NT-ProBNP > 2286 pg/ml in the Pisa cohort, >4753 pg/ml in the AHF-CORE cohort; BNP >991 pg/ml in the Siena cohort, >765 pg/ml in the Nancy cohort and 1488 pg/ml in the AHF-CORE cohort)

Study Outcomes

The primary outcome was the composite of hospitalization for HF or all-cause mortality during a period of 90 and 180 days. All patients were systematically followed-up after discharge in each institution; patients and their relatives were contacted regularly by mail or phone to collect clinical events of interest.

Statistical Analysis

Categorical data were presented as number and percentages; normally distributed continuous variables as mean and standard deviation (SD); non-normally distributed variables are presented as median and interquartile range (IQR). Continuous variables were compared using analysis of variance (ANOVA) or Kruskal-Wallis tests as required, while chi-squared test or exact Fisher were used for categorical variables.

To investigate the association between markers of congestion and clinical outcome during follow-up, crude and adjusted Cox proportional hazard regression models were assessed. The models were adjusted for age, sex, atrial fibrillation, systolic blood pressure (SBP), LVEF and estimated glomerular filtration rate (eGFR). Due to difference in study protocols at each site, each cohort was also added as strata in the Cox- regression model. Interactions between LVEF category and the association of congestion variables with outcome were tested using interaction terms in survival models while studies were added as strata. Hazard ratios and their 95% confidence intervals are reported. We constructed a basic clinical model (model 1), using variables selected a priori, based on clinical experience and previous research, that included age, sex, SBP, clinical markers of congestion and natriuretic peptides and then tested the additive value of ultrasound markers of congestion (and their combinations) in turn, by measuring the Harrell's C -index at 90 and 180 days the primary outcome. We also calculated the area under receiver-operating characteristic [ROC] curves using logistic regression models with death or HF hospitalization at 180 days as outcome for the following markers of congestion: clinical, IVC, E/e', PASP, B-lines and natriuretic peptides, adjusting for age, sex, atrial fibrillation, SBP, LVEF and eGFR, and study strata. Further, we plotted the inverse probability of treatment weighted-adjusted Kaplan-Meier survival curves for echocardiographic or LUS signs of congestion and NPs in patients free from respiratory rales and peripheral oedema at clinical examination. Log-rank tests were performed, and p-values are reported.

We considered statistically significant results associated with a p value <0.05. All analyses were performed using SAS version 9.4.6 (SAS Institute Inc., Cary, N.C., USA) and R version 3.6.1 (2019-07-05).

Results

Baseline characteristics

A total of 601 patients (mean age 74.9±10.8 years, 59% men) were included in this study. Compared to those with HFmrEF (N=110, 18%) and HFpEF (N=201, 34%), patients with HFrEF (N=290, 48%) were younger, had lower body mass index, and were more likely to have ischemic heart disease, but less likely to have hypertension. Patients with HFrEF also had higher NP levels and more severe right ventricular dysfunction, but the prevalence of clinical, echocardiographic and LUS signs of congestion was similar across populations of patients of different HF phenotype (Table 1).

In-hospital assessment of clinical, echocardiographic and LUS markers of congestion: association with outcome

The primary outcome occurred in 174 patients during 180 days of follow-up. In the entire cohort, clinical congestion (adjusted HR 3.24 [2.15 - 4.86]); $p < 0.001$), IVC ≥ 21 mm (adjusted HR 1.91 [1.21 - 3.03]), $p = 0.006$), E/e' ≥ 15 (adjusted HR 1.54 [1.04 - 2.28], $p = 0.031$) and B-lines ≥ 25 (adjusted HR 2.08 [1.34 - 3.24], $p = 0.001$) were all significantly associated with greater risk of heart failure hospitalisation or death (table 2). In adjusted models, clinical congestion, a dilated IVC and B-lines ≥ 25 were associated with an increased risk of all-cause mortality (Table 1 supplementary); clinical congestion and a greater number of B-lines, but not a dilated IVC (adjusted HR 1.71 [0.97-3.03], $p = 0.063$; Table 2 supplementary), were associated with an increased risk of HF hospitalisation. We found that clinical congestion was significantly associated with worse outcomes in patients with HFmrEF (adjusted HR 6.39 [2.21 - 18.50], $p = 0.0006$) and HFpEF (adjusted HR 8.16 [4.20 - 15.85], $p < 0.001$), but not in HFrEF (p for interaction < 0.001); the relationship between other markers of congestion with outcome did not change across LVEF phenotypes (Table 3 supplementary). Adding LUS or IVC and PASP to a model that included NP improved discrimination at 90 or 180 days. The greatest C-statistic was obtained when IVC, PASP and LUS were added together to the model (central figure). The adjusted AUCs for all markers of congestion were approximately 0.80 and are shown in supplementary figure 1.

