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ORIGINAL RESEARCH ARTICLE

Prevalence and prognostic impact of subclinical pulmonary congestion at discharge in patients with acute heart failure

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Abstract

Aims Residual pulmonary congestion at hospital discharge can worsen the outcomes in patients with heart failure (HF) and can be detected by lung ultrasound (LUS). The aim of this study was to analyse the prevalence of subclinical pulmonary congestion at discharge and its impact on prognosis in patients admitted for acute HF.

Methods and results This is a post-hoc analysis of the LUS-HF trial. LUS was performed by the investigators in eight chest zones with a pocket device. Physical exam was subsequently performed by the treating physicians. Primary outcome was a combined endpoint of rehospitalization, unexpected visit for HF worsening or death at 6- month follow-up. Subclinical pulmonary congestion at discharge was defined as the presence of ≥5 B-lines in LUS in absence of rales in the auscultation employing the area under the ROC curve. At discharge, 100 patients (81%) did not show clinical signs of pulmonary congestion. Of these, 41 had ≥5 B-lines. Independent factors related with the presence of subclinical pulmonary congestion were anaemia, higher New York Heart Association (NYHA) class, and N terminal pro brain natriuretic peptide (NT-proBNP). After adjusting by propensity score analysis including age, renal insufficiency, atrial fibrillation, NYHA class, NT-proBNP levels, clinical congestion, and the trial intervention, the presence of subclinical pulmonary congestion at discharge was a risk factor for the occurrence of the primary outcome (hazard ratio 2.63; 95% confidence interval: 1.08–6.41; P = 0.033).

Conclusions Up to 40% of patients considered 'dry' according to pulmonary auscultation presents subclinical congestion at hospital discharge that can be detected by LUS and implies a worse prognosis at 6- month follow-up. Comorbidities, high values of natriuretic peptides, and higher NYHA class are the factors related with its presence.

Keywords Heart failure; Lung ultrasound; Pulmonary congestion; Prognosis

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Introduction

Pulmonary congestion is a key feature in the pathophysiology of acutely decompensated heart failure (ADHF), and residual congestion at the time of hospital discharge is one of the main contributors of readmission risk.[1–3] Moreover, unacceptably high rates of hospital readmission have been observed even in patients without detectable clinical congestion,[4] possibly because of the persistence of subclinical pulmonary fluid overload. Typically, pulmonary congestion has been assessed through symptoms and signs from physical examination, as well as other tools such as biomarkers or chest X-ray.[5] However, these methods are subject to significant inter-observer variability and can be unreliable.[6]

Lung ultrasound (LUS) has emerged as a simple, non-invasive, semi-quantitative tool for the detection of

pulmonary congestion. This technique is based on the observation of vertical echogenic lines arising from the pleura (B-lines) in a pattern that resembles the tail of a comet. The number of B-lines has been found to be a reliable indicator of the presence of extravascular lung water and has allowed the identification of heart failure (HF) patients with a worse prognosis.[7–10] In addition, the LUS-HF trial has recently showed that the assessment of pulmonary congestion by LUS helps to guide treatment in patients with HF and to improve their prognosis.[11] However, there is a paucity of data about the prevalence of subclinical pulmonary congestion and its potential prognostic impact in patients discharged without clinically lung fluid overload.

Thus, the aim of this study was to identify the prevalence of subclinical pulmonary congestion at discharge, related factors, and its prognostic significance in patients admitted for ADHF.

