Prevalence, pattern and clinical relevance of ultrasound indices of congestion in out-patients with heart failure

Short title:- Congestion by ultrasound in Heart Failure

Word count: abstract 224; text: 3211.

[*,~]Pierpaolo Pellicori MD, FESC, [*]Parin Shah, [*]Joe Cuthbert, [*]Alessia Urbinati MD, [*,@]Jufen Zhang, PhD,[*] Anna Kallvikbacka-Bennett BA, [*]Andrew L Clark MA, MD, FRCP, [~,#]John GF Cleland MD, FRCP, FESC, FACC.

*Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull, HU16 5JQ, UK

#National Heart & Lung Institute and National Institute of Health Research Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London

~Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow, G12 8QQ.

@Faculty of Medical Science, Anglia Ruskin University, Chelmsford, UK

Corresponding author: Dr Pierpaolo Pellicori

Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow, G12 8QQ, UK.

Tel: +44 0 141 330 4744; Fax: +44 0 141 330 5094

Email: pierpaolo.pellicori@glasgow.ac.uk

Abstract

Aims and methods: Even if treatment controls symptoms, patients with heart failure may still be congested. We recorded clinical and ultrasound (lung B-lines; inferior vena cava (IVC) diameter; internal jugular vein diameter before and after Valsalva (JVD ratio)) features of congestion in patients with heart failure during a routine check-up to assess their prevalence, relationships and prognostic significance.

Results: Of 342 patients, predominantly in NYHA I or II (257; 75%), who attended, 242 (71%) had at least one feature of congestion, either clinical (139; 41%) or by ultrasound (199; 58%). Amongst patients (n=203, 59%) clinically free of congestion, 31 (15%) had $\geq$14 B-lines, 57 (29%) had a dilated IVC (> 2.0 cm), 38 (20%) had an abnormal JVD ratio (<4), 87 (43%) had at least one of these and 27 (13%) had two or more.

During a median follow-up of 234 (IQR: 136-351) days, 60 patients (18%) died or were hospitalized for heart failure. In univariable analysis, each clinical and ultrasound measure of congestion was associated with increased risk but, in multivariable models, only higher NT-proBNP and IVC, and lower JVD ratio, were associated with the composite outcome.

Conclusions: Many patients with chronic heart failure with few symptoms have objective evidence of congestion and this is associated with an adverse prognosis. Whether using these measures of congestion to guide management improves outcomes requires investigation.

Key words: lung ultrasound, congestion, B-lines, IVC, jugular vein ultrasound.

Introduction

Congestion is a common cause of hospitalization for patients with heart failure (1). Poorly controlled congestion may also lead to unfavourable atrial and ventricular remodelling, clinical progression of disease, recurrent admissions, and an increase in mortality (2-5).

Accurately quantifying congestion is difficult (6), and may commonly be missed unless it is obvious (7-9). Also, some clinical features of congestion are not specific for cardiac dysfunction and may occur with many other conditions, including nephrotic syndrome, liver or thyroid disease, or venous insufficiency, or as a side-effect of commonly prescribed drugs to treat hypertension, such as calcium channel blockers, or diabetes, such as glitazones.

Congestion can only be managed appropriately if it is recognised (10). Detection of congestion before it becomes clinically overt in patients with heart failure should lead to better management, particularly with respect to diuretic dose (11, 12). However, many apparently stable out-patients with heart failure without clinical evidence of congestion might have sub-clinical congestion detected by biomarkers, ultrasound or other non-invasive techniques.

We therefore investigated the prevalence and clinical relevance of congestion in out-patients with chronic heart failure (CHF) attending a routine follow-up clinic using ultrasound to detect, contemporaneously, pulmonary interstitial oedema (lung B-lines) and intra-vascular fluid overload (inferior vena cava (IVC) diameter, and the internal jugular vein diameter before and after a Valsalva manoeuvre (JVD ratio) (13-18).

Methods

Study Population

Between April 2016 and March 2017, we enrolled consecutive patients with a prior clinical diagnosis of heart failure attending a routine follow-up visit to a heart failure clinic serving a local population of about 550,000 people. In our clinic, stable out-patients on optimal treatment are reviewed by heart failure specialist nurses and doctors at regular intervals, usually every 12 months, unless an appointment is requested sooner by the patient, physician or specialist nurse. All subjects gave their written informed consent. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies.

Patients provided a detailed clinical history and had blood tests (including haematology, biochemistry profile and NT-proBNP), ECGs and echocardiograms done on the same day. The information was systematically recorded in a dedicated electronic health record stored on a secure NHS server. Treating clinicians had access to the entire echocardiographic exam performed prior to the visit, including B-lines, IVC and JVD examination; however, they were blinded to blood results, including NT-proBNP.

The minimum follow-up period was three months. The primary outcome of interest was a composite of all-cause mortality or HF hospitalization. Our hospital is the only one in the region offering acute medical services. With consent obtained from patients, we have access to both primary and secondary care records. Data regarding deaths and hospitalisations were collected from the hospital's electronic systems, supplemented by information from discharge letters, patients, and their family doctors. For the purpose of this study, a hospitalisation was

considered due to heart failure only if HF was mentioned as primary diagnosis on the discharge letter by the discharging physician from our hospital.

Clinical assessment

Clinical examinations were performed before echocardiography. A clinical congestion score was applied, based on lung auscultation (normal, presence of basal, mid zone or diffuse crackles), JVP (not visible, raised 1-4 cm, raised to earlobe), and peripheral oedema (none, ankles, below or above knees) with one point attributed for each degree of severity. When the total score was 0, patients were considered clinically uncongested; those scoring $\geq$3 were defined as severely congested (4).

Echocardiographic measurements

Echocardiography was performed by an experienced operator (AB) using a Vivid Seven (GE Health care, UK) system operating at 1.7-3.4MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical and subcostal views. Echocardiograms were stored and reviewed by an experienced operator (PP) using an EchoPAC station (GE Health care, UK). LVEF was measured using Simpson's biplane method. LA volume was measured in the four chamber view and indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess right ventricular (RV) systolic function. The maximum trans-tricuspid systolic gradient was also measured (based on the modified Bernoulli equation, $\Delta P = \text{Max TR velocity}^2 \times 4$). With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured between one and three centimeters before merger with the right atrium. The IVC collapse following deep inspiration (a brief sniff) was visually

estimated as ≥50 or <50 %. Intrahepatic veins were recorded as visible, and their maximum diameter during the cardiac cycle was measured, or not visible.

Jugular Vein ultrasound

With the patient semi-recumbent at 45°, jugular venous (JV) ultrasound was performed as previously described (19). Briefly, with the patient reclining and head and neck elevated at 45°, a linear high frequency probe (10 MHz) was placed on the left side of the neck below the angle of the jaw and moved inferiorly toward the angle of Louis until the left internal JV was identified. Internal JV diameter and its changes were then measured continuously by M-mode or in the 2-dimensional frame at rest (expiratory phase), during a Valsalva manoeuvre (performed by forceful expiration against a closed glottis) and, finally, during deep inspiration. The ratio between maximum JV diameter during Valsalva and diameter at rest was calculated (JVD ratio).

B-lines

B-lines, or lung comets, are echogenic, perpendicular signals arising from the pleura during lung ultrasound, often indicating the presence of extravascular lung water (20, 21). Although different methods to assess them have been proposed, we scanned a total of 28 chest sites (from the second to the fifth intercostal space on the right hemithorax, and from the second to the fourth intercostal space on the left hemithorax along the parasternal, mid-clavicular, anterior axillary and mid-axillary lines (22)) and counted the number of B-lines found at each site. All patients were analysed in a near-supine position with the same probe used for echocardiography. B-lines were recorded for at least 5 beats for each chest site, and images were subsequently stored and reviewed off-line by an experienced operator (PP).