Of those clinically free of peripheral and pulmonary congestion (25%), more than one in four had IVC \geq 21 mm, and two in three PASP \geq 40 mmHg (Figure 1). Compared to those with a smaller IVC or a lower PASP, these patients had a worse outcome. Amongst those without clinical congestion, there was no significant difference in prognosis for those who had B-lines \geq (19%) or $<$ 25 (Figure 2).

Discussion

Our results confirm the notion that congestion is associated with an adverse prognosis in patients with AHF, regardless of LVEF. These data are consistent with previous findings showing that pulmonary congestion assessed by B-lines is of prognostic relevance in patients admitted for heart failure, both in HFrEF and HFpEF (16). However, there are other important findings from this analysis, as we also showed that a combined assessment of ultrasound markers of congestion such as IVC and the number of B-lines improves risk stratification when added to clinical examination and other commonly measured clinical variables, including natriuretic peptides, in this population. These results provide support for a wider, routine use of an integrated evaluation of congestion in patients hospitalized with AHF. [17-20]

Several studies suggested that clinical signs of congestion at time of a hospitalization with AHF are associated with a poor prognosis. Clinical signs of congestion usually improve in response to treatments, but the risk of re-admission or death is still high even for those who have minimal or no congestion at hospital discharge, perhaps because many have sub-clinical congestion [16, 21]. Thus, subclinical congestion might be common and frequently under-recognised: we showed that, with ultrasound, it was possible to identify a substantial proportion of patients without peripheral edema and without respiratory rales who had, however, a dilated IVC or evidence of pulmonary hypertension, and a greater risk. This corroborates similar observations in other settings: Pellicori and colleagues showed that, amongst ambulatory patients with heart failure, half of those who were clinically euvolemic had signs of congestion by ultrasound and a greater cardiovascular risk [22]. In other words, ultrasound allows a more precise identification of congestion which might lead to individualised management of patients with AHF and potentially prevent or delay their clinical deterioration.

A comprehensive clinical evaluation requires time and skills. However, there is no specific algorithm to assess or grade clinical congestion, and decongestive strategies are still subjective and sub-optimal. It has proposed to monitor body weight, natriuretic peptides, symptoms and signs, or urinary sodium [2] to guide and assess diuretic response in ADHF. Based on our results, we believe that it might be practical and clinically relevant to test diagnostic and therapeutic strategies guided by a comprehensive evaluation of congestion by ultrasound in patients with AHF, for different reasons. Assessing IVC and B-lines can be done at same time of an echocardiogram when the presence of cardiac dysfunction or valve disease can be established or refuted [9]. The identification of a dilated IVC and a high number of B-lines might corroborate a diagnosis of HF, particularly when left ventricular ejection fraction is normal, regardless of the presence of signs of fluid overload and of their severity [23,24]. As training to acquire images of B-lines and IVC is rather short, the acquisition of ultrasonographic images of congestion could be done by different healthcare professionals, including medics – not only cardiologists – but also those who are likely to diagnose and manage patients with heart failure in their daily practice, for instance geriatrics, general practitioners, and specialists in internal medicine, or perhaps specialist heart failure nurses, and sonographers. [25, 26] The interpretation of ultrasound images of congestion is usually done in a few minutes, at the patients' bedside, and it might prompt timely life-saving therapeutic actions. Due to large availability of affordable, miniaturized, hand-held ultrasound devices assisted by artificial intelligence, congestion can be assessed virtually in any setting and its changes, or lack of, can be quantified with precision. Assessment of IVC or B-lines might be used to guide diuretic therapy or to identify those individuals resistant to diuretics, who should be subsequently referral to advanced therapies or palliative treatments.

