ORIGINAL ARTICLE

Lung ultrasound in outpatients with heart failure: the wet-to-dry HF study

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Abstract

Aims In ambulatory patients with chronic heart failure (HF), congestion and decongestion assessment may be challenging. The aim of this study is to assess the value of lung ultrasound (LUS) in outpatients with HF in characterizing decompensation and recompensation, and in outcomes prediction.

Methods and results Heart failure outpatients attended to establish HF decompensation were included. LUS was blindly performed at baseline (LUS1) and at clinical recompensation (LUS2). B-lines were counted in eight scanned areas. Diagnosis of no HF decompensation vs. right-sided, left-sided, or global HF decompensation, and patients' management were performed by physicians blinded to LUS1. Outcome was the composite of all-cause death or HF-related hospitalization. Two hundred and thirty-three suspicions of HF decompensation were included in 187 patients (71.4 ± 11.3 years, 66.8% men). Mean B-line (LUS1) was 17.6 ± 11.2 vs. 3.7 ± 4.5 for episodes with and without HF decompensation, respectively ($P < 0.001$). Global HF decompensation showed the highest number of B-lines (20.6 ± 11), followed by left-sided (19.7 ± 11.6) and right-sided (13.5 ± 9.8). B-lines declined to 6.9 ± 6.7 (LUS2) ($P < 0.001$ vs. LUS1) after treatment, within a mean time of 24.2 ± 23.7 days [median 13.5 days (interquartile range 6–40)]. B-lines were significantly associated with the composite endpoint at 30 days (hazard ratio [HR] 1.04 [95% confidence interval 1.01–1.07], $P = 0.02$), but not at 60 ($P = 0.22$) or 180 days ($P = 0.54$). In multivariable analysis, B-line number remained as an independent predictor of the composite endpoint at 30 days, [HR 1.04 (1.01–1.07), $P = 0.014$], with a 4% increase risk per B-line added. B-lines correlated significantly with CA125 ($R = 0.30$, $P = 0.001$).

Conclusions Lung ultrasound supports the diagnostic work-up of congestion and decongestion in chronic HF outpatients and identifies patients at high risk of short-term events.

Introduction

In outpatients with chronic heart failure (HF), an unplanned hospitalization is one of the strongest predictors of increased mortality.[1] Early detection of systemic congestion is key to improving patients' management, because it allows adjusting outpatient diuretic treatment and therefore avoid hospital admissions, but it might be difficult based only in clinical assessment and can be reliant on physicians' skills.

Clinical anamnesis and physical examination are cornerstones of congestion evaluation, but both have several limitations, showing high specificity but low sensitivity.[2,3] In this context, several decompensation risk scores to rule out congestion have been developed to improve patient's fluid status evaluation; however, they have built-in subjective,

highly variable measures that may not be applicable at initial stages and which diagnostic performance is at most intermediate. Therefore, diagnosing HF is a challenge, especially when based on clinical examination, as considerable diagnostic uncertainty may remain. Even in the absence of clinical findings of congestion, patients with HF may have elevated left ventricular filling pressures, and decompensation may not be timely recognized; on the other hand, symptoms such as fatigue, dizziness, or shortness of breath may appear in scenarios other than HF.

Complementary tests in addition to clinical evaluation can improve the diagnosis approach of patients with congestion, but not always are available in the outpatient setting (natriuretic peptides & echocardiography) or have limited accuracy (chest radiography).

Beyond clinical acumen, lung ultrasound (LUS) appears to be a reliable tool for the evaluation of interstitial syndromes including lung congestion detection and quantification, where the number and distribution of B-lines indicate the amount of extravascular fluid in the lung.[4] B-lines are a sonographic artefact caused by the interaction between air and water in the interstitial space.[5] Therefore, LUS may be an alternative method of lung fluid retention assessment, even in asymptomatic or mildly subclinical patients where lung congestion signs may go unnoticed. Advantages of LUS include bedside availability and feasibility, as its performance takes less than 15 min in experienced hands.

Lung ultrasound is already widely used in acute HF diagnosis and prognosis in the emergency setting,[6,7] reaching a sensitivity and specificity as high as 0.88 and 0.90, respectively[8]; nevertheless, its value has not been described well in outpatients with suspected HF decompensation. The wet-to-dry HF study aimed to characterize LUS in the entire process of ambulatory HF decompensation management, including initial evaluation, pulmonary congestion changes, and predictive value for HF hospitalizations. We hypothesized that LUS, performed during the visit, would add value to the diagnosis, monitoring, and prognosis of congestion in outpatients with established HF.