We defined congestion by ultrasound as an abnormal JVD ratio (<4), a distended IVC (>20 mm) or B-lines above or equal to the lower boundary of the highest tercile (≥14).

Statistical methods

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± SD and non-normally distributed continuous variables as median and interquartile range (IQR). We present the ultrasound variables as median and IQR to demonstrate the distribution of each variable within the studied population.

Patients with HF were grouped by phenotypes (heart failure with reduced (HFrEF, LVEF<40%), mid-range (HFmrEF, LVEF 40-49%), or preserved (HFpEF, LVEF≥50%) LVEF) or by terciles of B-lines, IVC and JVD ratio or NT-proBNP. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Analysis 1. Two different multivariable Cox proportional hazard regression models were used to investigate the relationship between JVD ratio, IVC and B-lines, and prognosis using a limited number of variables to prevent statistical overfitting. In Model A (Clinical Model) five candidate variables of interest (age, NYHA class III vs I/II, urea, haemoglobin and log [NT-proBNP]) were chosen prospectively in addition to each ultrasound measurement of congestion. For model B (Echocardiographic Model), the three echocardiographic variables that were most strongly associated with prognosis in univariable analysis (highest χ^2) were included in addition to each ultrasound measurement of congestion, age and Log [NT-proBNP].

Forward and backward procedures were used to determine which variables independently predicted the primary composite outcome. Assumptions of the models were tested, such as multicolinearity and proportional hazards.

Analysis 2 (Discrimination and reclassification improvement analysis). In order to estimate the predictive value of the different variables of interest, we constructed a basic a priori model, which included variables of clinical interest that are easily available in a heart failure clinic (age, sex, NYHA (III vs II/I), creatinine, haemoglobin and LVEF) and then tested the added value of each measure (and combinations of measures) of congestion, in turn. The variables of interest added to the basic model were: log[NT-proBNP]; and/or ultrasound measurements of congestion (either IVC diameter, JVD ratio or B-lines). The incremental value of the variables (the model's cumulative discrimination) was measured using Harrell's C statistic: the mean values of IVC diameter, JVD ratio and logNT-proBNP were used to impute missing values. The higher discriminative value associated with the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) for ultrasound measurements of congestion were assessed at 1 year of follow-up.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

All analyses were performed using SPSS and Stata software. A 2-sided P value < 0.05 was considered statistically significant.

Results

Patient characteristics (n=342, table 1)

Median age (inter-quartile range [IQR]) was 75 [68-82] years, and median plasma NT-proBNP was 1275 [461-2659] ng/L. Mean LVEF was 45 (±14) %. LVEF was <40% in 124 patients, 40-49% in 68 patients (39 previously had LVEF <40%) and 150 had LVEF ≥50% (45 previously had LVEF <40%). Approximately 85% of patients were treated with beta-blockers and ACE-inhibitors and 75% were taking loop diuretics.

Some evidence of clinical congestion was similarly common amongst the three heart failure phenotypes (36-44%), although patients with HFrEF were more likely to be treated with a loop diuretic and mineralocorticoid antagonist that those with HFmrEF or HFpEF. There was no difference in the number of patients amongst the phenotypes who had their diuretics increased or decreased at the clinical visit. There was no difference between the phenotypes in ultrasound measures of congestion (Table 1).

Clinical vs ultrasound congestion

It was possible to measure B-lines in all patients, whilst the IVC was not visualised in 7 (2%). Due to a technical problem (the 10 MHz linear probe needed repair) it was not possible to assess JVD ratio in 23 patients (7%).

Congestion by ultrasound was more common, and more severe, with increasing severity of clinical congestion (Table 1 supplementary). When clinical congestion was severe, B-lines were almost ubiquitous, IVC was dilated in around 90% of cases, and JVD ratio was abnormal in >80% patients. However, of the 187 patients with complete ultrasound data who had no clinical sign of congestion, 87 (47%) had at least 1 sign of congestion on ultrasound, with 10 (5%) having all three ultrasonic signs of congestion (figure 1).

Correlations amongst ultrasound measures of congestion were generally modest. Correlations between ultrasound measures of congestion and age, haemoglobin, left atrial volume, estimated PA pressure and NT-proBNP were also modest. Ultrasound measures of congestion

were poorly correlated with LVEF. There was an inverse correlation between body mass index (BMI) and B-lines, but not with JVD ratio or IVC diameter (table 2 and table 2a-d and 3 supplementary).

Compared to patients in sinus rhythm, those in atrial fibrillation had more severe congestion by ultrasound (table 3 supplementary).

Outcome

There were 60 primary outcome events during a median follow-up of 234 (IQR: 136-351) days. The first qualifying event was hospitalisation due to worsening HF in 35 patients and death in 25 patients.

Analysis 1. In univariable Cox regression analysis, worsening clinical congestion and increasing B-lines were associated with an increased risk of events (Table 4 supplementary and Figure 2). In multivariable analysis, increasing log [NT-proBNP] and IVC diameter, or decreasing JVD ratio (with increasing urea) were the only variables independently related to an adverse outcome in both Model A (Table 3a) and Model B (Table 3b).

Analysis 2. Discrimination and reclassification improvement analysis

For the entire cohort of patients, the baseline clinical model yielded a c-index 0.74, which did not increase significantly when logNT-proBNP or ultrasound measures of congestion were added singly or in combination. In contrast, adding any of logNT-proBNP or ultrasound measures of congestion improved prediction of outcome at 1 year and increased IDI and NRI. Adding JVD ratio to a model that included logNTproBNP further improved re-classification by IDI only. The greatest improvement by IDI was when B-lines and JVD ratio were

simultaneously added (Table 4).

Patients who were simultaneously in the top tercile of NT-proBNP (≥2045 ng/L) and the highest terciles of B-lines, JVD ratio or IVC diameter had the worst outcomes (Figure 3).

Discussion

This analysis confirms previous reports suggesting that increasing IVC diameter (17, 18) or number of B-lines by ultrasound (13-15) identify patients with CHF who have higher plasma concentrations of NT-proBNP and a greater risk of an adverse outcome, regardless of their LVEF. We also confirm the clinical and prognostic utility of a novel ultrasonic method to assess fluid overload; the JVD ratio (16, 23). However, probably the most important finding was that nearly 50% of ambulatory patients with CHF thought not to be congested had evidence of congestion on ultrasound and that when multiple such measures are present the prognosis is poor.

In the current era, practising evidence-based medicine should be the norm; however management of clinical congestion, and the use of diuretics in patients with heart failure, is still an inexact medical art. For patients hospitalized with cardiac decompensation, some clinical algorithms for the evaluation and assessment of congestion have been proposed, but they are constructed on subjective variables, such as symptoms and signs, and obviously open to bias (24, 25). For patients with CHF, recommendations to detect, monitor and treat congestion during follow-up are rather vague, and will vary according to local organisation and resources (26).

NT-proBNP is a consistently strong prognostic marker for patients with stable CHF, although its prognostic utility in the acute setting is more doubtful (27, 28) and values may be affected by comorbidities, such as atrial fibrillation and renal dysfunction. Several randomized clinical trials have assessed whether serial measurements of plasma natriuretic peptide concentrations might be used to guide treatment for HF; their results are controversial, perhaps because guideline-recommended treatment is effective and perhaps because trials of a natriuretic peptide-guided strategy have not lead to substantial differences in therapy between randomised groups (29-30). Natriuretic peptides are a measure of congestion rather than of cardiac dysfunction or its cause, which is both their strength and weakness; their strength because congestion is strongly related to prognosis; their weakness because congestion may be renal or cardiac in origin to varying degrees and because it is important to know the cause of heart failure in order to decide on treatment**.** It is also possible that renal dysfunction leads to reduced clearance of NT-proBNP and an increase in plasma concentration unrelated to congestion, although it is likely that reduced renal clearance of NT-proBNP is associated with diuretic resistance and reduced salt and water excretion. However, ultrasound can determine the presence of congestion and quantify similarly in the presence or absence of renal dysfunction. Clearly, a measurement of renal function is important to determine both the reason for an elevated NT-proBNP and the cause of congestion. Whether a strategy starting with measuring NT-proBNP and urea/creatinine first followed by ultrasound evaluation when results indicate congestion; or whether ultrasound could supplant natriuretic peptides is worthy of investigation. In a primary-care setting, blood markers are likely to be the preferred strategy for the evaluation of congestion. However, in a cardiology clinic where echocardiography is readily available, obtaining an instantaneously available measurement of congestion along with the opportunity to gather information on valve and ventricular function, ultrasonic evaluation might be favoured.