Interestingly, an estimated PASP \geq 40 mmHg was not significantly associated to adverse outcomes in all patients. This may be related to the rapid changes of PASP following treatment with diuretics. Alternatively, it might be that elevated PASP could reflect primarily a chronic lung disease in some. However, it might be also possible that PASP will only increase when intravascular volume is substantial, as recent animal experiments and clinical work suggest [27], which would further highlight the relevance of assessing IVC to individualise heart failure management and potentially improve well-being and prognosis even when congestion is less severe or in the early stages of decompensation.

Limitations

This is an observational study, and we did not assess for causality. The study is retrospective, and the research question was developed post-hoc. Moreover, ultrasound machines and protocols used in each centre were different. Assessment of IVC diameter and B-lines quantification may depend on physician experience, patient's body habitus and, partially, by the ultrasound machine used [28] and the protocol applied [29]. B-lines were analysed off-line. Due to heterogeneity in the length of the duration of stored clips amongst studies, this might have led to a lower count of B-lines in some patients [30]. Diagnosis of HFmrEF and HFpEF, particularly, might be difficult; therefore, selection bias (ie, the more likely inclusion of patients with an obvious diagnosis of HFmrEF and HFpEF due to substantial congestion) cannot be excluded and might have impacted on results. Moreover, our clinical assessment of congestion was only based on lung auscultation and evaluation of peripheral oedema; findings might have been different if we had opted for a more comprehensive clinical evaluation. We evaluated congestion at different times, from hours to a few days after hospitalisation, with variations in protocols across different cohorts; in many patients enrolled in this study congestion might have already improved at the time of assessment due to intense diuretic treatment. However, this could also increase generalizability of our findings: it is unlikely that, in routine clinical practice, patients with heart failure are assessed by ultrasound as soon as they are hospitalised. Moreover, in sensitivity analysis, we excluded patients enrolled in the AHF-Core study, where LUS was conducted up to 72 hours from admission: overall, findings did not change (data not showed). Echocardiography was only done once, and we did not evaluate the changes in congestion between admission and discharge: a pre-discharge evaluation is probably best for risk prediction [12, 1]. Yet, echocardiography might be more cumbersome and less likely to be repeated in a busy hospital in patients with AHF, whilst a rapid look at IVC and signs of pulmonary congestion by ultrasound prior to discharge can be more appealing and, nevertheless, still clinically informative.

Conclusions

In patients hospitalized for AHF, assessment of LUS and use of echocardiography focused on identification of signs of congestion, such as a dilated inferior vena cava, improved risk stratification. This might be a practical strategy to identify patients at highest risk for early re-hospitalisation and death, irrespectively of LVEF. Further studies should test whether decongestion-management guided by an integrated evaluation of congestion, clinical and by ultrasound, can improve in-hospital management of patients with AHF and long-term outcomes.

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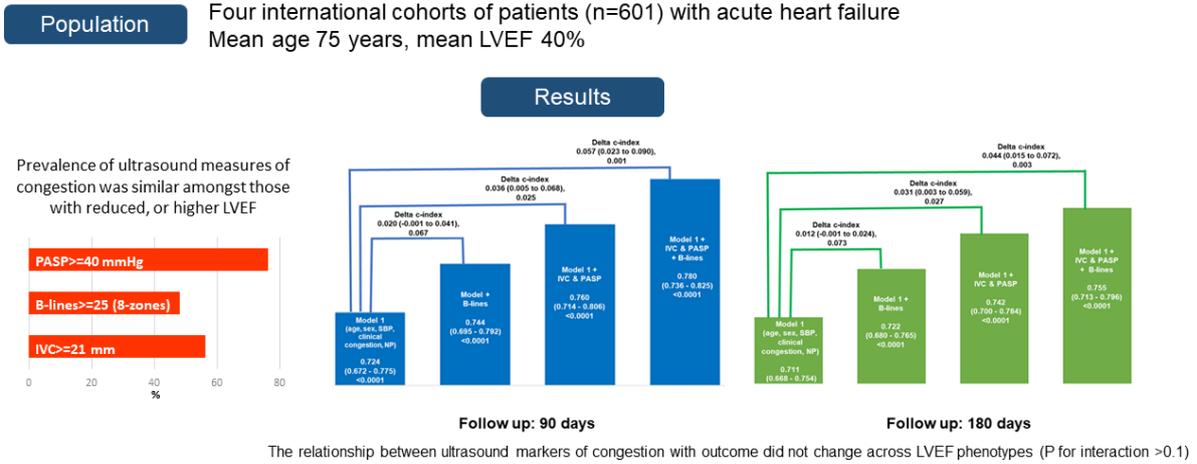
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Legend to figures