Methods

Study design and patients

This is a prospective single-centre observational cohort study of ambulatory patients examined at a specific HF clinic that they visited due to suspicion of HF decompensation. Criteria for referral to the HF unit have been reported elsewhere[9,10]; briefly, the main criterion is having HF according to the ESC definition, with at least one hospitalization and/or reduced left ventricular ejection fraction (LVEF) < 40%, irrespective of aetiology. Less than 5% of patients are admitted to the HF unit for asymptomatic reduced LVEF after acute myocardial infarction. Since 2001, all patients have been seen regularly during follow-up according to a set schedule and their clinical needs [REGI-UNIC register (PI-18-037)]. Structured follow-up includes quarterly nurse visits and one visit from a physician (cardiologist, internist, or family physician) every 6 months; a transthoracic Doppler-echocardiogram is performed routinely by scheduled protocol at 1 year and every 2 years thereafter, and as many times as needed according to the clinical situation by experienced echocardiographers with a Philips iE33 system using a 3.5 MHz bandwidth sector transducer. For clinical needs, patients can contact the clinic spontaneously for an unscheduled visit in case of suspected HF decompensation and be reassessed as many times as necessary. The clinic has the infrastructure for short-term diuretic and other intravenous drug administration.

For this study, we included consecutive patients older than 18 years evaluated due to suspicion of HF decompensation from 11 July 2016 to 31 July 2017. Exclusion criteria for the analysis were previous diagnosis of pulmonary fibrosis, lung cancer, congenital lung or heart disease, dialysis, or previous major thoracic surgery. We also excluded patients with radiological pachypleuritis by checking the annual chest x-ray performed in our scheduled follow-up protocol. The study was performed in accordance with the Guidelines of the Helsinki Declaration.

Data collection

Visits were performed by physicians of the HF clinic (MdA, PM, ES-V, JS, & PC), blinded to LUS results and biomarker values. Clinical evaluation included decompensation assessment, using the HF clinical disease severity score (CDSS),[11,12] with a decompensated patient defined as having a score ≥ 2. Each of the major criteria counts for 1 point (paroxysmal nocturnal dyspnoea, pulmonary crackles, elevated jugular venous pressure, & third heart sound); each of the minor criteria counts for 0.5 point (orthopnoea, reduced exercise tolerance, resting sinus tachycardia, jugular venous pressure > 4 cm, hepatomegaly, & peripheral oedema). Demographic and clinical data were recorded from the computerized medical record review by one of the researchers (MD).

As a part of the study, peripheral venous blood samples were obtained for a biomarker panel performance. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured using Cobas Elecsys kits (Roche Diagnostics), cancer antigen 125 (CA125) by use of an Architect CA 125 II assay (Abbott Diagnostic) and soluble ST2 (sST2) by use of a human soluble neprilysin/CD10 ELISA kit (Aviscera Bioscience).

Lung ultrasound assessment

Lung ultrasound examination was performed in situ with a pocket portable device (V-scan handheld single-probe device, General Electric) by one of the two experienced investigators (MD& LC), blinded to clinical and visit data. Eight areas, established by a previous expert panel[13] and validated against other approach in an emergency setting, were examined (two upper and two lower areas of each hemithorax); patients were examined while in a semi-supine position during the exam (*Figure 1*). LUS was performed using a phased-array transducer, perpendicular to the ribs, with an imaging depth of 14 cm, and 2 s clip videos were recorded. LUS images were analysed offline by one of the two trained investigators (MD & LC), who recorded the number of B-lines in the sagittal scan of every thoracic area. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artefact that arises from the pleural line, extends to the bottom of the screen without fading, and moves synchronously with lung sliding.[13] Pleural effusion was considered equivalent to 10 B-lines. The sum of B-lines across the eight lung zones was used for the main analyses, as previous studies have done in HF cohorts.[14,15] A simplified 4-lung-zones protocol (an upper anterior and a lower lateral area of each hemithorax) was also performed in a sensitivity analysis[16] (*Figure 1*).

Follow-up

Final diagnosis by the physician in charge of the initial clinical evaluation included four categories (no HF decompensation, right-sided HF decompensation, left-sided HF decompensation, and global HF decompensation), according to the HF guidelines of the European Society of Cardiology[17] [left-sided: orthopnoea, paroxysmal nocturnal dyspnoea, pulmonary rales (bilateral), peripheral oedema (bilateral); right-sided: jugular venous dilatation, peripheral oedema (bilateral), congested hepatomegaly, hepatojugular reflux, ascites, symptoms of gut congestion]; global HF decompensation included symptoms/signs of both left and right HF. As LUS data were blinded to treating physicians, complementary test for diagnostic purposes (blood test, chest x-ray, and other explorations) and management of HF decompensation was based on the routine workup. Patients without HF decompensation were no longer followed for study purposes; those with diagnosed HF decompensation were visited for clinical assessment, and intravenous treatment if needed, as many times as necessary.