Methods

Study design

This is a post-hoc analysis of the LUS-HF trial.[11] Briefly, this was a single-centre, single-blind, randomized clinical trial evaluating whether a LUS-guided follow-up protocol improves the outcomes in patients with HF. Patients were required to be aged ≥18 years and to have been hospitalized for ADHF defined by shortness of breath, pulmonary congestion on X-ray, and high N terminal pro brain natriuretic peptide (NT-proBNP) values in the first 24 h of admission (cut-off values: 450 ng/L in patients aged <50 years; >900 ng/L in patients aged 50–75 years; >1800 ng/L in patients aged >75 years). Exclusion criteria were inability to attend follow-up visits, a life expectancy of <6 months, haemodialysis, and the presence of severe lung disease preventing LUS interpretation. The primary endpoint was a composite of urgent visit, hospitalization for worsening HF, and death during follow-up. Urgent visits for worsening HF were defined as visits to the emergency department or unscheduled visits to the HF unit as a result of signs and/or symptoms of worsening HF that required intravenous diuretic treatment or diuretic increase with an hospital stay of <24 h. Hospitalization for worsening HF was defined as a stay in hospital for >24 h mainly as a result of signs and/or symptoms of worsening HF. Secondary outcomes were the separate components of the primary outcome. Visits were scheduled in the HF clinic at 14, 30, 90, and 180 days after discharge. Eligible patients were randomized at discharge to either the LUS non-guided (control) group or the LUS-guided group. LUS was performed in both groups, but the result was only available to the treating physician in the LUS-guided arm. In both groups, patients were treated according to current guidelines,[12] but treating physicians were encouraged to modify diuretic therapy in accordance with the number of B-lines in the LUS-guided group. The protocol was approved by the ethics committee of the study institution, and it was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Lung ultrasound protocol

Lung ultrasound studies were performed with a pocket ultrasound device (VScan®; GE Healthcare, Chicago, IL, USA) with a cardiac phased array transducer. According to a current expert consensus document,[13] LUS was recorded at four sites in each hemithorax with the transducer perpendicular to the ribs and at a 16 cm imaging depth being the patient in the semi-recumbent position (*Figure 1*). Video clips were obtained and stored for later review. The number of B-lines reported in real time was the sum of the B-lines visualized in each thoracic site, and investigators were blinded to clinical findings. Additional investigations assessing clinical congestion (physical exam and natriuretic peptides) were performed at the same time as the LUS studies by the treating physicians.