Multi-modality assessment of congestion in acute heart failure: associations with left ventricular ejection fraction and prognosis



Conclusions In patients admitted to hospital with acute heart failure, assessment of intravascular (inferior vena cava) and pulmonary congestion (B-lines) by ultrasound improved risk stratification

Central figure. C-index of different clinical models (n=369 patients) that included ultrasound signs of congestion (B-lines, inferior vena cava (IVC) & pulmonary artery systolic pressure (PASP) in turn or in combination at 90 (left) and 180 days (right). Abbreviations used: LVEF – left ventricular ejection fraction.

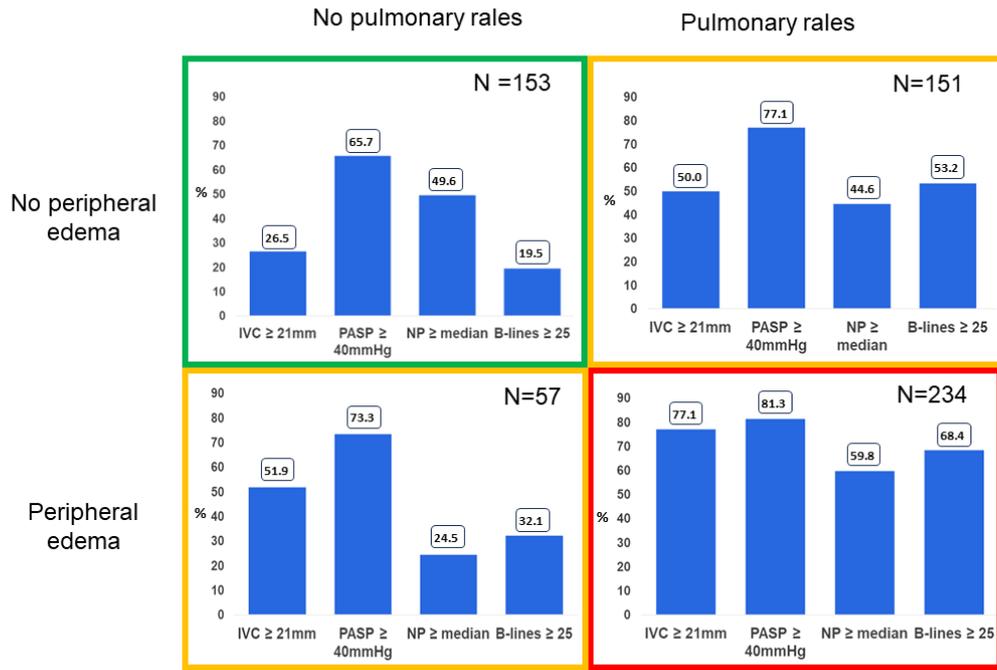


Figure 1. Prevalence of ultrasound signs of congestion according to presence/absence of pulmonary rales or peripheral edema. Percentages were calculated for patients with available data.