Blinded LUS follow-up included a first thoracic scan at the initial visit (Wet-LUS1), and a second study (Dry-LUS2) at the time the patient was considered clinically recompensated. For prognostic purposes, the primary endpoints were the composite of all-cause death

Figure 1 The eight thoracic areas scanned in the wet-to-dry HF study (upper panel): lung areas 1, 4, 5, and 8 (green border) were used for the simplified 4-lung-zones protocol; examples of LUS scans showing decreasing lung congestion (lower panel). LUS, lung ultrasound.
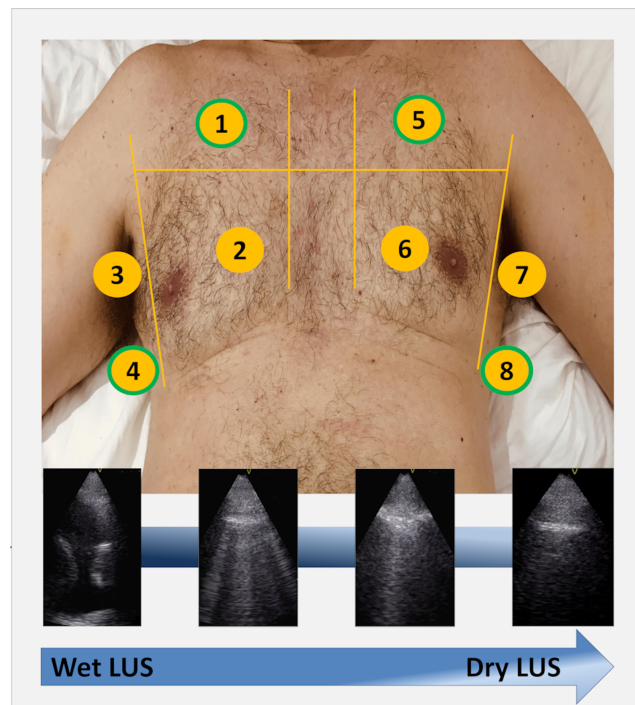
or HF-related hospitalization at 1, 2, and 6 months. All patients completed 6 months of follow-up or until death.

Data analysis and statistics

Each episode of suspected or confirmed HF decompensation was treated as an individual independent data point in the analyses, although some of them occurred in the same patient. Categorical values are described as absolute numbers (percentages) and continuous variables as means (standard deviation) or medians (interquartile ranges), depending on whether data distribution was normal or non-normal as assessed by normal Q–Q plots. All episodes of suspicion of HF decompensation were included, even if they occurred in the same patient, for the B-lines group analyses. In contrast, only HF-decompensation episodes were used for the prognosis analysis. Differences in clinical variables among groups were assessed by χ^2 test, t-test, Mann Whitney U-test, and means comparison (ANOVA) with Scheffe post-hoc analysis, as appropriate. Differences in B-lines [per lung area (LA) and total sum] between episodes with and without the diagnosis of HF decompensation were assessed by mean comparisons for independent data (t-test). Differences in B-lines (per LA and total sum) among episodes of the three different categories of HF were assessed by means comparison (ANOVA) with Scheffe post-hoc analysis. Differences between LUS1 and LUS2 were assessed by paired t-test. Correlation between the total B-lines sum and biomarker concentrations was assessed using Pearson correlation. Univariable Cox regression analyses were performed using the composite endpoint as the dependent variable and the total sum of B-lines as the independent variable. In a second step, multivariable Cox regression analysis (backward stepwise conditional) was performed for the composite endpoint at 30 days, adding age, sex, New York Heart Association (NYHA) functional class, LVEF, and NT-proBNP at the decompensation visit as covariates given their clinical relevance. In a sensitivity analysis, this multivariable Cox regression was performed by patients and not by episodes (only the last episode per patient).

Results

Baseline demographics

Two hundred and thirty-three suspected independent decompensations in 187 patients were prospectively evaluated (152 patients with one, 27 with two, 5 with three, and 3 with four episodes of suspicion of HF) (Supporting Information, *Figure S1*). *Table 1* shows demographic and clinical characteristics of the 187 patients at the first episode of suspicion of HF decompensation. In summary, the mean age of the total co-

Table 1 Demographic and clinical characteristics of the 187 patients at first decompensation

	Total, N = 187	N
Age	71.4 ± 11.3	187
Male sex, n (%)	125 (66.8)	187
White	183 (97.9)	187
Aetiology		187
Ischaemic heart disease	83 (44.4)	
Dilated CM	32 (17.1)	
Hypertensive	17 (9.1)	
Alcohol CM	6 (3.2)	
Drug-induced CM[a]	5 (2.7)	
Valvular	19 (10.2)	
Hypertrophic CM	6 (3.2)	
Other	19 (10.2)	
HF duration (months)	61.0 (26.9–127.5)	187
NYHA class, n (%)		187
I–II	67 (35.8)	
III–IV	120 (64.2)	
CDSS score	1.75 ± 1.04	187
LVEF (%)	42.5 ± 14.3	187
COPD, n (%)	37 (19.8)	187
Hypertension	134 (71.7)	187
Diabetes	102 (54.5)	187
Atrial fibrillation/flutter, n (%)	78 (41.7)	187
Anaemia[b]	109 (58.3)	182
Renal insufficiency[c], n (%)	125 (66.8)	187
BMI (kg/m^2)	29.2 ± 6.2	181
Systolic pressure (mm)	122.8 ± 20.2	187
Heart rate (bpm)	75.4 ± 15.7	187
Urea (mg/dL)	69 (52–105)	187
Na (mEq/L)	137.8 ± 3.2	186
K (mEq/L)	4.3 ± 0.5	185
NT-proBNP (ng/L)	6,792 ± 8,478	183
sST2 (ng/mL)	75.4 ± 56.2	135
CA125 (U/mL)	61.1 ± 81.3	123
Treatments		187
ACEI or ARB	132 (70.6)	
Sacubitril/Valsartan	33 (17.6)	
Beta-blockers	165 (88.2)	
MRA	112 (59.9)	
Loop diuretics	157 (84.0)	
Digoxin	34 (18.2)	
Ivabradine	28 (15.0)	
CRT	27 (14.4)	
ICD	39 (20.9)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CA125, cancer antigen 125; CDSS, HF clinical disease severity score; CM, cardiomyopathy; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; sST2, soluble interleukin-1 receptor-like 1.
Data in mean ± SD, median (Q1–Q3), or n (%).
[a]Chemotherapy agents.
[b]Haemoglobin < 120 g/L in women and <130 g/L in men.
[c]Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation) < 60 mL/min per 1.73 m^2.

