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Pulmonary congestion evaluated by lung ultrasound predicts decompensation in heart failure outpatients☆

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ABSTRACT

Background: Pulmonary congestion is the main cause of hospital admission among heart failure (HF) patients. Lung ultrasound (LUS) assessment of B-lines has been recently proposed as a reliable and easy tool for evaluating pulmonary congestion.
Objective: To determine the prognostic value of LUS in predicting adverse events in HF outpatients.
Methods: Single-center prospective cohort of 97 moderate-to-severe systolic HF patients (53 ± 13 years; 61% males) consecutively enrolled between November 2011 and October 2012. LUS evaluation was performed during the regular outpatient visit to evaluate the presence of pulmonary congestion, determined by B-lines number. Patients were followed up for 4 months to assess admission due to acute pulmonary edema.
Results: During follow-up period (106 ± 12 days), 21 hospitalizations for acute pulmonary edema occurred. At Cox regression analysis, B-lines number ≥ 30 (HR 8.62; 95%CI: 1.8–40.1; p = 0.006) identified a group at high risk for acute pulmonary edema admission at 120 days, and was the strongest predictor of events compared to other established clinical, laboratory and instrumental findings. No acute pulmonary edema occurred in patients without significant pulmonary congestion at LUS (number of B-lines < 15).
Conclusion: In a HF outpatient setting, B-line assessment by LUS identifies patients more likely to be admitted for decompensated HF in the following 4 months. This simple evaluation could allow prompt therapy optimization in those patients who, although asymptomatic, carry a significant degree of extravascular lung water.
Condensed abstract: Pulmonary congestion is the main cause of hospital admissions among heart failure patients. Lung ultrasound can be used as a reliable and easy way to evaluate pulmonary congestion through assessment of B-lines. In a cohort of heart failure outpatients, a B-lines cutoff ≥ 30 (HR 8.62; 95%CI: 1.8–40.1) identified patients most likely to develop acute pulmonary edema at 120-days.

1. Background

Heart failure (HF) outpatient care is usually based on clinical status and physical examination. However, clinical evaluation has limitations even for the most skilled doctors, showing high specificity but low sensitivity for the detection of pulmonary congestion (PC) [1,2]. Thus, cases of decompensation may not be recognized in time to avoid rehospitalization.

Reducing HF admissions improves patient outcomes and reduces costs. Different tools have been proposed to improve clinical assessment. Natriuretic peptides and echocardiography could help identify clinically silent decompensation and titrating therapy during follow-up [3–5]. Nevertheless, neither method is usually performed during outpatient visits, due to logistical and cost limitations. Ideally, tools for assessing decompensation should be low-cost, feasible, fast, safe, and predictive of adverse outcomes.

Lung ultrasound (LUS) evaluation of B-lines has been proposed as a simple, non-invasive and semi-quantitative tool to assess PC [6,7]. B-lines have been related to extravascular lung water, pulmonary

Abbreviation: CCS, clinical congestion score; CXR, Chest X-ray; EACVI, European Association of Cardiovascular Imaging; E/e′, ratio of early diastolic mitral inflow velocity to early diastolic velocity of the mitral annulus; EVLW, extravascular lung water; HF, heart failure; LUS, lung ultrasound; LV, left ventricular; MLHFQ, *Minnesota Living with Heart Failure Questionnaire*; NT-proBNP, amino-terminal portion of the brain natriuretic peptide; PC, pulmonary congestion; ROC, receiver operating characteristic; 6mWT, 6-minute walk test.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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capillary wedge pressure [8], NT-proBNP [9] and E/e′ in HF patients [10]. LUS can also identify clinically silent pulmonary edema [10–12], suggesting its additional value to improve hemodynamic profiling and treatment optimization [13].