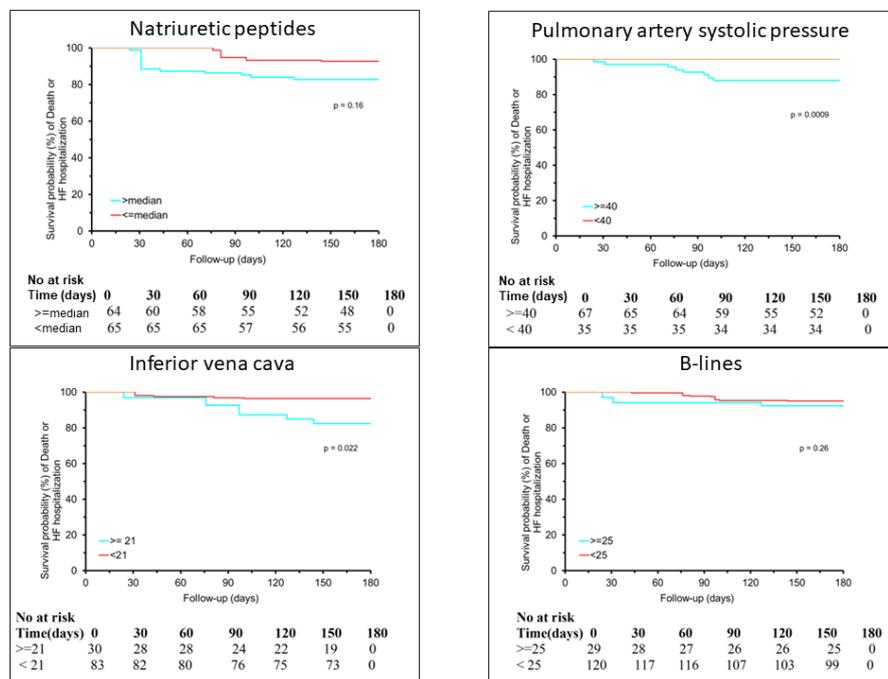
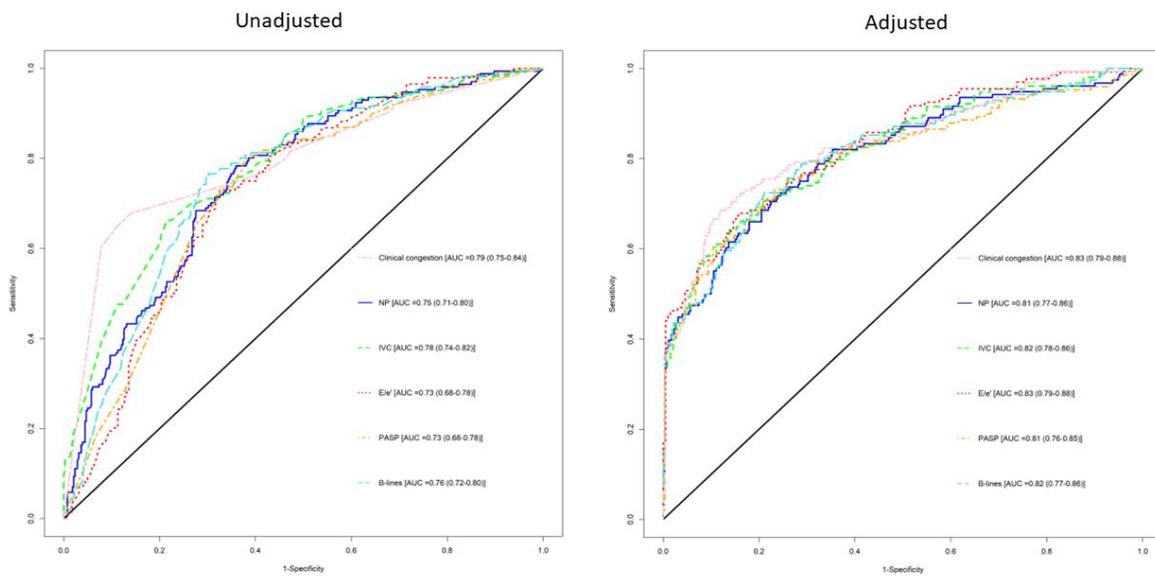


Figure 2. Prevalence of ultrasound signs of congestion in patients without pulmonary rales and peripheral edema and associations with outcome.



Supplementary figure 1: crude (left) and adjusted (right) ROC curves. The adjustment variables were age, sex, systolic blood pressure, atrial fibrillation, eGFR, left ventricular ejection fraction and study site. To plot the ROC curve, a composite outcome of death or hospitalization for HF censored at 180 days was considered.