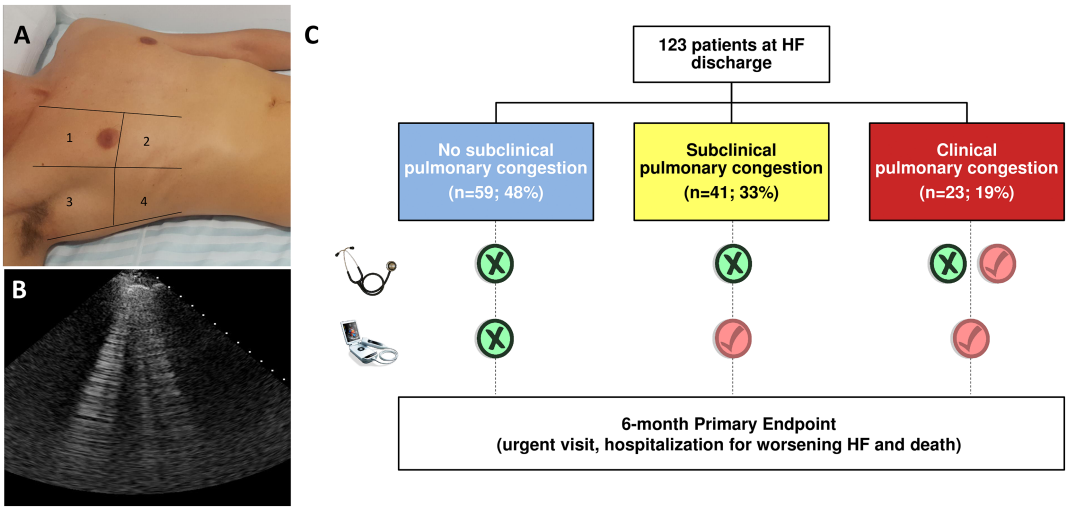
Subclinical pulmonary congestion

Subclinical pulmonary congestion at discharge was defined as the presence of B-lines in the LUS exam in absence of rales in the auscultation. In order to select a cut-off of B-lines, we employed the area under the ROC curve to identify the best number of them to predict the primary outcome applying the Youden criteria (see Supporting Information, *Figure S1*). Thus, subclinical pulmonary congestion at discharge was defined as the presence of ≥5 B-lines in the LUS test in absence of rales in the auscultation. For this post-hoc analysis, patients were compared according to the presence of clinical (rales in auscultation) or subclinical pulmonary congestion at discharge, irrespective of the intervention received in the LUS-HF trial.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation, or median and interquartile range, as appropriate. Differences in continuous variables were tested by ANOVA or Student's *t*-test for independent samples. Categorical variables were presented as frequency and percentage. Differences in the categorical variables were assessed by the χ^2 test or by Fisher's exact test. To identify the factors related with the presence of subclinical pulmonary congestion at discharge, a stepwise multivariable logistic regression was

Figure 1 (A) LUS protocol with eight scan sites, four in each hemithorax; (B) example of B-lines; (C) Flow-chart study according to the presence of rales and ≥5 B-lines in the LUS exam. HF, heart failure; LUS, lung ultrasound.



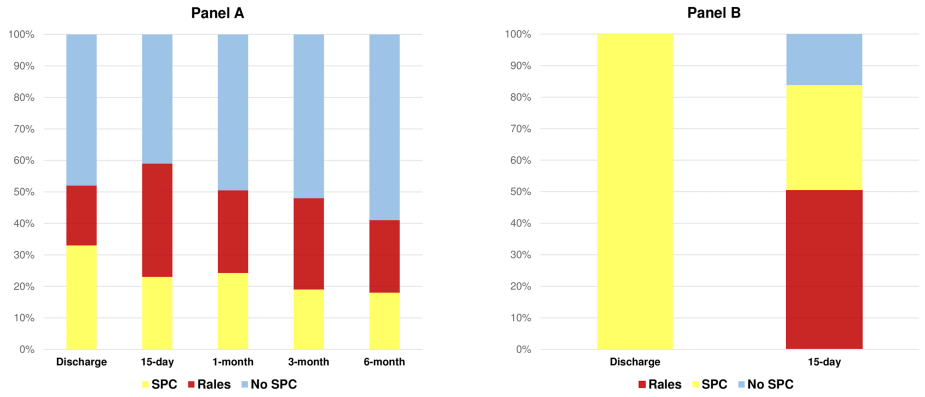
performed. Time to the primary outcome was evaluated with the use of Kaplan–Meier curves. A propensity score to determine the likelihood of having subclinical pulmonary congestion was created including age, renal insufficiency, atrial fibrillation, anaemia, NYHA class, NT-proBNP levels, and the presence of systemic clinical congestion (oedema, jugular ingurgitation, and hepatomegaly). Cox proportional hazards models were performed to analyse the prognostic role of the presence of subclinical pulmonary congestion adjusted by the propensity score and the intervention group. The assumption of proportionality of hazards was tested based on Schoenfeld residuals. Two-sided significance levels of 0.05 were used in all analyses. Data were analysed using STATA SE Version 13.0 (StataCorp LLC, College Station, TX, USA).

Results

Prevalence of pulmonary congestion at discharge and clinical characteristics of the study population

Out of 123 patients included in the LUS-HF trial from 10 November 2016 to 19 June 2018, 100 (81%) were discharged without rales in the auscultation. In this subgroup of patients considered clinically without pulmonary congestion, LUS test detected ≥5 B-lines in 41 patients. Therefore, the prevalence of subclinical pulmonary congestion at discharge in the study population was 33% (*Figure 1*). This prevalence decreased significantly during the follow-up (*Figure 2*, Panel A), especially

Figure 2 (A) Prevalence at discharge and evolution of the pulmonary congestion patterns during the 6- month follow-up. (B) Short-term evolution of the pulmonary congestion in patients with subclinical pulmonary congestion at discharge. SPC, subclinical pulmonary congestion.