Currently, B-lines are mostly used for the differential diagnosis of acute dyspnea, whereas prognostic data on HF patients are scarce. This study aimed to determine the prognostic value of LUS to predict adverse events, compared to clinical, radiographic, echocardiographic, and biochemical parameters in a cohort of moderate-to-severe systolic HF patients in an outpatient setting.

2. Methods

2.1. Study design and population

Single-center prospective cohort study of 132 consecutive patients (Supplemental material – Fig. 1) from a HF outpatient clinic at the Cardiology Institute of Rio Grande do Sul, Brazil, between November 2011 and October 2012, as part of a project aimed to study the LUS in HF outpatients. This same study population was already included in a previous paper describing the capability of LUS to diagnose pulmonary congestion in a cross-sectional study design [10]. Here, the data on the mid-term follow-up are shown. Inclusion criteria: 1) Age > 18 years; 2) Diagnosis of left ventricular (LV) systolic dysfunction for >6 months regardless of cause as defined by Framingham criteria [14] and European Society of Cardiology guidelines [15]; 3) Moderate-to-severe systolic dysfunction (ejection fraction ≤ 40%); 4) No prior diagnosis of pulmonary fibrosis; 5) Absence of congenital heart disease.

Clinical assessment, NT-proBNP analysis, echocardiography, chest X-ray (CXR), and LUS were independently performed after the clinical appointment (T0) with at most 5-h in-between. Then, all patients filled out the *Minnesota Living with Heart Failure Questionnaire* (MLHFQ) and 100-mm analog-visual dyspnea scale (AVDS), and performed the 6-min walk test (6mWT). There was no interference with the patient's treatment, which was defined by their assistant physician based only on clinical judgment. The study protocol was approved by the Ethics Committee of our Institution (UP4467.11).

A previously validated clinical congestion score (CCS, ranging from 1 to 22 points) [16] was used to objectively classify the patients, by summing the values obtained in clinical assessment of HF signs and symptoms and consisted of: orthopnea (0–4); pulmonary rales (0–4); increased central venous pressure (0–4); peripheral edema (0–4); third heart sound (0–1); hepato-jugular reflux (0–1); functional NYHA class (1–4). Patients with ≥3 points were considered decompensated [16].

Peripheral venous blood samples were obtained at T0. An NT-proBNP level > 1000 pg/ml was the cut-off for decompensated HF.

A comprehensive transthoracic echocardiogram was performed using a Vivid-I (GE Vingmed, Horten, Norway) equipped with 3S probe (1.5–3.6 MHz). All measurements were performed by experienced sonographers according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations [17,18].

2.2. Lung ultrasound

After routine clinical visit, and just before 6mWT, patients underwent LUS to assess B-lines using the same probe and echocardiographic machine adjusted for a 10 cm deep and 75° wide sector. We analyzed the anterior and lateral hemithoraces, scanning along parasternal, midclavicular, anterior axillary and mid-axillary lines from the second to the fifth intercostal space on the right hemithorax and the second to the fourth intercostal space on the left, totalizing twenty-eight chest scanned sites as previously described [19]. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artifact starting from the pleural line, extending to the bottom of the screen and moving synchronously with lung sliding (Supplemental material - Figs. 2 and 3 and Videos 1 and 2) [7]. The total number of B-lines among the 28 scanned sites (0–10 for each site) was recorded generating a B-lines score (total score from 0 to 280) [20–22]. B-lines ≥ 15 was considered the cut-off for significant PC [10]. All LUS and echocardiographic examinations were recorded and reviewed in a blind manner.

The interobserver variability of the B-lines scores was assessed by 2 independent observers (MHM and LG, who had received standardized training and had extensive experience in joint reading) in a set of 49 videos. The intraclass correlation coefficient (ICC) for single measures is 0.96 (95%CI: 0.93–0.98; $p < 0.0001$), and for average measures is 0.98 (95%CI: 0.96–0.99; $p < 0.0001$). The intraobserver variability of MHM, who performed all examinations, was assessed in a set of 20 consecutive patients resulting in 1.4 ± 6% (95%CI: 0.29–3.12) with an ICC for single measures of 0.97 (95%CI: 0.96–0.99; $p < 0.0001$), and for average measures of 0.98 (95%CI: 0.98–0.99; $p < 0.0001$).