	Overall (n=601)		HFrEF (LVEF <40%) (n=290)		HFmrEF (40<=LVEF <50%) (n=110)		HFpEF (LVEF >=50%) (n=201)		
Characteristics	n	Mean ± SD /	n	Mean ± SD /	n	Mean ± SD /	n	Mean ± SD /	P-value
		n(%)		n(%)		n(%)		n(%)	
Age (years)	601	74.9 ± 10.8	290	73.4 ± 11.1	110	76.4 ± 11.0	201	76.1 ± 9.8	0.003
Sex (Male)	601	356 (59)	290	210 (72)	110	62 (56)	201	84 (42)	<0.0001
BMI – kg/m ²	546	27.45 (4.28)	262	26.93 (4.27)	99	27.62 (4.11)	185	28.12 (4.31)	0.014
Ischemic heart disease	600	275 (46)	290	185 (64)	110	48 (44)	200	42 (21)	<0.0001
Atrial fibrillation	596	184 (31)	287	76 (27)	109	41 (38)	200	67 (34)	0.060
Heart rate (bpm)	573	84.2 ± 17.4	278	83.3 ± 18.4	104	85.6 ± 16.1	191	84.7 ± 16.7	0.48
Systolic blood pressure (mmHg)	575	128.3 ± 22.0	279	119.7 ± 20.3	104	130.3 ± 18.7	192	139.9 ± 20.4	<0.0001
Clinical signs of congestion									
Peripheral edema	595	291 (49)	285	144 (51)	110	60 (55)	200	87 (44)	0.13
Respiratory rales	596	386 (65)	286	176 (62)	110	77 (70)	200	133 (67)	0.25
No clinical signs	595	153 (26)	285	84 (30)	110	22 (20)	200	47 (24)	0.11
Respiratory rales and peripheral edema	595	234 (39)	285	118 (41)	110	49 (45)	200	67 (34)	0.10
Blood tests									
BNP (pg/ml)	420	848	193	973	82	908	145	703	<0.001

		[543 - 1509]		[576 - 1760]		[558 - 1468]		[449 -1020]	
NT-proBNP (pg/ml)	269	2455 [1304 - 5034]	155	2791 [1464 -5894]	36	2197 [1157- 5546]	78	2025 [991-3416]	0.002
eGFR (ml/min/1.73m ²)	591	56.8 (25.1)	282	57.2 (24.7)	109	56.6 (29.5)	198	56.5 (23.2)	0.67
Echocardiography and LUS									
LVEF (%)	601	39.6 ± 13.6	290	27.5 ± 6.9	110	42.9 ± 2.7	201	55.2 ± 4.9	<0.0001
E/e'	366	15.7 ± 5.1	161	15.6 ± 4.9	78	15.4 ± 4.2	127	16.0 ± 5.8	0.88
E/e' ≥15	366	208 (57)	161	89 (55)	78	45 (58)	127	74 (58)	0.87
TAPSE (mm)	478	17.5 ± 4.5	234	16.5 ± 4.4	86	18.1 ± 4.5	158	18.8 ± 4.2	<0.0001
PASP (mmHg)	478	47.4 ± 12.8	219	47.7 ± 12.5	88	46.0 ± 12.3	171	47.8 ± 13.5	0.54
PASP ≥40 mmHg	478	364 (76)	219	169 (77)	88	65 (74)	171	130 (76)	0.83
Inferior vena cava (mm)	523	21.1 ± 5.6	251	20.6 ± 5.4	94	21.2 ± 4.4	178	21.9 ± 6.4	0.62
Inferior vena cava ≥21mm	523	295 (56)	251	140 (56)	94	55 (59)	178	100 (56)	0.90
B-lines	576	22.0 ± 14.1	274	22.3 ± 14.7	109	22.3 ± 13.8	193	21.5 ± 13.5	0.87
B-lines ≥25	576	277 (48)	274	131 (48)	109	56 (51)	193	90 (47)	0.73

Table 1: Characteristics of patients with heart failure at enrolment, according to left ventricular ejection fraction (LVEF): reduced (HFrEF), mildly reduced (HFmrEF), preserved (HFpEF). Abbreviations used: BNP - B-type natriuretic peptide; NT-proBNP - N-terminal pro B-type na-

triuretic peptide; eGFR - estimated glomerular filtration rate; LUS – lung ultrasound; PASP - pulmonary artery systolic pressure; TAPSE - tri-cuspid annular plane systolic excursion.