Absence of congestion on ultrasound might be a measure of treatment success associated with an excellent outcome and might also help avoid over-treatment especially for patients who have other reasons for their breathlessness such as chronic obstructive pulmonary disease. On the other hand, persistence of sub-clinical congestion might be a measure of inadequate treatment. Quantifying congestion by ultrasound might also provide an objective measure of response to novel treatments, help guide the intensity of diuretic use, facilitate personalised therapy tailored to the individual patient's needs and decide on the frequency of follow-up appointments or determining when it might be appropriate to reassure patients and discharge them back to primary care. The increasing availability of hand-held, low-cost ultrasound devices and the demonstration that skills can be rapidly taught to people with little or no prior experience increases the feasibility of this approach (31).

Limitations

In our cohort, agreement amongst different methods for assessing congestion by ultrasound was modest when clinical congestion was absent, but increased as clinical congestion became more evident. This might be because the cut-offs used to define "congestion by ultrasound" were not optimal, or it might be because congestion is heterogeneous amongst different organs and compartments. Some patient characteristics, such as a high BMI, might decrease the number of identifiable lung comets, perhaps reflecting less advanced disease (32) or a technical obstruction to their visualisation (14). High BMI or non-uniform body anatomy could affect IVC assessment, or the visualization of intra-hepatic veins.

This was a single centre study of consecutive patients previously diagnosed with HF, regardless of their LVEF. In the absence of a general consensus on how to diagnose HFpEF, it might be possible that our population of patients with HFpEF differs from those from other centres.

There is no recommendation that HF treatment should be guided by signs of congestion on ultrasound, and not all physicians can interpret B-lines, or JVD ratio; however, it is still possible that evidence of congestion on ultrasound might have led to adjustments in treatment in a few patients, and particularly to an increase in diuretic dose. This might have affected our final results. None of our patients had received novel treatments such as sacubitril/valsartan prior to follow-up. Compared to ACE-I, sacubitril/valsartan might decrease NT-proBNP (33).

The number of patients enrolled, and events recorded, are modest: more studies will be needed to clarify whether measuring the upstream consequences of a dysfunctional right ventricle (reduced JVD ratio or dilated IVC diameter) provides more powerful prognostic information than measuring the upstream consequences of a dysfunctional left ventricle (greater number of B-lines). Similarly, more work is needed to see whether these novel ultrasound methods might be used to identify different phenotypes of patients with heart failure, who need different therapies.

However, to the best of our knowledge this is the largest prospective study evaluating B-lines in out-patients with HF (13), also coupled with a detailed and comprehensive clinical, ultrasound and biomarker evaluation of congestion.

B-lines are not specific evidence of lung congestion and may also reflect parenchymal lung disease. We enrolled patients whether or not they had co-morbid lung disease. This might have increased the number of B-lines measured in some patients. We also assessed B-lines in the near-supine position, exploring 28 antero-lateral chest zones, using clips recording 5 heart beats only: the number of B-lines may vary with gravity and postural changes, and might increase with longer evaluations (34). Findings might have been different if other protocols (ie, the 8 antero-lateral chest sites) were used.

We did not study the prevalence of congestion by ultrasound in a control group. It is likely that some people without other evidence of heart or lung disease will have an abnormal number of B-lines, or dilated IVC (35).

Conclusions

Many patients with heart failure free of clinically overt congestion remain sub-clinically congested; these patients have a worse prognosis. Further research to determine whether management guided by ultrasonic measures of congestion improves outcome is warranted.

References

1) Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, Djahit A, Goode K, Wong K, Rigby A, Clark A, Cleland J. Breathlessness at rest is not the dominant presentation of patients admitted with heart failure. Eur J Heart Fail. 2014;16:1283-91.
2) Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland JGF. The effects of short-term omission of daily medication on the pathophysiology of heart failure. Eur J Heart Fail. 2017;19:643-649.
3) Braunschweig F, Linde C, Eriksson MJ, Hofman-Bang C, Rydén L. Continuous haemodynamic monitoring during withdrawal of diuretics in patients with congestive heart failure. Eur Heart J. 2002;23:59-69.
4) Pellicori P, Cleland JG, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, Kazmi S, Clark AL. Cardiac Dysfunction, Congestion and Loop Diuretics: their Relationship to Prognosis in Heart Failure. Cardiovasc Drugs Ther. 2016 ;30:599-609.
5) Melenovsky V, Andersen MJ, Andress K, Reddy YN, Borlaug BA. Lung congestion in chronic heart failure: haemodynamic, clinical, and prognostic implications. Eur J Heart Fail. 2015;17:1161-71.
6) Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. 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. 2010;12:423-33.

7) Gadsbøll N, Høilund-Carlsen PF, Nielsen GG, Berning J, Brunn NE, Stage P, Hein E, Marving J, Løngborg-Jensen H, Jensen BH. Symptoms and signs of heart failure in patients with myocardial infarction: reproducibility and relationship to chest X-ray, radionuclide ventriculography and right heart catheterization. Eur Heart J. 1989;10:1017-28.

8) McGee SR. Physical examination of venous pressure: a critical review. Am Heart J. 1998;136:10-8.

9) Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1:170-7.

10) Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, Cleland JGF, Clark AL. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail. 2017;19:768-778.

11) Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial StudyGroup.Sustained efficacy of pulmonary artery pressure t o guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet. 2016;387:453-61.

12) Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131:34-42.

13) Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. Eur J Heart Fail. 2017;19:1154-1163.

14) Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, Hempel D, Wilson C, Frasure SE, Jhund PS, Cheng S, Solomon SD. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. Eur Heart J. 2016;37:1244-51.

15) Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N.Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. Eur J Heart Fail. 2015;17:1172-81.

16) Pellicori P, Kallvikbacka-Bennett A, Dierckx R, Zhang J, Putzu P, Cuthbert J, Boyalla V, Shoaib A, Clark AL, Cleland JG. Prognostic significance of ultrasound-assessed jugular vein distensibility in heart failure. Heart. 2015;101:1149-58.

17) Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, Cleland JG. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. JACC Cardiovasc Imaging. 2013;6:16-28.

18) Pellicori P, Kallvikbacka-Bennett A, Khaleva O, Carubelli V, Costanzo P, Castiello T, Wong K, Zhang J, Cleland JG, Clark AL. Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging. 2014;30:69-79.

19) Pellicori P, Kallvikbacka-Bennett A, Zhang J, Khaleva O, Warden J, Clark AL, Cleland JG. Revisiting a classical clinical sign: jugular venous ultrasound. Int J Cardiol. 2014;170:364-70.

20) Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. Eur Heart J. 2016;37:2097-104.

21) Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E.Exercise-induced B-lines identify worse functional and prognostic stage in heart failure patients with depressed left ventricular ejection fraction. Eur J Heart Fail. 2017;19:1468-1478.

22) Gargani L, Frassi F, Soldati G, Tesorio P, Gheorghiade M, Picano E. Ultrasound lung comets for the differential diagnosis of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. Eur J Heart Fail. 2008;10:70-7.