2.3. Follow-up and adverse outcomes

Follow-up data were collected by telephone 4 months after T0 to assess the patient's clinical status and inquire about adverse outcomes. Occurrence of endpoints such as need for emergency department evaluation, hospital admission, need for intravenous loop diuretics and death were sought [23]. Data collection was based on a standardized clinical questionnaire performed by a researcher blind to all clinical records. In case of an endpoint, all information regarding this event was collected from medical records, emergency department reports, and the patient.

The primary outcome was admission due to acute pulmonary edema (APE), defined as acutely decompensated chronic HF with respiratory distress with alveolar edema on chest X-ray, O_2 saturation < 90% on room air, pulmonary crackles, and orthopnea [23]. Secondary outcomes were: 1) Major adverse cardiovascular events (acute myocardial infarction, ischemic stroke, cardiac arrest, and death); 2) All fatal and non-fatal events [23].

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or 25th, 50th, and 75th quantiles; categorical variables as counts and percentages. Univariate comparisons were made with χ^2, two-sample *t*-test or Mann-Whitney *U* test. Diagnostic utility of LUS (as well as any other diagnostic methods) in predicting adverse events was determined using the receiver operating characteristic (ROC) curve and expressed using the C statistic. The best threshold for APE was obtained by selecting the ROC point that maximized both sensitivity and specificity. The prognostic capacity of LUS, compared to other diagnostic methods, was studied using univariable and multivariable COX regression analyses, considering first all dichotomous variables according to the cut-off point obtained from ROC and/or defined by the literature. The selection of variables in a multivariate Cox regression analysis was performed using the positive likelihood ratio statistics interactive method of backward elimination. Assumption of hazards proportionality was assessed by the Schoenfeld residuals correlation over time. The prognostic capacity of LUS in association with MLHFQ was determined using a parallel testing. Survival probabilities were estimated by Kaplan-Meier method and differences between survival curves analyzed using the log-rank test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the IBM SPSS Statistics version 21.0.0.

3. Results

3.1. Baseline evaluation

Thirty-five patients were excluded (Supplemental material – Fig. 1). Demographic characteristics, baseline evaluation parameters, and

medical treatment of the remaining 97 patients at T0 are listed in Table 1 and Supplemental material – Table 1. At T0, significant PC was identified in 68% of patients by LUS (B-lines ≥ 15) with 100% feasibility and a mean examination duration of 8.7 ± 2 min (including recording 28 videos). Patients with B-lines ≥ 15 presented patterns of multiple, diffuse, bilateral B-lines, homogeneously distributed in all scanned sites. A number of patients showed criteria for decompensated HF according to NT-proBNP (53.6%), CCS (57.7%) and CXR (37.5%). NYHA functional class ≥ III was present in 29%. Elevated LA pressure estimated by E/e′ ≥ 15 was found in 65.3% of patients. Restrictive diastolic dysfunction, pseudo-normalization patterns, abnormal relaxation, and normal diastolic function were identified in 41.7%, 28.1%, 29.1% and 1.1% of patients, respectively. Mitral regurgitation was recognized as mild in 61.9%, moderate in 13.4%, severe in 2.1% and absent in 22.6% of patients.

3.2. Follow-up outcomes

During the follow-up period of 106 ± 12 days (interquartile range: 89–115 days), 21 hospitalizations for APE (primary end-point)

Table 1
Baseline demographic characteristics and evaluation parameters.