hort was 71 years; patients were predominantly male and of ischemic aetiology, and they were mainly in NYHA functional class III. Last previous LVEF was 42.5% ± 14.3 (the first LVEF at first clinic visit of the studied cohort was 34% ± 12.7). Patients were treated according to international guidelines and more than 75% received loop diuretics.

Mean CDSS of the cohort was 1.75 ± 1.04 points, being intrinsically higher in the independent data points classified as a HF decompensation (2.15 ± 0.97) (*Table 2*). Lung basal crackles, orthopnoea, paroxysmal nocturnal dyspnoea, and jugular ingurgitation were unusual in those episodes without the final diagnosis of HF decompensation (*Table 2*).

Acute respiratory infection (19.3%) and anaemia/iron deficiency (8.8%) were the most frequent diagnosis in the episodes considered non-HF decompensation (*N* = 57). In 27 episodes (47.4%), the cause of symptoms was not found, and one patient was diagnosed with pulmonary embolism. Tiredness (38.6%) and dyspnoea (31.6%), followed by oedema and cough, were the most frequent symptoms in this group.

Lung ultrasound association with clinical data

The mean number of B-lines in LUS1 assessment of all the HF suspicion episodes was 14.2 ± 11.6. *Table 2* shows clinical and LUS1 data as well as biomarker profiles of the 233 episodes, according to the final HF diagnosis. Episodes without HF decompensation had significantly lower total B-line counts (3.7 ± 4.5) than the 176 with HF decompensation (17.6 ± 11.2) ($P < 0.001$). Independent data points with right-sided decompensation had significantly lower B-lines count than left-sided and global HF-decompensation (13.49 ± 9.81 vs. 19.67 ± 11.58, $P = 0.01$ and 20.64 ± 11.09, $P = 0.001$ respectively, *Table S1*).

Regarding LA sites, the number of B-lines was significantly higher in all LA in episodes with decompensated HF (*Table 3*). Lower areas, especially lateral zones (LA4 and LA8), were those with the highest number of B-lines ($P < 0.001$ for both LA4 and LA8 vs. all the other LA; $P = 0.61$ between LA4 and LA8). This was specifically observed in episodes with the diagnosis of HF decompensation (again $P < 0.001$ for both LA4 and LA8 vs. all the other LA; $P = 0.93$ between LA4 and LA8). *Table S2* shows the number of B-lines by LA according to the type of HF decompensation.

Table 2 Clinical characteristics of patients in 233 episodes studied for possible decompensation

	No HF diagnosis, N = 57	HF diagnosis, N = 176	P value
CDSS score	0.68 ± 0.51	2.15 ± 0.97	0.001
NYHA class III–IV, *n* (%)	24 (42.1)	129 (73.3)	<0.001
Systolic BP (mmHg)	121.7 ± 19.1	122 ± 20	0.92
Heart rate (bpm)	70 ± 12.6	77.0 ± 16.32	0.004
Urea (mg/dL)	55 (43.5–80)	77 (55–122)	<0.001
eGFR (mL/min/1.73 m^2)	59 ± 27.9	44.2 ± 22.4	<0.001
Haemoglobin (g/dL)	12.9 ± 2.1	11.7 ± 1.9	<0.001
Na (mEq/L)	137.6 ± 3.1	137.8 ± 3.3	0.69
K (mEq/L)	4.4 ± 0.5	4.2 ± 0.5	0.04
NT-proBNP (ng/L)[a]	3145 ± 6425	8388 ± 8775	<0.001
sST2 (ng/mL)[b]	46 ± 41.4	86.7 ± 53.9	<0.001
CA125 (U/mL)[c]	15 (10–21.5)	38 (18–38)	<0.001
Clinical findings			
Crackles	1 (1.8)	62 (35.2%)	<0.001
Jugular venous distention	4 (7.0)	70 (39.8%)	<0.001
Orthopnoea	1 (1.8)	49 (27.8%)	<0.001
Paroxysmal nocturnal dyspnoea	1 (1.8)	28 (15.9%)	0.003

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CA125, cancer antigen 125; CDSS, HF clinical disease severity score; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation); LUS, lung ultrasound; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; sST2, soluble Interleukin-1 receptor-like 1.
Data in mean ± SD, median (Q1–Q3), or *n* (%).
[a]*N* = 225.
[b]*N* = 171.
[c]*N* = 159.