	Univariable		Adjusted*	
	HR (95% CI)	p	HR (95% CI)	p
Clinical signs of congestion				
Peripheral edema and rales (vs edema or rales, or no signs)	3.69 (2.60 - 5.23)	<0.0001	3.24 (2.15 - 4.86)	<0.0001
Echocardiographic and LUS signs of congestion				
E/e' \geq 15	1.69 (1.18 - 2.41)	0.004	1.54 (1.04 - 2.28)	0.031
PASP \geq 40 mmHg	1.25 (0.84 - 1.87)	0.27	0.98 (0.65 - 1.48)	0.93
Inferior vena cava \geq 21 mm	2.59 (1.70 - 3.95)	<0.0001	1.91 (1.21 - 3.03)	0.006
B-lines \geq 25	1.66 (1.10 - 2.50)	0.015	2.08 (1.34 - 3.24)	0.001
Biochemical signs of congestion				
BNP/NT-ProBNP Z-score \geq Median (Each cohort)	1.50 (1.11 - 2.03)	0.009	1.37 (0.98 - 1.92)	0.067
BNP/NT-ProBNP Z-score \geq Median (Pooled cohorts)	1.53 (1.13 - 2.08)	0.007	1.34 (0.97 - 1.86)	0.073

Table 2: Association of clinical, ultrasound and biochemical markers of congestion with the combined outcome of heart failure hospitalization or death. *Adjusted for age; sex, atrial fibrillation, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate and the study site as strata. Abbreviations used: BNP - B-type natriuretic peptide; NT-proBNP - N-terminal pro B-type natriuretic peptide; LUS – lung ultrasound; PASP - pulmonary artery systolic pressure.

	Univariable			Adjusted*		
	N events, HR (95% CI)		p	N events, HR (95% CI)		p
Clinical signs of congestion						
Peripheral edema and rales (vs edema or rales, or no signs)	83	4.00 (2.39 - 6.70)	<0.0001	74	3.64 (1.97 - 6.71)	<0.0001
Echocardiographic and LUS signs of congestion						
E/e' \geq 15	67	1.51 (0.90 - 2.51)	0.12	62	1.23 (0.70 - 2.18)	0.47
PASP \geq 40 mmHg	79	0.90 (0.53 - 1.50)	0.68	77	0.64 (0.38 - 1.10)	0.11
Inferior vena cava \geq 21 mm	78	3.51 (1.77 - 6.93)	0.0003	72	2.20 (1.06 - 4.55)	0.034
B-lines \geq 25	82	2.33 (1.24 - 4.36)	0.008	72	2.85 (1.41 - 5.79)	0.004
Biochemical signs of congestion						
BNP/NT-ProBNP Z-score \geq Median (Each cohort)	75	1.43 (0.92 - 2.23)	0.11	71	1.27 (0.77 - 2.08)	0.35
BNP/NT-ProBNP Z-score \geq Median (Pooled cohort)	81	1.23 (0.78 - 1.94)	0.37	72	1.16 (0.70 - 1.90)	0.57

Table 1 supplementary: Association of clinical, ultrasound and biochemical markers of congestion with the outcome of **death at 180 days**. *Adjusted for age; sex, atrial fibrillation, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate and the study site as strata. Abbreviations used: BNP - B-type natriuretic peptide; NT-proBNP - N-terminal pro B-type natriuretic peptide; LUS – lung ultrasound; PASP - pulmonary artery systolic pressure.

	Univariable			Adjusted*		
	N events	HR (95% CI)	p	N events	HR (95% CI)	p
Clinical signs of congestion						
Peripheral edema and rales (vs edema or rales, or no signs)	102	3.19 (2.06 - 4.96)	<0.0001	94	2.50 (1.51 - 4.14)	0.003
Echocardiographic and LUS signs of congestion						
E/e' \geq 15	82	1.76(1.10 - 2.83)	0.019	76	1.72 (1.02 – 2.89)	0.042
PASP \geq 40 mmHg	90	1.61 (0.91 - 2.85)	0.10	85	1.31 (0.73 - 2.35)	0.37
Inferior vena cava \geq 21 mm	97	2.05 (1.23 - 3.43)	0.006	89	1.71 (0.97 - 3.03)	0.063
B-lines \geq 25	100	1.59 (0.96 - 2.65)	0.072	92	1.76 (1.02 - 3.02)	0.04
Biochemical signs of congestion						
BNP/NT-ProBNP Z-score \geq Median (Each cohort)	101	1.67 (1.12 - 2.50)	0.016	93	1.43 (0.91 - 2.22)	0.12
BNP/NT-ProBNP Z-score \geq Median (Pooled cohorts)	91	1.73 (1.13 - 2.64)	0.011	88	1.52 (0.97 - 2.40)	0.069