	Overall (n = 97)	Acute pulmonary edema admission		p
		No (n = 76)	Yes (n = 21)	
Age (years)	53 ± 13	53 ± 13	52 ± 12	0.45
Caucasian (n)	78(80%)	60(79%)	18(86%)	0.48
Male (n)	59(61%)	47 (62%)	12(57%)	0.44
Body mass index (kg/m^2)	28 ± 5	28 ± 5	29 ± 7	0.47
Comorbidities				
Hypertension (n)	52(53%)	41(54%)	11(52%)	0.54
Dyslipidemia (n)	43(44%)	35(46%)	8(38%)	0.51
Diabetes mellitus (n)	22(23%)	16(21%)	6(29%)	0.46
Coronary artery disease (n)	29(30%)	22(29%)	7(33%)	0.66
COPD (n)	2(2%)	2(3%)	–	0.45
Heart failure etiology				0.47
Dilated cardiomyopathy	52(54%)	35(53%)	17(55%)	
Post-ischemic	26(27%)	16(24%)	10(32%)	
Hypertension	10(10%)	8(12%)	2(6.5%)	
Myocarditis	4(4%)	2(3%)	2(6.5%)	
Toxic - alcohol	3(3%)	3(4%)	–	
Arrhythmia	1(1%)	1(2%)	–	
Chagas	1(1%)	1(2%)	–	
Clinical parameters				
Heart rate (beats per minute)	74 ± 13	73 ± 12	78 ± 15	0.36
Systolic arterial pressure (mm Hg)	120 ± 23	122 ± 23	111 ± 22	0.18
Diastolic arterial pressure (mm Hg)	75 ± 14	76 ± 14	72 ± 14	0.45
Minnesota	39 ± 22	34 ± 18	58 ± 24	<0.0001
NYHA class	2.1 ± 0,8	2 ± 0.7	2.7 ± 0.9	0.002
II (n)	49(50%)	40(53%)	9(43%)	0.29
III (n)	22(23%)	16(21%)	6(29%)	0.32
IV (n)	6(6%)	1(1%)	5(24%)	0.002
CCS (points)	3 (2; 6)	3 (2; 5)	6 (3; 8)	0.004
Analog-visual dyspnoea scale (mm)	13 (0; 36)	10 (0; 28)	35 (10; 54)	0.006
6-minute walk test distance (m)	276 ± 147	300 ± 139	182 ± 144	0.004
LUS – B-Lines number	26 (11; 47)	20 (8; 34)	51 (38; 74)	<0.0001
Echocardiography				
Left ventricular ejection fraction (%)	28 ± 7	29 ± 7	27 ± 9	0.3
Indexed left atrium volume (ml/m^2)	36 (26; 57)	34 (24; 53)	51 (34; 84)	0.013
E/e′	17 (13; 30)	16 (12; 27)	25 (16; 30)	0.008
LA pressure by E/e′ ratio[a] (mm Hg)	23 (18; 39)	22 (17; 36)	33 (22; 40)	0.008
MPAP[b] (mm Hg)	39.1 ± 10.9	38.2 ± 10,8	42 ± 10.6	0.07
LA Pressure[c] (mm Hg)	22.1 ± 10.5	20.9 ± 10.6	26 ± 8.9	0.025
RA Pressure (mm Hg)	10 (5; 15)	10 (5; 15)	15 (12; 20)	<0.001
Pulmonary congestion on CXR (n)	36(37%)	23(31%)	13(62%)	0.01
Laboratory tests				
NT-proBNP (pg/ml)	1118 (473; 2962)	761 (277; 1821)	2787 (1138; 5149)	0.001
Creatinine (mg/dl)	0.98 ± 0.3	0.97 ± 0.4	1 ± 0.3	0.62
CC (mL/min/1.73 m^2)	100 ± 41	101 ± 43	99 ± 33	0.56
<30 (n)	1(1%)	1(1.5%)	–	0.78
30–59 (n)	15(15%)	10(15%)	5(16%)	0.59
≥60 (n)	81(83%)	55(83%)	26(84%)	0.53
Sodium (meq/l)	139 ± 3	139 ± 4	138 ± 3	0.26
Hemoglobin (g/dl)	13 ± 1.5	13 ± 1.5	13 ± 1.2	0.32
Electrocardiogram				
Sinus rhythm (n)	75(77%)	60(79%)	15(71%)	0.53
Atrial fibrillation (n)	16(16%)	11(14%)	5(24%)	0.24
Paced rhythm (n)	4(4%)	3(4%)	1(5%)	0.63
QRS ≥ 150 ms (n)	40(42%)	32(43%)	8(38%)	0.14