Table 3 Total LUS1 data by lung areas and based on the diagnosis of HF decompensation

	Total suspicions of decompensation, N = 233	No HF diagnosis, N = 57	HF diagnosis, N = 176	P value
LA1	1.36 ± 2.02	0.33 ± 1.14	1.70 ± 2.13	<0.001
LA2	1.64 ± 2.07	0.39 ± 0.68	2.05 ± 2.20	<0.001
LA3	1.48 ± 2.21	0.47 ± 1.43	1.81 ± 2.32	<0.001
LA4	2.94 ± 3.26	0.89 ± 1.54	3.60 ± 3.39	<0.001
LA5	1.15 ± 1.53	0.25 ± 0.85	1.44 ± 1.59	<0.001
LA6	0.75 ± 1.20	0.11 ± 0.31	0.96 ± 1.30	<0.001
LA7	1.73 ± 1.92	0.40 ± 0.80	2.15 ± 1.99	<0.001
LA8	3.09 ± 3.14	0.86 ± 1.91	3.81 ± 3.13	<0.001
Total B-lines sum	14.2 ± 11.6	3.7 ± 4.5	17.6 ± 11.2	<0.001

LA, lung area.

In HF decompensation episodes, the mean number of B-lines moderately correlated with CDSS (R = 0.31, P < 0.001) and NYHA functional class at the moment of the visit (P for trend = 0.01), and inversely with LVEF (R = −0.29, P < 0.001). In contrast, we did not found a correlation with age (R = −0.05, P = 0.54), sex (men 17.4 ± 11.0 vs. women 17.9 ± 11.6, P = 0.76), or the presence of atrial fibrillation/flutter (present 18.9 ± 9 vs. absent 17.3 ± 11.2, P = 0.78).

Relative to biomarkers, NT-proBNP was available in 171 out of the 176 episodes of HF decompensation, sST2 was available in 125, and CA125 in 113. The highest correlation of B-line count was found with CA 125 (R = 0.30, P = 0.001), followed by NT-proBNP (R = 0.21, P = 0.006), and finally sST2 (R = 0.22, P = 0.02).

Of the 176 HF decompensation episodes, a second LUS at the time of recompensation (LUS2) was available in 110, within a mean time of 24.2 ± 23.7 days [median 13.5 days (interquartile range 6–40)] (*Figure S1*). Interestingly, when patients were considered clinically compensated in every independent data point (LUS2), the total sum of B-lines decreased from 17.3 ± 11.0 to 6.9 ± 6.7 (P < 0.001). This significant decrease in B-lines occurred in all LA (all P < 0.001) (*Table 4*). Remarkably, the number of residual B-lines in those recompensated episodes (dry) was still significantly higher than that observed in the initially considered non-decompensated (6.9 ± 6.7 vs. 3.7 ± 4.5, P = 0.002).

Lung ultrasound and outcomes in HF decompensation episodes

During the 6 months of follow-up, 66 primary composite endpoints were recorded in 61 decompensation episodes (53 HF-related hospitalizations—4 patients had 2 hospitalizations—and 26 deaths). Twenty-seven composite endpoints occurred during the first month (23 HF hospitalizations in 23 patients and 7 deaths) and 41 during the first 2 months (35 HF hospitalizations in 35 patients and 10 deaths). In the Cox regression analyses, total B-line sum was significantly associated with the composite endpoint at 30 days (*Table 5*), but not at 60 days [HR 1.02 (95% CI 0.99–1.04), P = 0.22] nor at 6 months [HR 1.01 (95% CI 0.99–1.03), P = 0.54]. *Figure 2* shows event-free survival curves up to 30 days based on the B-line sum, comparing first quartile (0–8 B-lines) vs. quartiles second to fourth (≥9 B-lines). In the multivariable analysis including age, sex, NYHA functional class, LVEF, and NT-proBNP, the total B-line sum remained statistically significantly associated with the composite endpoint at 30 days, carrying an increase of 4% in risk per every additional B-line [HR 1.04 (1.00–1.07), P < 0.05], together with NYHA functional class (*Table 5*). Of note, NT-proBNP was neutrally associated with outcome.

Short-term prognostic value of B-lines sum was quite homogeneous among several subgroups based on demographic and clinical data (*Figure 3*).

In the sensitivity analysis performed by patients and not by episodes (only last episode per patient), B-lines sum remained significantly associated with the composite endpoint at 30 days (*Table 6*). *Figure S2* shows event-free survival curves up to 30 days based on the B-line sum, comparing first quartile vs. quartiles second to fourth based on patients and not on episodes (only last episode per patient).