23) Pellicori P, Clark AL, Kallvikbacka-Bennett A, Zhang J, Urbinati A, Monzo L, Dierckx R, Anker SD, Cleland JGF. Non-invasive measurement of right atrial pressure by near-infrared spectroscopy: preliminary experience. A report from the SICA-HF study. Eur J Heart Fail. 2017;19:883-892.

24) Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M; EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34:835-43.

25) Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW. Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). Circ Heart Fail. 2015;8:741-8.

26) Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18:891-975.

27) Cleland JGF, Teerlink JR, Davison BA, Shoaib A, Metra M, Senger S, Milo O, Cotter G, Bourge RC, Parker JD, Jondeau G, Krum H, O'Connor CM, Torre-Amione G, van Veldhuisen DJ, McMurray JJV; VERITAS Investigators. Measurement of troponin and natriuretic peptides shortly after admission in patients with heart failure-does it add useful prognostic information? An analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERITAS). Eur J Heart Fail. 2017;19:739-747.

28) Cleland JG, McMurray JJ, Kjekshus J, Cornel JH, Dunselman P, Fonseca C, Hjalmarson A, Korewicki J, Lindberg M, Ranjith N, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J.; CORONA Study Group. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol. 2009;54:1850-9.

29) Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, Erntell H, Persson H, O'Connor CM, Moertl D, Karlström P, Dahlström

U, Gaggin HK, Januzzi JL, Berger R, Richards AM, Pinto YM, Nicholls MG. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J. 2014;35:1559-67.

30) Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. 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. 2017;318:713-720.

31) Dalen H, Gundersen GH, Skjetne K, Haug HH, Kleinau JO, Norekval TM, Graven T. Feasibility and reliability of pocket-size ultrasound examinations of the pleural cavities and vena cava inferior performed by nurses in an outpatient heart failure clinic. Eur J Cardiovasc Nurs. 2015;14:286-93.

32) Futter JE, Cleland JG, Clark AL. Body mass indices and outcome in patients with chronic heart failure. Eur J Heart Fail. 2011;13:207-13.

33) Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, Solomon SD. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. J Am Coll Cardiol. 2016;68:2425-2436.

34) Pivetta E, Baldassa F, Masellis S, Bovaro F, Lupia E, Maule MM.Sources of Variability in the Detection of B-Lines, Using Lung Ultrasound. Ultrasound Med Biol. 2018;44:1212-1216.

35) Dwyer KH, Merz AA, Lewis EF, Claggett BL, Crousillat DR, Lau ES, Silverman MB, Peck J, Rivero J, Cheng S, Platz E. Pulmonary Congestion by Lung Ultrasound

in Ambulatory Patients With Heart Failure With Reduced or Preserved Ejection Fraction and Hypertension. J Card Fail. 2018;24:219-226.

Legend to figures

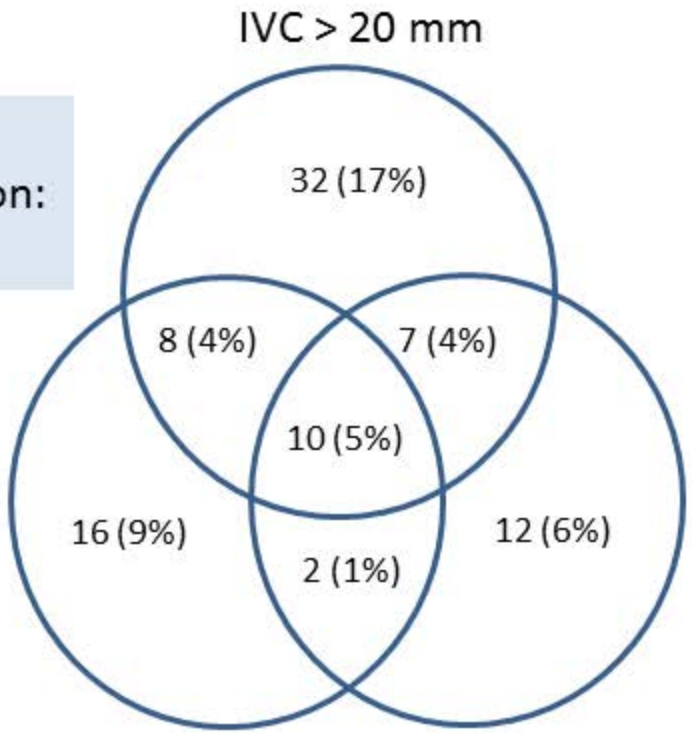
Figure 1: Of the 187 patients with complete ultrasound data who had no clinical sign of congestion, 87 (47%) had at least 1 sign of congestion on ultrasound (a dilated inferior vena cava (IVC), greater than 20 mm, an abnormal JVD ratio (lower than 4), or B-lines greater or equal to the lower boundary of the highest tercile (14)). 10 (5%) patients had all three ultrasonic signs of congestion and the highest levels of NT-proBNP.

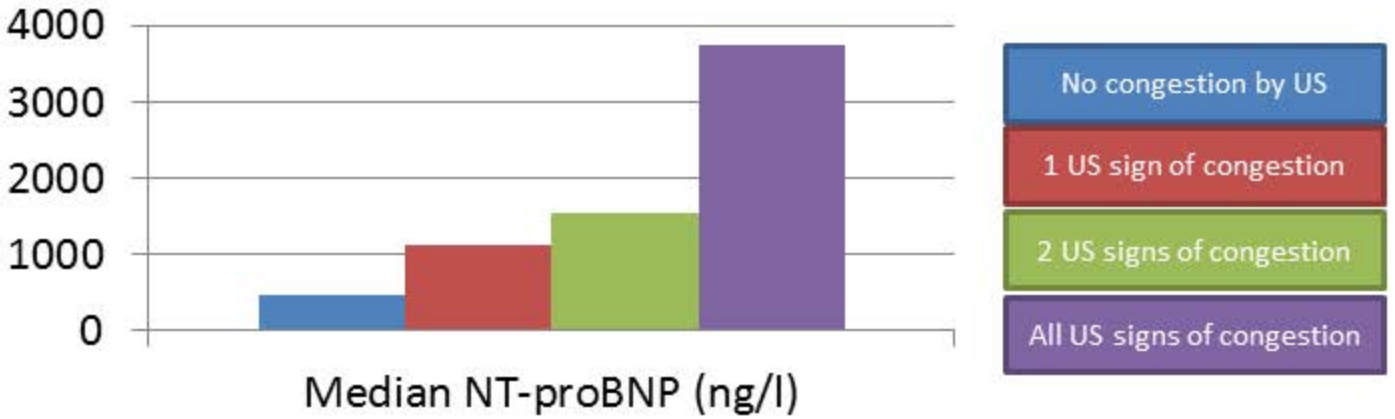
Figure 2. Multi-panel KM for primary outcome of death from all causes (ACM) and heart failure hospitalizations (HFH) for each echocardiographic marker of congestion by tercile: IVC diameter (top-right; Tercile 1:≤1.7 cm, Tercile 2:1.8-2.2 cm, Tercile 3>2.2 cm), JVD ratio (mid-left: Tercile 1:≥6.6, Tercile 2: 4.0-6.5, Tercile 3<4), intrahepatic vein diameter (mid-right; Tercile 1:≤0.5 cm, Tercile 2: 0.6-0.8 cm, Tercile 3>0.8 cm) and B-lines (bottom-centre; Tercile 1:≤3 B-lines, Tercile 2:4-13 B-lines, Tercile 3≥14 B-lines). Also, KM curve for IVC collapsibility (above or below 50%) and outcome are shown (top-left).