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because of an early increase in the proportion of patients with rales at the 15 day visit. In fact, nearly 50% of patients with subclinical pulmonary congestion at discharge developed clinical signs of lung fluid overload before the first ambulatory check-up (*Figure 2*, Panel B).

Table 1 compares the clinical characteristics of the study population according to the presence of pulmonary congestion at discharge. Briefly, patients with subclinical pulmonary congestion were mostly male, older, and had more cardiovascular risk factors and comorbidities than those without subclinical pulmonary fluid overload. Moreover, they had higher frequency of prior HF history, ischemic heart disease, atrial fibrillation, and a more advanced HF stage reflected by higher NYHA class, plasma levels of natriuretic peptides, and other markers of residual congestion in physical examination. Indeed, patients with subclinical pulmonary congestion were discharged more frequently on loop diuretics and at a higher dose than those without subclinical pulmonary congestion. Overall, patients with subclinical pulmonary congestion at discharge represented an intermediate HF severity group, between patients without rales and no B-lines in the LUS exam and subjects with clinically detectable congestion.

Factors related to the presence of subclinical pulmonary congestion

Among patients without rales, anaemia [odds ratio (OR) 8.60; 95% confidence interval (CI): 2.25–32.89], NYHA III class (3.13; 95% CI: 1.08–9.04), and NT-proBNP (per each 100 ng/L increase) (OR 1.04; 95% CI: 1.02–1.06) were the independent factors related with the presence of subclinical pulmonary congestion at discharge (*Table 2*) after the multivariable analysis. *Figure S2* shows the area under the ROC curve of this model (0.829; 95% CI: 0.75–0.91).

Prognostic impact of subclinical pulmonary congestion at discharge

Patients with subclinical pulmonary congestion at discharge presented a higher incidence of the primary outcome during the 6- month follow-up than those without subclinical pulmonary congestion [19 (46%) vs. 9 (15%), $P < 0.001$, respectively]. Moreover, this difference could be attributed to a higher HF admission rate in the group of patients with subclinical pulmonary congestion [15 (37%) vs. 4 (7%), $P = 0.001$, respectively]. Although there was not a significant difference in death rates between groups, a trend to a higher mortality rate was observed in patients with subclinical pulmonary congestion [3 (7%) vs. 0 (0%), $P = 0.066$, respectively]. Interestingly, outcome rates between patients with subclinical pulmonary congestion and patients with rales at discharge were similar as is shown in *Table 3*.

After adjusting by a propensity score including age, renal insufficiency, atrial fibrillation, anaemia, NYHA class, NT-proBNP levels, the presence of systemic clinical congestion (oedema, jugular ingurgitation, and hepatomegaly), and the group intervention (LUS-guided strategy), the presence of subclinical pulmonary congestion at discharge was a risk factor for the occurrence of primary outcome (HR 2.63; 95% CI: 1.08–6.41, $P = 0.033$), similar to being discharged with rales (HR 2.69; 95% CI: 1.03–7.01, $P = 0.043$). *Figure 3* illustrates the Kaplan–Meier curves for the occurrence of the primary outcome. Interestingly, the survival curves for patients with subclinical pulmonary congestion and rales were very similar.

Discussion

Main findings

This is the first study describing the prevalence and prognosis of the subclinical pulmonary congestion at discharge in patients admitted for ADHF based on LUS criteria. Our results showed that up to 40% of patients considered 'lung-dry' according to the auscultation presented subclinical fluid overload detected by LUS. This unnoticed clinical condition was observed more frequently in patients with anaemia, higher NT-proBNP levels, and in those with a higher NYHA class and implied a worse prognosis at 6- month follow-up, comparable with those with clinical pulmonary congestion.