Table 2 supplementary: Association of clinical, ultrasound and biochemical markers of congestion with the outcome of **heart failure hospitalisation** at 180days. *Adjusted for age; sex, atrial fibrillation, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate and the study site as strata. Abbreviations used: BNP - B-type natriuretic peptide; NT-proBNP - N-terminal pro B-type natriuretic peptide; LUS – lung ultrasound; PASP - pulmonary artery systolic pressure.

	n	Interaction P-value	HF_rEF (LVEF <40%)		HF_{mr}EF (40<=LVEF <50%)		HF_pEF (LVEF >=50%)	
			HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Clinical signs of congestion								
Peripheral edema and rales (vs edema or rales, or no signs)	593	<0.001	1.57 (0.95 - 2.59)	0.079	7.36 (2.84 - 19.06)	<0.0001	7.60 (4.24 - 13.63)	<0.0001
Echocardiographic and LUS signs of congestion								
E/e' >= 15	363	0.7	1.46 (0.87 - 2.46)	0.16	1.66 (0.81 - 3.41)	0.17	2.08 (1.09 - 3.96)	0.026
PASP >= 40 mmHg	475	0.65	1.01 (0.57 - 1.80)	0.97	1.46 (0.60 - 3.57)	0.40	1.48 (0.72 - 3.03)	0.28
IVC >= 21 mm	520	0.51	3.31 (1.74 - 6.33)	0.0003	1.99 (0.80 - 4.93)	0.14	2.10 (1.11 - 3.96)	0.022
B-lines >= 25	573	0.59	1.93 (1.12 - 3.32)	0.017	1.26 (0.55 - 2.88)	0.59	1.44 (0.78 - 2.65)	0.24
Biochemical signs of congestion								
BNP/NT-ProBNP Z-score >=Median (Each cohort)	550	0.36	1.89 (1.15 - 3.11)	0.012	1.05 (0.53 - 2.08)	0.90	1.34 (0.77 - 2.32)	0.30
BNP/NT-ProBNP Z-score >= Median (Pooled cohorts)	550	0.49	1.75 (1.07 - 2.85)	0.025	1.07 (0.54 - 2.13)	0.84	1.33 (0.77 - 2.30)	0.31
Adjusted*								
Clinical signs of congestion								

Peripheral edema and rales (vs edema or rales, or no signs)	550	<0.001	1.01 (0.58 - 1.77)	0.96	6.39 (2.21 - 18.50)	0.0006	8.16 (4.20 - 15.85)	<0.0001
Echocardiographic and LUS signs of congestion								
E/e' >=15	332	0.43	1.37 (0.78 - 2.38)	0.27	1.18 (0.55 - 2.53)	0.68	2.22 (1.07 - 4.58)	0.032
PASP >= 40 mmHg	446	0.23	0.66 (0.37 - 1.21)	0.18	1.05 (0.42 - 2.64)	0.92	1.52 (0.72 - 3.20)	0.27
IVC >= 21 mm	487	0.99	1.88 (0.93 - 3.78)	0.078	1.90 (0.72 - 5.07)	0.20	1.88 (0.94 - 3.74)	0.073
B-lines >= 25	531	0.81	2.15 (1.23 - 3.74)	0.007	1.67 (0.69 - 4.03)	0.25	2.32 (1.15 - 4.67)	0.018
Biochemical signs of congestion								
BNP/NT-ProBNP Z-score >= Median (Each cohort)	507	0.27	1.83 (1.08 - 3.11)	0.025	0.88 (0.43 - 1.79)	0.72	1.33 (0.74 - 2.42)	0.34
BNP/NT-ProBNP Z-score >= Median (Pooled cohorts)	507	0.62	1.65 (0.98 - 2.78)	0.060	1.08 (0.53 - 2.22)	0.84	1.30 (0.72 - 2.36)	0.38

Table 3 Supplementary: Association of clinical, ultrasound and biochemical markers of congestion with the combined outcome of **death and/or heart failure** hospitalization, according to left ventricular ejection fraction (LVEF). Abbreviations used: BNP - B-type natriuretic peptide; NT-proBNP - N-terminal pro B-type natriuretic peptide; LUS – lung ultrasound; PASP - pulmonary artery systolic pressure; IVC – inferior vena cava. * Adjusted for age, sex, AF, SBP, LVEF and eGFR. Cox regression models were performed for each congestion variable including an interaction between LVEF groups, the considered congestion variable, and the study site as strata.