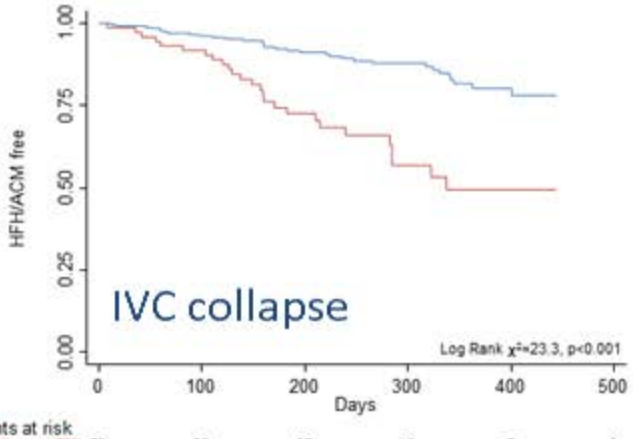
Figure 3. Multi-panel KM for primary outcome of death from all causes (ACM) and heart failure hospitalizations (HFH) showing additive value of measuring congestion by ultrasound in patients in the highest NT-proBNP tercile (≥2045 ng/L).

Patients without clinical signs of congestion and complete ultrasound (US) data (n=187)

No congestion by any ultrasound definition: 100 (53%)

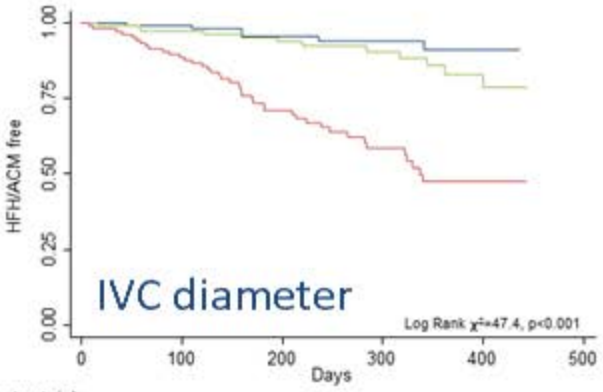






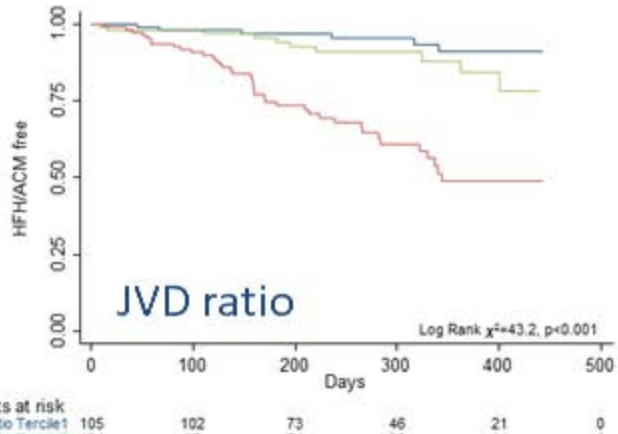
Patients at risk

IVC collapse<50%	73	66	37	16	7	0
IVC Collapse≥50%	262	241	163	87	37	0



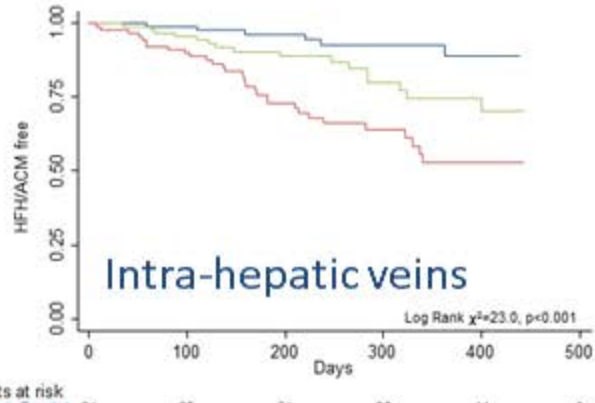
Patients at risk

IVC Tercile1	115	111	71	33	12	0
IVC Tercile2	114	104	73	43	19	0
IVC Tercile3	106	92	56	27	13	0



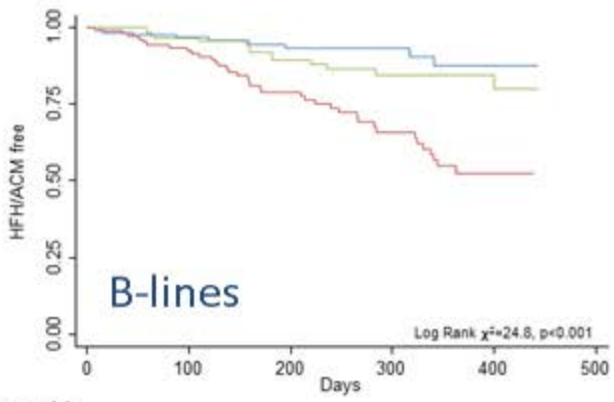
Patients at risk

JVD ratio Tercile1	105	102	73	46	21	0
JVD ratio Tercile2	104	96	64	30	14	0
JVD ratio Tercile3	110	97	58	27	9	0



Patients at risk

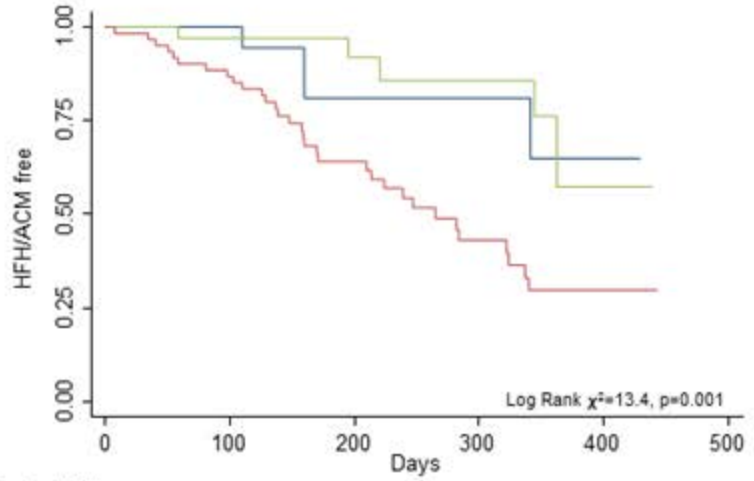
I-Hep vein Tercile1	94	89	61	36	11	0
I-Hep vein Tercile2	89	82	57	30	17	0
I-Hep vein Tercile3	89	79	48	23	12	0



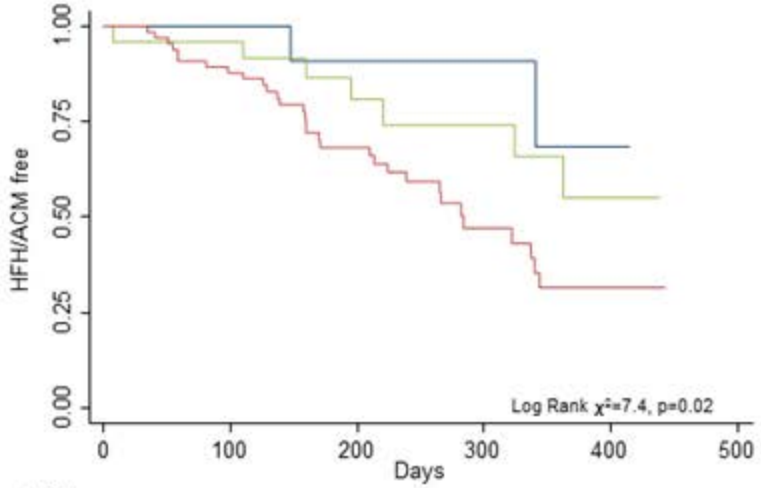
Patients at risk

B-line Tercile1	122	112	68	33	16	0
B-line Tercile2	114	104	70	36	19	0
B-line Tercile3	106	98	66	36	9	0