Prognosis of residual congestion in heart failure

Fluid congestion is still present before discharge in up to half of ADHF patients, and the majority of those who are discharged without any clinical sign of fluid retention will develop it at short term.[4] Moreover, pulmonary congestion at discharge and early recurrence after are both associated with a worse prognosis. Thus, a proper lung decongestion therapy during HF hospitalization and a close clinical monitoring during the first weeks after discharge are main goals for both clinicians and HF care pathways.[14,15] Our results highlight this clinical situation, showing that up to 50% of patients were discharged clinically fluid overloaded or with subclinical pulmonary congestion. Furthermore, half of patients developed rales before 2 weeks in the latest group.

Evaluation and monitoring of fluid excess status in patients admitted for ADHF is currently based on clinical history, physical examination, chest X-ray, and natriuretic peptides.[5] However, all these have inherent substantial inter-observer variability and may be non-specific,[6,16] and plasma levels of biomarkers have a limited capacity to assess quantitatively the extent of fluid retention.[17] Right heart catheterization and chest-computed tomography are much more accurate

Table 1 Clinical characteristics of the study population according to the presence of pulmonary congestion at discharge

	Without subclinical pulmonary congestion (n = 59; 48%)	With subclinical pulmonary congestion (n = 41; 33%)	P value	With clinical pulmonary congestion (n = 23; 19%)	P value[a]
Age (years)	65 ± 14	70 ± 10	0.051	75 ± 9	0.002
Male sex	41 (69)	30 (73)	0.690	18 (78)	0.720
BMI (kg/m^2)	27 ± 5	26 ± 6	0.224	28 ± 5	0.354
Cardiovascular risk factors					
Hypertension	38 (64)	31 (76)	0.234	20 (87)	0.104
Dyslipidaemia	39 (66)	29 (71)	0.625	16 (70)	0.878
Diabetes	19 (32)	18 (44)	0.233	13 (56)	0.115
Smokers or former smoker	34 (57)	30 (63)	0.131	14 (61)	0.294
Comorbidities					
COPD	12 (20)	11 (27)	0.448	8 (35)	0.383
Renal insufficiency[b]	12 (20)	22 (54)	0.001	12 (52)	<0.001
Stroke	10 (17)	6 (15)	0.756	3 (13)	0.894
Anaemia[c]	4 (7)	13 (32)	0.001	8 (35)	0.002
Charlson index	2.4 ± 1.6	3.0 ± 1.6	0.073	3.0 ± 1.5	0.064
Past CV history					
Previous HF	24 (41)	29 (71)	0.003	15 (65)	0.007
HF admissions in prior year	16 (27)	18 (44)	0.081	10 (43)	0.157
Ischaemic HF aetiology	22 (37)	20 (49)	0.252	12 (52)	0.353
Atrial fibrillation	26 (44)	26 (63)	0.057	16 (70)	0.050
Type of HF			0.667		0.197
HFrEF	31 (53)	25 (63)		12 (52)	
HFmrEF	15 (26)	8 (20)		2 (9)	
HFpEF	12 (21)	7 (18)		9 (39)	
LVEF (%)	38 ± 13	39 ± 14	0.943	42 ± 17	0.461
Characteristics at discharge					
Systolic blood pressure (mmHg)	113 ± 19	112 ± 17	0.657	111 ± 16	0.789
Heart rate (bpm)	68 ± 10	70 (13)	0.585	66 ± 10	0.411
NYHA class					
II	47 (80)	21 (51)	0.002	14 (61)	0.009
III	10 (17)	20 (49)		9 (39)	
6MWT (m)	374 ± 108	320 ± 103	0.019	277 ± 101	0.001
Minnesota LWHF	55 ± 23	54 ± 21	0.853	48 ± 21	0.429
eGFR (mL/kg/min/1.73 m^2)	71 ± 24	55 ± 23	0.001	57 ± 22	0.002
Albumin (g/L)	40 ± 4	38 ± 3	0.023	38 ± 3	0.026
Bilirubin (umol/L)	15 ± 8	15 ± 8	0.645	14 ± 7	0.629
GGT (UI/l)	44 (32–108)	68 (29–100)	0.908	47 (23–75)	0.569
NT-proBNP (ng/L)	1,071 (621–1947)	3,235 (1,559–5,799)	<0.001	3,088(1,073–6,086)	<0.001
Jugular ingurgitation	3 (5)	11 (27)	0.002	48 (11)	<0.001
Leg oedema	3 (5)	8 (20)	0.023	10 (44)	<0.001
Hepatomegaly	3 (5)	11 (27)	0.002	8 (35)	0.001
Any sign of clinical congestion	9 (15)	17 (41)	0.003	23 (100)	<0.001
No signs of clinical congestion	50 (85)	24 (59)	0.003	0 (0)	<0.001
Number of LUS B-lines	2 (1–3)	7 (6–13)	<0.001	7 (5–9)	<0.001
Treatment at discharge					
Loop diuretics	36 (61)	36 (88)	0.011	22 (97)	<0.001
Mean furosemide dose or equivalent (mg/day)	22 ± 24	53 ± 31	<0.001	56 ± 26	<0.001
Thiazide diuretics	3 (5)	0 (0)	0.341	1 (4)	0.607
ACE inhibitors/ARB	46 (78)	36 (88)	0.208	17 (74)	0.321
Sacubitril/valsartan	3 (5)	1 (2)	0.963	0 (0)	0.475
Beta-blocker	51 (86)	32 (78)	0.272	21 (91)	0.318
Mineralocorticoid antagonist	37 (63)	25 (61)	0.860	12 (52)	0.676
Implantable cardioverter-defibrillator	7 (12)	8 (20)	0.292	5 (22)	0.435
Cardiac resynchronisation therapy	3 (13)	2 (5)	0.337	3 (13)	0.493