Data are presented as the mean ± standard deviation, median (percentile 25; percentile 75) or n (%). CC: Creatinine clearance; CCS: clinical congestion score; COPD: Chronic obstructive pulmonary disease; CXR: chest X-ray; LA: left atrium; LUS: lung ultrasound; MPAP: mean pulmonary arterial pressure; NYHA: New York Heart Association functional class; RA: right atrium.

[a] Nagueh formula.
[b] Mahan formula.
[c] Henry formula.

occurred, two patients were admitted for acute myocardial infarction and resuscitated cardiac arrest after ventricular tachycardia, and three patients died due to ischemic stroke, acute myocardial infarction, or sepsis (Supplemental material – Fig. 1 and Table 2). No patient was lost during the study follow-up.

Decompensated HF signs at T0 were clearer in patients who developed APE compared to those without, according to commonly used clinical (CCS, NYHA, 6MWT and AVDS), biochemical (NT-proBNP), and imaging parameters (LUS, echocardiography and CXR) (Table 1). There were no significant differences in prescribed medical therapy, excepting a higher number of APE patients using diuretics (Supplemental material – Table 1).

3.3. Determination of discrimination abilities

LUS yielded the highest C statistic of 0.82 (95%CI: 0.74 to 0.9; $p < 0.001$) for the primary endpoint, providing best accuracy with 81% sensitivity (95%CI: 0.6 to 0.9) and 78% specificity (95%CI: 0.7 to 0.8), compared to 0.74 for NT-proBNP (95%CI: 0.63 to 0.86; $p = 0.001$), 0.71 for NYHA functional class (95%CI: 0.59 to 0.84; $p = 0.003$), 0.70 for CCS (95%CI: 0.57 to 0.82; $p = 0.005$), and 0.69 for E/e′ (95%CI: 0.59 to 0.80; $p = 0.008$) (Table 2 and Supplemental material – Fig. 4 and Tables 3 and 4). Statistical differences were found in ROC areas between LUS compared with E/e′ and LA pressure: 0.13 (95%CI: 0.03 to 0.2; $p = 0.006$) and 0.17 (0.05 to 0.3; $p = 0.004$), respectively (Supplemental material – Table 3). The same analysis performed for the secondary end-points showed similar results (Supplemental material – Tables 3 and 4).

Cut-offs derived from ROC analysis for APE, as well as the cut-offs mentioned in literature for CCS, NHYA, 6mWT, AVDS, LUS, echocardiography, and NT-proBNP, were tested to determine the positive likelihood ratio (Supplemental material – Fig. 5).

3.4. Univariable and multivariable predictors

Predictors of APE hospitalization at 120-day follow-up by univariable and multivariable Cox regression analysis are reported in Table 3. In multivariable Cox models, LUS at T0 maintained the strongest independent predictive value for APE at 120 days (B-lines ≥ 30) followed by MLHFQ.

3.5. Combined evaluation – LUS in association with MLHFQ

In a parallel testing evaluation strategy, the combination of LUS B-lines ≥30 and MLHFQ ≥ 45 yielded the highest specify and positive likelihood ratio for APE admission, whereas the presence of LUS B-lines ≥ 30 or MLHFQ ≥ 45 maximized just the sensitivity and the negative predictive value (Supplemental material – Table 5).