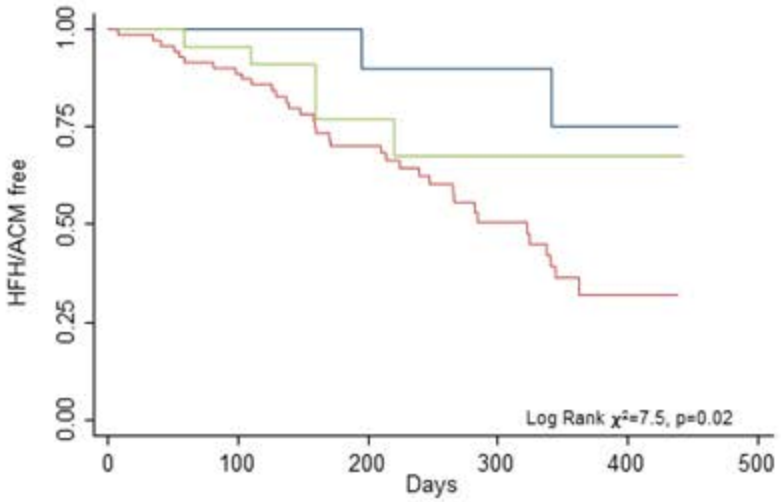
Patients in the Highest NT-proBNP Tercile (≥2045 ng/L)



Patients at risk						
IVC Tercile1	18	18	12	5	2	0
IVC Tercile2	33	31	17	9	3	0
IVC Tercile3	61	53	29	13	4	0



Patients at risk						
JVD ratio Tercile1	16	16	8	4	1	0
JVD ratio Tercile2	24	23	14	9	5	0
JVD ratio Tercile3	66	57	33	12	3	0



Patients at risk						
B-line Tercile1	20	19	9	6	3	0
B-line Tercile2	22	21	10	3	2	0
B-line Tercile3	71	63	40	18	4	0

Table 1 **Variable**	**Missing**	**HFrEF** **LVEF <40%** **N=124**	**HFmrEF#** **LVEF 40-49%** **N=68**	**HFpEF#** **LVEF ≥50%** **N=150**	**P-value**
Demographics					
Age – years	0	74 (64-81)	76 (68-82)	77 (69-84)	0.03
Men – no. (%)	0	100 (81)	48 (71)	81 (54)	<0.001
NYHA I	0	16 (13)	7 (10)	27 (18)	0.14
NYHA II		69 (55)	46 (68)	92 (61)	
NYHA III		39 (31)	15 (22)	31 (21)	
IHD – no. (%)	0	86 (69)	31 (46)	50 (33)	<0.001
DM – no. (%)	0	41 (33)	18 (27)	40 (27)	0.45
Hypertension – no. (%)	0	54 (43)	37 (54)	97 (65)	0.002
Smoker – no. (%)	0	17 (14)	7 (10)	19 (13)	0.79
Atrial fibrillation – no. (%)	0	44 (36)	38 (56)	82 (55)	0.002
COPD – no. (%)	0	24 (19)	13 (19)	29 (19)	0.99
SBP – mmHg	0	132 (19)	141 (28)	144 (26)	<0.001
DBP – mmHg	0	72 (11)	74 (11)	76 (12)	0.052
Heart rate – bpm	0	73 (13)	72 (16)	72 (14)	0.83
BMI – kg/m^2	0	29 (5)	30 (6)	30 (7)	0.42
BSA – m^2	0	2.0 (0.2)	1.9 (0.2)	1.9 (0.3)	0.45
Clinical congestion					
No signs of congestion – no. (%)	0	80 (64)	39 (57)	84 (56)	0.34
Oedema – None – no. (%)	0	87 (70)	44 (65)	94 (63)	0.49
Oedema –Ankles – no. (%)		15 (12)	13 (19)	22 (15)	
Oedema ->ankles – no. (%)		22 (18)	11 (16)	34 (23)	
Lung crackles – None – no. (%)		112 (90)	59 (87)	131 (87)	0.68
Lung crackles – Basal – no. (%)		12 (10)	9 (13)	19 (13)	
JVP – not raised – no. (%)		99 (80)	52 (77)	121 (81)	0.73
JVP – 1 to 4 cm – no. (%)		20 (16)	14 (21)	21 (14)	
JVP – to earlobe – no. (%)		5 (4)	2 (3)	8 (5)	
Blood tests					
Creatinine – µmol/l	0	110 (90-139)	100 (84-130)	100 (79-127)	0.05
Urea – mmol/l	0	9.0 (6.8-12.3)	9.4 (6.9-11.9)	8.1 (6.4-11.0)	0.18
Haemoglobin – g/dl	0	13.2 (1.7)	13.3 (1.5)	13.0 (1.8)	0.42

Albumin – g/l	0	36 (3)	37 (3)	36 (3)	0.38
Bilirubin – µmol/l	0	12 (9-15)	11 (9-15)	10 (8-13)	0.006
NT-proBNP – ng/l	2	1494 (684-3502)	1330 (382-2881)	1100 (354-1994)	0.003
NT-proBNP – ng/l (SR only)	2	1124 (436-2257)	352 (192-542)	349 (126-1172)	<0.001
Treatment					
Beta-blocker – no. (%)	0	113 (91)	58 (85)	116 (77)	0.008
ACE-I or ARB – no. (%)	0	111 (90)	59 (87)	120 (80)	0.08
MRA – no. (%)	0	83 (67)	38 (56)	45 (30)	<0.001
Loop diuretic – no. (%)	0	104 (84)	47 (69)	107 (71)	0.022
LD increased – no. (%)	0	10 (8)	9 (13)	16 (11)	0.51
LD decreased/stopped – no. (%)	0	5 (4)	3 (4)	9 (6)	0.74
MRA added – no. (%)	0	9 (7)	4 (6)	18 (12)	0.23
Thiazide added – no. (%)	0	2 (2)	1 (2)	2 (1)	0.98
CRT – no. (%)	0	20 (16)	7 (10)	1 (<1)	<0.001
Echocardiography					
LVEDV – ml	0	214 (166-261)	135 (110-173)	110 (90-136)	<0.001
LVEDD – cm	0	6.2 (5.8-6.9)	5.3 (4.8-5.9)	4.9 (4.5-5.4)	<0.001
LVEF - %	0	32 (25-35)	45 (43-47)	57 (53-61)	NA
History of LVEF <40% – no. (%)	0	NA	39 (58)	45 (30)	NA
LAD – cm	0	4.6 (4.0-5.1)	4.2 (3.8-4.9)	4.3 (3.8-4.8)	0.03
LAVI - ml/m^2	0	44 (36-57)	45 (33-63)	42 (32-55)	0.19
Septal E/E'	29	18 (13-24)	13 (10-18)	13 (10-16)	<0.001
Lateral E/E'	13	13 (9-17)	10 (7-13)	10 (7-13)	<0.001
TAPSE – mm	9	1.7 (1.4-2.1)	1.9 (1.5-2.4)	2.1 (1.7-2.4)	<0.001
TR gradient – mmHg	49	29 (21-38)	30 (22-38)	29 (24-37)	0.92
Mitral regurgitation; None/Trivial – no. (%)	0	50 (40)	36 (53)	76 (51)	0.37
Mitral regurgitation; Mild– no. (%)		66 (53)	29 (43)	68 (45)	
Mitral regurgitation; ≥Moderate – no. (%)		8 (7)	3 (4)	6 (4)	
Tricuspid regurgitation; None/Trivial – no. (%)	0	65 (52)	36 (53)	80 (53)	0.40
Tricuspid regurgitation; Mild– no. (%)		57 (46)	30 (44)	61 (41)	
Tricuspid regurgitation; ≥Moderate – no. (%)		2 (2)	2 (3)	9 (6)	
Congestion by ultrasound					
IVC – cm	7	2.0 (1.7-2.4)	2.0 (1.6-2.4)	2.0 (1.7-2.3)	0.98
IVC collapse>50% – no. (%)	7	93 (76)	50 (77)	119 (80)	0.68