Abbreviations: 6MWT, 6 min walk test; ACE inhibitor, angiotensin converting–enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease Study formula); HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LUS, lung ultrasound; Minnesota LWHF, Minnesota Living With Heart Failure quality of life scale; NT-proBNP, amino terminal pro brain natriuretic peptide; NYHA, New York Heart Association.

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range), as appropriate.

[a]P value refers to the comparison of the three groups.

[b]Renal insufficiency refers to estimated glomerular filtration rate <60 mL/min/1.73 m^2.

[c]Anaemia refers to haemoglobin <13 g/dL in man and <12 g/dL in women.

Table 2 Independent predictors for subclinical pulmonary congestion

	Odds ratio (95% confidence interval)	*P* value
Anaemia	8.60 (2.25–32.89)	0.002
NYHA III class	3.13 (1.08–9.04)	0.035
NT-proBNP (per 100 ng/L)	each1.04 (1.02–1.06)	0.001

Abbreviations: NT-proBNP, amino terminal pro brain natriuretic peptide; NYHA, New York Heart Association.

methods to assess pulmonary fluid overload, but both cannot be used repeatedly in the day-to-day clinical practice. Thus, LUS emerges as a promising predictive test easy to perform, non-invasive, and cheap. Indeed, several studies have reported the prognostic capacity of the presence of B-lines in HF,[7–10,18–23] although none of them has analysed the performance of B-lines in the absence of other markers of HF congestion. To the best of our knowledge, this is the first study showing the prognostic capacity of the presence of B-lines in patients in whom their treating physicians considered them properly lung decongested. From that perspective, subclinical pulmonary congestion seems to have similar deleterious effect to overt clinical pulmonary congestion, with more than two-fold higher risk of the primary outcome.

How should subclinical pulmonary congestion be defined?

There is not a standardized definition for *subclinical* pulmonary congestion. Previous authors have reported several cut-off values for B-lines with prognostic significance according to the LUS protocol performed and the clinical setting.[9,10,19,21,22,24,25] An expert consensus document was recently released describing the checklist for quantification of pulmonary congestion by LUS in HF,[13] but no specific number of B-lines was proposed. Our proposal is based on the fact that ≥5 B-lines at discharge showed the best discriminating value for the event risk.