Sensitivity analysis of simplified 4-area lung ultrasound protocol

Independent episodes with a clinical final diagnosis of HF decompensation had significantly more B-lines than those with-

Table 4 LUS1 (wet) and LUS2 (dry) data of the 110 episodes diagnosed as HF decompensation with LUS2 study available

	Wet (LUS1)	Dry (LUS2)	P value
Total B-lines sum	17.3 ± 11.0	6.9 ± 6.6	<0001
LA1	1.7 ± 2.0	0.4 ± 0.9	<0.001
LA2	1.9 ± 2.0	0.0 ± 1.5	<0.001
LA3	1.7 ± 2.1	0.7 ± 1.5	<0.001
LA4	3.5 ± 3.30	1.8 ± 2.8	<0.001
LA5	1.5 ± 1.6	0.5 ± 1.0	<0.001
LA6	1.0 ± 1.3	0.3 ± 0.6	<0.001
LA7	2.2 ± 2.0	0.7 ± 1.0	<0.001
LA8	3.8 ± 3.1	1.6 ± 2.2	<0.001

LA, lung area.

Table 5 Cox regression analyses for the primary composite endpoint at 30 days by decompensation HF episodes

|	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Total B-lines sum	1.04	1.01–1.07	0.021	1.04	1.01–1.07	0.014
Age	0.98	0.95–1.02	0.35	—	—	—
Female sex	0.60	0.20–1.73	0.34	—	—	—
NYHA class	2.48	1.09–5.7	0.031	—	—	—
LVEF	1.00	0.98–1.03	0.91	—	—	—
NT-proBNP[a]	1.00	1.00–1.00	0.57	—	—	—

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
[a]Per 100 ng/L.

Figure 2 Event-free survival at 30 days for the composite endpoint of all-cause death or HF hospitalization, based on B-lines sum quartiles [Q1 (≤8) vs. Q2–Q4 (9–52)].
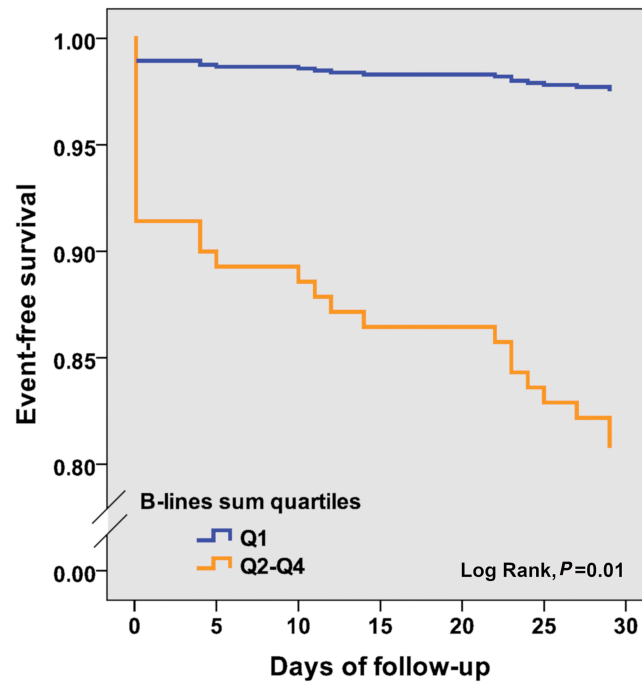
Figure 3 Forest plots for B-lines sum for the composite endpoint of all-cause death or HF hospitalization at 30 days according to several subgroups. Circles represent hazard ratio values, while the horizontal lines through the circles illustrate the length of the confidence interval.
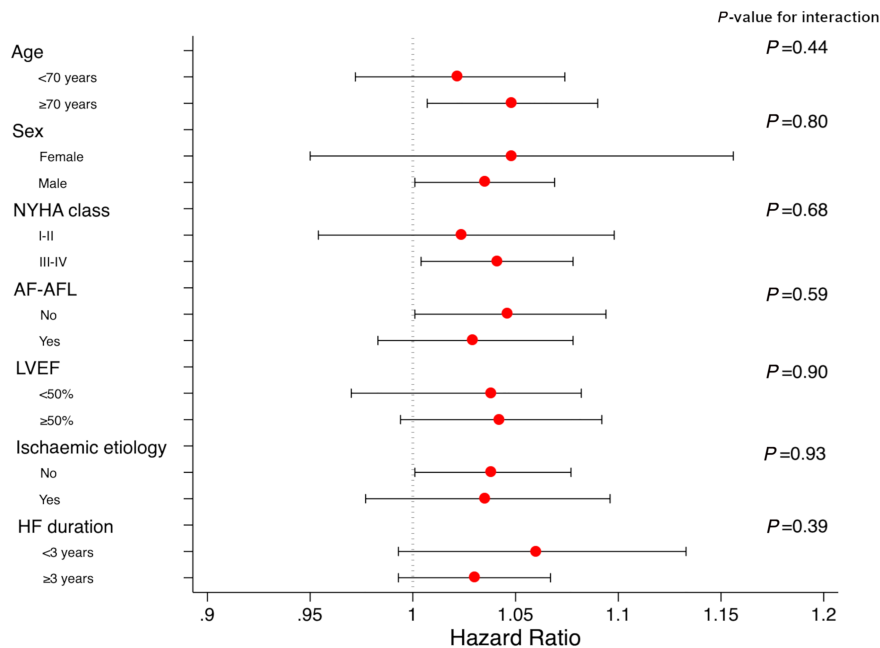
out (10.5 ± 7.1 vs. 2.3 ± 3.2, *P* < 0.001) in the 4-zone protocol. Global HF decompensation showed the highest number of B-lines (12.8 ± 7.5), followed by left-sided (10.6 ± 6.2) and right-sided (8.5 ± 6.8); significant differences were only found between right-sided and global HF decompensation (*P* = 0.002).