Visible intrahepatic veins – no. (%)	4	93 (76)	49 (74)	130 (87)	0.035
Max intrahepatic vein diameter - cm	4	0.7 (0.5-1.0)	0.8 (0.5-0.9)	0.7 (0.4-0.9)	0.59
JVD Ratio	23	5.1 (2.9-6.7)	5.5 (3.1-7.3)	5.4 (3.3-7.4)	0.37
B-lines	0	6 (2-21)	6 (2-20)	7 (2-15)	0.55
B-lines = 0	0	17 (14)	16 (16)	28 (19)	0.54

Table 1: Characteristics of patients with HF by clinical phenotype, heart failure with reduced (HFrEF), mid-range (HFmEF), or preserved (HFpEF) left ventricular ejection fraction (LVEF). List of abbreviation used: IHD - ischemic heart disease; DM – diabetes mellitus; COPD - chronic obstructive pulmonary disease; SBP - systolic blood pressure; DBP - diastolic blood pressure; BMI - body mass index; BSA – body surface area; NTproBNP - N-terminal B-type natriuretic peptide;; JVP - jugular venous pressure; ACE- angiotensin-converting-enzyme inhibitor; ARB - Angiotensin II receptor blocker; MRA - mineralocorticoid receptor antagonist; LD – loop diuretic; CRT - cardiac resynchronization therapy; LVEDD - left ventricle end-diastolic diameter; LVEDV - left ventricle end diastolic volume; LAD – left atrial diameter; LAVI - left atrial volume index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient, IVC – inferior vena cava; JVD – jugular vein diameter. # includes HF with recovered LVEF for the purposes of this exercise

Correlation coefficient							
	NT-proBNP	**NT-proBNP (if in SR)**	**NT-proBNP (if in AF)**	**JVD ratio**	**Intrahepatic vein size**	**IVC**	**B-lines**
NT-proBNP – ng/l	-	**-**	**-**	**-0.487*** **	**0.472*** **	**0.483*** **	**0.424*** **
NT-proBNP (if in SR)	-	**-**	**-**	**-0.365*** **	**0.388*** **	**0.427*** **	**0.352*** **
NT-proBNP (if in AF)	-	**-**	**-**	**-0.440*** **	**0.348*** **	**0.318*** **	**0.460*** **
JVD ratio	-	-	-	-	**-0.449*** **	**-0.443*** **	**-0.391*** **
Intrahepatic vein size - cm	-	-	-	-	-	**0.829*** **	**0.326*** **
IVC – cm	-	-	-	-	-	-	**0.368*** **
Age- years	**0.489*** **	**0.461*** **	**0.394*** **	**-0.322*** **	0.180**	**0.219*** **	**0.294*** **
BMI- kg/m^2	-0.159**	-0.167*	**-0.287*** **	-0.024 (ns)	-0.012 (ns)	0.019 (ns)	**-0.235*** **
SBP – mmHg	0.066 (ns)	0.123 (ns)	-0.022 (ns)	-0.092 (ns)	-0.065 (ns)	-0.003 (ns)	0.125*
Creatinine µmol/l	0.186**	0.187*	**0.291*** **	-0.054 (ns)	0.067 (ns)	0.057 (ns)	0.016 (ns)
Haemoglobin – g/dl	**-0.248*** **	**-0.322*** **	**-0.341*** **	0.169**	-0.170**	-0.170**	-0.149**
LVEF - %	**-0.211*** **	**-0.343*** **	**-0.343*** **	0.086 (ns)	-0.089 (ns)	-0.032 (ns)	-0.067 (ns)
LA volume – ml	**0.469*** **	**0.374*** **	**0.332*** **	**-0.293*** **	**0.462*** **	**0.493*** **	**0.247*** **
TR gradient - mmHg	**0.453*** **	**0.431*** **	**0.367*** **	**-0.381*** **	**0.446*** **	**0.460*** **	**0.448*** **

Table 2. Correlations amongst biochemical and ultrasound measures of congestion. Correlation with other clinical, biochemical and echocardiographic variables of interest is also shown. A log transformation for NTproBNP before conducting the analysis was done to satisfy the model assumptions. Legend: *** p<0.001 (also shown in bold), ** p<0.01, * P<0.05, ns = p>0.05

Variable	Association with the Composite of First HFH or Death Multivariable analysis											
	Models including B-Lines			Models including JVD Ratio			Models including IVC			Model including clinical congestion		
	HR (95% CI)	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**
Age – year	a)1.01 (0.98-1.05) b)1.01 (0.98-1.05) c) 1.01 (0.98-1.05)	0.3 0.3 0.3	0.57 0.58 0.58	a) 1.01 (0.97-1.05) b) 1.01 (0.97-1.05)	0.2 0.2	0.67 0.61	a) 1.01 (0.98-1.05) b) 1.01 (0.97-1.04)	0.4 0.1	0.51 0.79	1.01 (0.97-1.04)	0.1	0.76
NYHA class (III vs. I/II)	a) 1.70 (0.94-3.06) b) 1.67 (0.93-3.00) c) 1.69 (0.94-3.05)	3.1 2.9 3.1	0.08 0.09 0.08	a) 1.33 (0.72-2.48) b) 1.40 (0.76-2.58)	0.8 1.1	0.36 0.29	a) 1.69 (0.94-3.04) b) 1.61 (0.89-2.91)	3.1 2.5	0.08 0.11	1.64 (0.92-2.93)	2.8	0.10
Urea – mmol/l	a) 1.03 (0.99-1.07) b) 1.04 (0.99-1.08) c) 1.03 (0.99-1.08)	2.3 2.6 2.3	0.12 0.11 0.13	**a) 1.04 (1.00-1.08)** **b) 1.04 (1.00-1.09)**	**3.9** **4.2**	**0.048** **0.040**	a) 1.03 (0.99-1.07) b) 1.04 (1.00-1.08)	2.2 3.0	0.14 0.08	1.03 (0.99-1.07)	1.8	0.18
Haemoglobin -g/dl	a) 0.96 (0.82-1.13) b) 0.97 (0.83-1.14) c) 0.96 (0.82-1.13)	0.2 0.2 0.2	0.66 0.69 0.65	a) 0.96 (0.81-1.12) b) 0.96 (0.81-1.13)	0.3 0.3	0.58 0.62	a) 0.99 (0.84-1.16) b) 0.98 (0.84-1.15)	0.0 0.1	0.90 0.80	0.97 (0.83-1.14)	0.1	0.72
Log [NT-proBNP]	**a) 5.18 (2.64-10.20)** **b) 5.27 (2.54-10.95)** **c) 5.25 (2.69-10.24)**	**22.7** **19.8** **23.7**	**<0.001** **<0.001** **<0.001**	**a) 4.11 (1.99-8.45)** **b) 4.32 (2.12-8.80)**	**14.7** **16.3**	**<0.001** **<0.001**	**a) 4.08 (2.04-8.15)** **b) 3.76 (1.85-7.64)**	**15.9** **13.4**	**<0.001** **<0.001**	**5.09 (2.61-9.90)**	**22.9**	**<0.001**
Signs of congestion (vs no signs)	-	-	-	-	-	-	-	-	-	1.70 (0.93-3.11)	3.0	0.084
B-lines: **Continuous variable** **Terciles (compared to T1)** ***Tercile 2*** ***Tercile 3*** **Above median (≥7 vs <7)**	 a) 1.004 (0.99-1.01) *b) Reference* 1.65 (0.71-3.85) 1.54 (0.68-3.48) c) 1.23 (0.65-2.35)	 0.4 - 1.3 1.1 0.4	 0.51 - 0.25 0.29 0.53	-	-	-	-	-	-	-	-	-
JVD Ratio: **Continuous variable**	-	-	-	 **a) 0.84 (0.72-0.98)**	 **5.3**	 **0.022**	-	-	-	-	-	-