Clinical implications

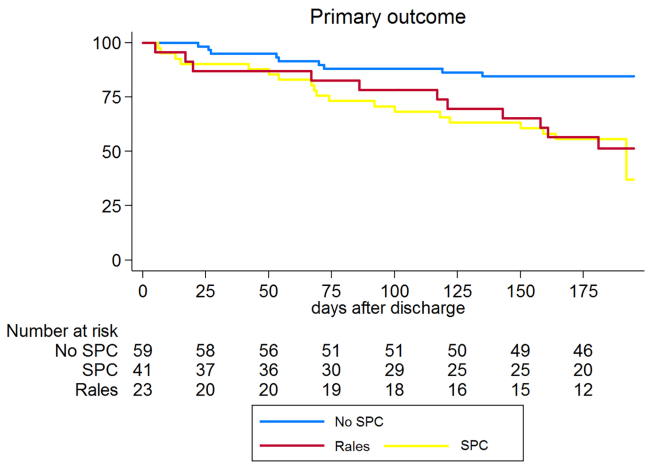
Hospital readmission of patients with HF is a major public health problem, and residual pulmonary congestion at discharge is one of the leading responsible conditions. In last years, LUS has emerged as an attractive tool in HF because of it is a rapid point-of-care test with a fast learning curve and a high inter-observer agreement.[1,26,27] Moreover, our group recently showed that a LUS-guided strategy signifi-

Table 3 Outcomes according to the presence of pulmonary congestion at discharge

	Without subclinical pulmonary congestion (*n* = 59; 48%)	With subclinical pulmonary congestion (*n* = 41; 33%)	*P* value	With clinical pulmonary congestion (*n* = 23; 19%)	*P* value[a]
Primary outcome	9 (15)	19 (46)	<0.001	11 (48)	<0.001
HF admission	4 (7)	15 (37)	<0.001	8 (35)	<0.001
Urgent visit for worsening HF	6 (10)	6 (15)	0.499	4 (17)	0.636
Death	0 (0)	3 (7)	0.066	2 (9)	0.038

Abbreviation: HF, heart failure. Data are expressed as number (%).
[a]*P* value refers to the comparison of the three groups.

Figure 3 Kaplan–Meier survival curves for the occurrence of the primary endpoint according to the presence of subclinical pulmonary congestion at discharge. SPC, subclinical pulmonary congestion.



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cantly improved the combined endpoint of urgent visit, hospitalization for worsening HF, and death during a 6 month follow-up in patients after HF admission.[11] Then, it is conceivable that adding LUS to clinical practice will reinforce the ability of clinicians to promptly detect and treat fluid overload and, ultimately, improve the prognosis of patients with HF. In addition, we have identified that patients with anaemia, higher NYHA class, and high levels of natriuretic peptides at discharge are at risk for presenting residual lung congestion and therefore, require a close follow-up.

Study limitations

The single-centre design of this study may hamper the broader applicability of our results. However, the wide inclusion criteria and the feasibility of the follow-up protocol support the assumption that the LUS technology can be applied in other centres. The 5 B-lines cut-off based on a 2 s clip length could underestimate the number of B-lines, and therefore, further studies are needed to be validated for longer clip lengths and higher-end ultrasound systems in special populations such as obese patients.[28,29] As this is a post-hoc analysis, we cannot exclude a higher rate of false positives because of multiple testing and possible selection bias. We consider our study as hypothesis generating and acknowledge the need of validation in a prospective trial, especially with the calculated cut-off of 5 B-lines.

Conclusions

Up to 40% of patients considered 'dry' according to pulmonary auscultation presents subclinical congestion at hospital discharge that can be detected by LUS and implies a worse prognosis at 6 month follow up. Comorbidities, high values of natriuretic peptides, and higher NYHA class are the factors related with its presence.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Area under the ROC curve of the ≥5 B-lines cutoff to predict the primary outcome in patients without rales at discharge.
Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive.
Figure S2: *Area under the ROC curve of the model predicting subclinical pulmonary congestion containing the following variables: anaemia, NYHA class and NT-proBNP levels.*

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