Table 6 Cox regression analyses for the primary composite endpoint at 30 days by patient (last HF episode, *N* = 145)

	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Total B-lines sum	1.04	1.01–1.07	0.025	1.04	1.01–1.08	0.017
Age	0.98	0.94–1.02	0.26	—	—	—
Female sex	0.58	0.20–1.68	0.31	—	—	—
NYHA class	2.44	1.04–5.70	0.04	—	—	—
LVEF	1.01	0.98–1.03	0.71	—	—	—
NT-proBNP[a]	1.00	1.00–1.00	0.85	—	—	—

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
[a]Per 100 ng/L.

In the sensitivity multivariable analysis, the B-line sum did not remain statistically significantly associated with the composite endpoint at 30 days [HR 1.06 (1.00–1.12), *P* = 0.07], although a 6% increase in risk per additional B-line was found.

Discussion

Lung ultrasound has been widely evaluated in acute dyspnoea settings, especially in the emergency room and critical care wards, showing more diagnostic accuracy for HF than chest radiography or NT-proBNP.[18] Nevertheless, few studies have addressed its value in chronic HF ambulatory patients to refine (less obvious and less acute) decompensated HF diagnosis. In our cohort of HF outpatients with mostly mild-to-moderate systolic dysfunction, our results show that (i) LUS is a useful tool in the diagnosis of HF decompensation and allows the monitoring of pulmonary congestion during follow-up; (ii) pulmonary congestion by LUS is present in all HF clinical subtypes (i.e. right-sided/left-sided HF) but more importantly so in left-sided and global HF; (iii) LUS significantly predicts short-term outcomes in ambulatory patients with decompensated HF whereas NT-proBNP did not; and (iv) the number of B-lines correlates with known congestion biomarkers (*Figure S3*).

Lung ultrasound findings

This single-centre study shows that in situ LUS can aid the diagnostic workup of acute congestion in patients with established HF, becoming a key element in the initial evaluation, because the number of B-lines increases in the episodes with confirmed HF decompensation, similarly to what is reported in other smaller studies.[19] Specifically, episodes with HF decompensation have a significantly and markedly higher total count of B-lines (17.6 ± 11.23) than those without congestion in our cohort (3.7 ± 4.5). Similarly, in the 4-zone protocol, episodes with a final clinical diagnosis of HF decompensation also had significantly more B-lines than those without (10.5 ± 7.1 vs. 2.3 ± 3.2), suggesting that this simplified protocol could

also be useful in the initial evaluation in this setting, although 8-zone protocol has been found to be superior in other studies.[20] Although all LA can be affected by pulmonary congestion, the lower zones are classically the first to exhibit extravascular fluid in all profiles of patients with HF.[21] As expected, data from our study also show that the highest number of B-lines is found in lower lateral areas (LA4 and LA8).

Previous data from our group and from other studies performed in stable patients have demonstrated that subclinical pulmonary congestion is common in patients with chronic HF,[22,23] even in the absence of symptoms and clinical findings. Therefore, it is not surprising that, in this study, episodes without a clinical final diagnosis of HF decompensation showed 3.7 ± 4.5 B-lines on LUS, quite comparable with the sum of B-lines we found in HF stable patients.[22] As expected, episodes classified as having left or global HF decompensation had higher numbers of B-lines, even taking into consideration the fact that pleural effusion, which can also be observed in right HF decompensation, accounted for 10 B-lines.

Furthermore, LUS is a reliable tool for monitoring pulmonary fluid overload changes during outpatient follow-up, because the B-line profile varies according to the timing of assessment. In this context, we also performed a second LUS to evaluate residual pulmonary congestion after clinical improvement. In our cohort, B-lines decreased significantly from 17.26 ± 11.0 to 6.85 ± 6.66, the latter number being very similar to that we have previously reported in stable patients (5.1 ± 6.1),[22] but still significantly higher than that in the episodes considered as non-decompensation. That fact probably reflects that some pulmonary congestion still remains despite the observed clinical improvement. This result suggests that LUS could be useful for clinicians in tailoring HF diuretic therapy during decompensation; in fact, LUS-guided treatment has been reported to be effective in both chronic and acute HF post discharge,[24,25] because LUS examination might be more sensitive in detecting congestion than clinical evaluation in several HF scenarios.[16,21,22,26]

Other technologies are arising for early HF decompensation evaluation in outpatients such as impedance measurement, home telemonitoring, and wearable technology and

devices that measure pulmonary artery or left atrial pressure wirelessly. Integrating LUS with some of these tools could become a novel approach that have to be investigated.