Terciles (compared to T1)				*b) Reference*	-	-						
Tercile 2				1.43 (0.51-3.99)	0.5	0.49						
Tercile 3				**2.64 (1.03-6.79)**	**4.0**	**0.044**						
IVC – cm:	-	-	-	-	-	-				-	-	-
Continuous variable							**a) 1.78 (1.17-2.72)**	**7.2**	**0.007**			
Terciles (compared to T1)							*b) Reference*					
Tercile 2							1.26 (0.47-3.41)	0.2	0.64			
Tercile 3							**2.93 (1.15-7.48)**	**5.0**	**0.025**			

Table 3a: Model A – Clinical Variables - five candidate variables of interest (age, NYHA class III vs I/II, urea, haemoglobin and log [NTproBNP]) were chosen prospectively in addition to clinical and ultrasound measurements of congestion. A small number of variables were selected to avoid over-fitting. Four separate analyses are shown to test the independent association of different clinical and ultrasound measurements of congestion with outcome, including B-lines (left column), JVD ratio (mid column, left), IVC diameter (mid column, right) and presence of clinical signs of congestion (right column). Variables independently associated with outcome are shown in bold.

Three different models were constructed for B-lines, used as a continuous variable (a, top line), in terciles (b, mid line) or above or equal to (vs below) median (c, bottom line). B-lines were recorded for at least 5 beats for each chest site, but the number of B-lines might vary with time of acquisition. Adding heart rate to a model with B-lines as a continuous variable did not change results (only log [NT-proBNP] remained associated with outcome; HR (95% CI): 5.32 (2.71-10.45), $p<0.001$).

Two different models were constructed for JVD ratio and IVC diameter, used as a continuous variable (a, top line), or in terciles (b, bottom line).

Variable	Association with The Composite of First HFH or Death Multivariable analysis								
	Model including B-Lines			Model including JVD Ratio			Model including IVC		
	HR (95% CI)	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**
Age - year	a) 1.02 (0.98-1.05)	1.0	0.33	1.02 (0.98-1.05)	0.6	0.44	1.02 (0.98-1.05)	1.0	0.33
	b) 1.02 (0.98-1.05)	0.9	0.33						
	c) 1.02 (0.98-1.05)	0.8	0.35						
Log [NT-proBNP]	**a) 5.58 (2.66-11.72)**	**20.6**	**<0.001**	**4.16 (1.89-9.15)**	**12.6**	**<0.001**	**4.80 (2.82-10.11)**	**17.0**	**<0.001**
	b) 5.80 (2.69-12.48)	**20.1**	**<0.001**						
	c) 5.69 (2.72-11.90)	**21.3**	**<0.001**						
E/E' lateral	a) 1.02 (0.98-1.05)	0.7	0.39	1.02 (0.98-1.05)	0.7	0.40	1.02 (0.99-1.06)	1.6	0.21
	b) 1.01 (0.98-1.05)	0.7	0.42						
	c) 1.02 (0.98-1.05)	0.8	0.38						
LAVI – ml/m^2	a)1.01 (1.00-1.02)	1.3	0.26	1.01 (0.99-1.02)	1.0	0.32	1.01 (0.99-1.02)	0.5	0.50
	b) 1.01(0.99-1.01)	1.1	0.29						
	c) 1.02 (0.98-1.05)	0.8	0.38						
TR gradient - mmHg	a) 1.00 (0.97-1.02)	0	0.83	1.00 (0.97-1.02)	0	0.99	1.00 (0.97-1.02)	0	0.71
	b) 1.00 (0.98-1.02)	0	0.99						
	c) 1.00 (0.98-1.02)	0	0.90						
B-lines:									
Continuous variable	a) 1.01 (0.99-1.02)	0.9	0.36	-	-	-	-	-	-
Terciles (compared to T1)	*b) Reference*	-	-						
Tercile 2	1.53 (0.61-3.84)	0.8	0.36						
Tercile 3	1.52 (0.65-3.55)	0.9	0.34						
Above median (≥7 vs <7)	c) 1.38 (0.69-2.77)	0.8	0.37						
JVD Ratio	-	-	-	**0.85 (0.73-0.99)**	**4.3**	**0.037**	-	-	-
IVC – cm	-	-	-	-	-	-	**1.95 (1.19-3.19)**	**7.1**	**0.007**

Table 3b: Model B – Echocardiographic Variables - In addition to age and Log [NT-proBNP], the three echocardiographic variables that were most strongly associated with prognosis in univariable analysis were included in addition to ultrasound measurements of congestion. A small number of variables were selected to avoid over-fitting.

Three separate analyses are shown to test the independent association of different ultrasound measurements of congestion with outcome, including B-lines (left column), JVD ratio (mid column), and IVC diameter (right column). Variables independently associated with outcome are shown in bold.

Three different models were constructed for B-lines, used as a continuous variable (a, top line), in terciles (b, mid line) or above or equal to (vs below) median (c, bottom line).

	Discrimination				Reclassification#			
Model No.	Model	C-statistics (95%CI)	Difference		cNRI (95%CI)	p-value	IDI (95%CI)	p-value
1	Base model*	0.74 (0.68-0.80)	Compared to 1 (p-value)	Compared to 2a (p-value)	-	-	-	-
2a	1 + log(NT-proBNP)	0.77 (0.71-0.83)	0.26	-	0.76 (0.41-1.11)	<0.001	0.16 (0.10-0.21)	<0.0001
2b	1+ B-lines	0.75 (0.69-0.81)	0.75	-	0.35 (0.00-0.70)	0.047	0.04 (0.01-0.07)	0.027
2c	1 + IVC	0.77 (0.71-0.83)	0.09	-	0.56 (0.21-0.91)	0.002	0.06 (0.02-0.10)	0.006
2d	1 + JVD ratio	0.76 (0.70-0.82)	0.37	-	0.73 (0.38-1.08)	<0.001	0.10 (0.04-0.15)	0.0003
2e	1+ clinical signs of congestion (vs no signs)	0.76 (0.69-0.82)	0.39	-	0.50 (0.15-0.85)	0.005	0.02 (-0.01,0.04)	0.13
3	2a + B-lines	0.77 (0.71-0.83)	0.31	0.85	0.03 (-0.32, 0.38)	0.88	0.00 (-0.00, 0.01)	0.92
4	2a+ IVC	0.78 (0.73-0.84)	0.09	0.11	0.08 (-0.27, 0.43)	0.65	0.01 (-0.01, 0.02)	0.45
5	2a + JVD ratio	0.79 (0.73-0.85)	0.10	0.09	0.17 (-0.18, 0.52)	0.34	0.03 (0.00-0.06)	0.029
6	2a+ B-lines and IVC	0.78 (0.72-0.84)	0.09	0.12	0.07 (-0.28, 0.42)	0.68	0.01 (-0.01, 0.02)	0.46
7	2a + B-lines and JVD ratio	0.79 (0.75-0.88)	0.10	0.08	0.23 (-0.12, 0.58)	0.19	0.03 (0.01-0.06)	0.023

Table 4: The model's discrimination and reclassification. *base model: age, sex, NYHA (III vs II/I), creatinine, haemoglobin and left ventricular ejection fraction (LVEF). # note that the reclassification is based on the event at 1 year (n=125 patients with 59 events) as the method is based on logistic regression.