3.6. Event-free survival

Hazard ratio for APE increased in step with B-line number, as shown by Kaplan-Meier curves. Severe pulmonary congestion at LUS (≥30 B-lines) was related to worse outcomes with highest relative risk of APE in the 120-day follow-up (HR 8,62 (95%CI: 1.8–40.1); $p = 0.006$) and with average APE-free survival of 93.5 ± 6 days (95%CI: 80.5–106.5) (Fig. 1). The event-free survival showed better outcomes for those

Table 2
Accuracy of clinical, imaging and laboratorial parameters in determine acute pulmonary edema admissions.

	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (IC 95%)	NPV % (IC 95%)
MLHFQ (points)				
>23	85.7 (63.6–96.8)	30.7 (20.5–42.4)	25.7 (16–37.5)	88.4 (69.8–97.4)
>45[a]	76.2 (52.8–91.7)	76 (64.7–85.1)	47.1 (29.8–64.8)	91.9 (82.2–97.3)
NYHA				
≥III[a]	52.4 (29.8–74.2)	77.6 (66.6–86.4)	39.3 (21.5–59.4)	85.5 (74.6–92.8)
CCS (points)				
≥3	80.9 (58.1–94.4)	48.7 (37–60.4)	30.4 (18.8–44.1)	90.2 (76.8–97.2)
≥5[a]	52.4 (29.8–74.2)	71 (59.5–80.8)	33.3 (17.9–51.8)	84.4 (73.1–92.2)
AVDS (mm)				
≥14.5[a]	76.2 (52.8–91.7)	62.7 (50.7–73.6)	36.4 (22.4–52.2)	90.4 (78.9–96.8)
6minWT (m)				
<253[a]	77.8 (52.3–93.4)	65.7 (53.4–76.5)	36.8 (21.8–54)	92 (80.7–97.7)
<300	83.3 (58.5–96.2)	60 (47.6–71.5)	34.8 (21–50.9)	93.3 (81.7–98.5)
LUS (B-lines number)				
≥5	100 (83.7–100)	6.6 (2.2–14.7)	22.8 (14.7–32.7)	100 (47.9–100)
≥15	100 (83.7–100)	40.8 (29.6–52.7)	31.8 (20.9–44.4)	100 (88.7–100)
≥30	90.5 (69.6–98.5)	64.5 (52.6–75.1)	41.3 (27–56.7)	96.1 (86.5–99.4)
≥35[a]	80.9 (58.1–94.4)	77.6 (66.6–86.4)	50 (32.4–67.5)	93.6 (84.5–98.2)
E/e′				
≥15[a]	100 (82.2–100)	43.4 (32.1–55.3)	30.6 (19.6–43.6)	100 (89.3–100)
MPAP[b] (mm Hg)				
>25	95.2 (76.1–99.2)	12 (5.6–21.5)	23.2 (14.8–33.6)	90 (55.4–98.30
LA pressure[c] (mm Hg)				
>20.5	80 (56.3–94.1)	47.2 (35.3–59.3)	29.6 (17.9–43.6)	89.5 (75.2–96.9)
RA pressure (mm Hg)				
>12.5[a]	76.2 (52.8–91.8)	73.7 (62.3–83.1)	44.4 (27.9–61.4)	91.8 (81.9–97.3)
CXR				
Radiologist impression	61.9 (38.4–81.8)	69.3 (57.6–79.5)	36.1 (20.8–53.8)	86.6 (75.4–94)
≥2 radiologic findings[a]	71.4 (47.8–88.6)	72 (60.4–81.7)	41.6 (25.5–59.2)	90 (79.5–96.2)
NT-proBNP (pg/ml)				
>1000	76.2 (52.8–91.7)	52.6 (40.8–64.2)	30.8 (18.7–45.1)	88.9 (75.9–96.2)
>2020[a]	66.7 (43–85.4)	78.95 (68.1–87.4)	46.67 (28.4–65.6)	89.5 (79.6–95.7)

6minWT: 6-minute walk test; AVDS: Analog-visual dyspnoea scale; CCS: clinical congestion score; CXR: chest X-ray; LA: left atrium; LUS: lung ultrasound; MLHFQ: *Minnesota Living with Heart Failure Questionnaire*; MPAP: mean pulmonary arterial pressure; NYHA: New York Heart Association functional class; RA: right atrium; NPV: negative predictive value; PPV: positive predictive value.