Lung ultrasound prognosis

Assessing pulmonary congestion accurately is critical to providing the optimal approach to hospitalized HF patients, because the number of B-lines at admission and discharge predicts short-term outcomes.[27–31] Our data further show that B-lines assessment in an ambulatory setting also strongly predicted outcomes; specifically, each B-line added increased by 4% the composite endpoint of all-cause death or HF-related hospitalization at 30 days. Furthermore, the sum of B-lines across all LA, together with NYHA functional class, remained as an independent prognostic factor in the multivariable analysis, outperforming natriuretic peptides. Remarkably, patients with ≤8 B-lines (quartile 1) showed significantly less events at 30 days. This added prognostic value was proved only in short-term follow-up, different from what has been observed in acute or stable chronic HF patients. We speculate that it may be due to various reasons. First, our clinic provides a structured follow-up, including unscheduled visits. Similar to our results, Rivas-Lasarte *et al*.,[25] with a specified high intensity intervention, did not find significant differences in HF hospitalizations during a 6 month follow-up. Second, we treated decompensated HF episodes with ambulatory IV diuretics within the first 30 days, thus decreasing the likelihood of HF admissions (and association with HF admissions) for longer follow-ups.

Because a previous study by Platz *et al*.[16] reported that, in patients hospitalized for acute HF, a 4-zone LUS is highly correlated for prognostic purposes with the 8-zone LUS, we also evaluated this protocol in our cohort. However, our data show that in ambulatory decompensations, the B-line count was not significantly associated with short-term outcomes when using this simplified protocol.

Lung ultrasound and biomarkers

In our study, CA125 showed the best correlation between the number of B-lines and established cardiac biomarkers. CA125 is a glycoprotein synthesized by epithelial serosal cells at sites such as the pericardium, pleura, and peritoneum, with proved usefulness for fluid overload assessment in patients with acute HF.[32] Moreover, as a risk stratification tool, serum CA125 levels have been associated with poor outcomes, and have even been used to guide diuretic treatment.[33] Although LUS and CA125 are both congestion and short-term prognostic markers,[34,35] there is little evidence of their association in acute and chronic HF. Our finding supports hypothesized correlations between B-lines

and cardiac biomarkers other than CA125 in HF patients, as we have previous reported.[36]

Limitations

This was a single-centre study with patients treated at a specific multidisciplinary HF clinic at a day-hospital in a tertiary-care hospital. Most of our patients had high risk of unfavourable outcomes because they were referred after at least one hospital admission and partially recovered LVEF. We cannot disregard selection bias by disease severity and management. Each episode of suspected or confirmed HF decompensation was treated as an individual independent data point in the analyses, although some of them occurred in the same patient. This should be taken into account when analysing our results as they can be influenced by the existence co-dependence in some variables. The number of B-lines may be impacted by the clip duration[37]; in our study, due to the characteristics of the device, we recorded 2 s video clips that may have underrepresented the number of B-lines; However, such recording strategy is likely to be the one used in routine proactice. Finally, we did not perform other emerging types of point-of-care ultrasound for assessing venous congestion, such as the Venous Excess Ultrasound Score protocol.[38]

Conclusions

Our data show that LUS is a valuable tool to identify HF decompensation in chronic HF outpatients. B-lines count identifies clinical profile of congestion (right-sided, left-sided, or global) and appears to precisely assess pulmonary congestion changes during follow-up. B-line count added prognostic information regarding short-term outcomes in ambulatory patients with confirmed HF decompensation. CA125 showed the best correlation between the B-line count and several biomarkers.

Conflict of interest

N.G. reports honoraria from AstraZeneca, Bayer, Boehringer, Novartis, and Vifor. The rest of the authors have no conflict of interest regarding the present study.

Funding

Consent to participate

All participants provided written informed consent.

Consent for publication

the local ethical committee and all participants gave their written consent to publish the study.

Supporting information

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

Figure S1. Study flow-chart.
Figure S2. Event-free survival at 30 days for the composite end-point of all-cause death or HF hospitalization, comparing quartiles (Q1 [≤8] vs. Q2-Q4 [9–52]) based on patients and not on episodes (only last episode per patient).
Figure S3. Summary of the study. LUS protocol performed in patients with HF decompensation suspicion (left panel) allows to confirm HF diagnosis, classify HF type and assess recopensation. B-lines sum significantly difer according to HF situation (right-upper panel) and showed short-term prognostic value (right-lower panel).
Table S1. Clinical characteristics of patients in the 176 diagnosed HF decompensations based on type of HF
Table S2. LUS1 (Wet) data by lung areas based on the type of HF decompensation

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