[a] Point in the ROC curve that maximized both sensitivity and specificity.

[b] Mahan formula.

[c] Henry formula.

Table 3
Cox regression analysis demonstrating the relation of adverse outcomes with predictors' variables.

Independent variables	Acute pulmonary edema admission				All events			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p
MLHFQ > 45[a]	6.697 (2.436–18.416)	<0.001	2.599 (0.881–7.667)	0.084	3.832 (1.697–8.653)	0.001	1.447 (0.543–3.857)	0.460
NYHA ≥ III[b]	2.805 (1.174–6.699)	0.020	–	–	2.172 (0.993–4.750)	0.052	–	–
Clinical congestion score ≥ 3[c]	3.890 (1.300–11.642)	0.015	–	–	2.967 (1.184–7.434)	0.020	–	–
Analog-visual dyspnea scale (AVDS)[d]	Reference	0.007	–	–	Reference	0.019	–	–
30 mm < AVDS ≤ 60 mm	2.919 (1.082–7.872)	0.034	–	–	1.940 (0.772–4.878)	0.159	–	–
AVDS > 60 mm	5.841 (1.789–19.074)	0.003	–	–	5.099 (1.808–14.38)	0.002	–	–
6-min walk test distance < 300 m[e]	5.883 (1.688–20.504)	0.005	0.531 (0.121–2.323)	0.4	3.287 (1.285–8.412)	0.013	1.397 (0.455–4.288)	0.559
LUS – B-lines number ≥ 30[f]	17.229 (3.849–77.119)	<0.001	8.618 (1.851–40.116)	0.006	9.280 (3.105–27.735)	<0.001	6.854 (4.234–21.344)	0.001
Indexed left atrium volume > 40 ml/m^2[g]	1.538 (0.630–3.758)	0.345	–	–	1.392 (0.629–3.079)	0.415	–	–
E/e′ ratio ≥ 15[h]	2.856 (1.072–7.611)	0.036	–	–	2.209 (0.956–5.103)	0.064	–	–
MPAP[†] > 25 mm Hg[i]	2.966 (0.400–22.435)	0.285	–	–	3.833 (0.518–28.376)	0.188	–	–
LA pressure[‡] > 20.5 mm Hg[j]	3.096 (1.025–9.350)	0.045	–	–	3.198 (1.192–8.580)	0.021	–	–
RA pressure > 12.5 mm Hg[k]	5.760 (2.100–15.795)	0.001	2.554 (0.886–7.536)	0.089	4.040 (1.750–9.331)	0.001	2.309 (0.938–5.687)	0.069
CXR ≥ 2 radiological findings [l]	4.463 (1.713–11.625)	0.002	–	–	4.155 (1.791–9.640)	0.001	–	–
NT-proBNP > 1000 pg/ml[m]	3.213 (1.170–8.820)	0.024	–	–	2.681 (1.122–6.407)	0.026	–	–
NT-proBNP > 2020 pg/ml[n]	5.408 (2.152–13.592)	< 0.001	–	–	4.243 (1.903–9.462)	<0.001	–	–

6minWT: 6-minute walk test; AVDS: Analog-visual dyspnoea scale; CCS: clinical congestion score; CXR: chest X-ray; LA: left atrium; LUS: lung ultrasound; MLHFQ: *Minnesota Living with Heart Failure Questionnaire*; MPAP: mean pulmonary arterial pressure; NYHA: New York Heart Association functional class; RA: right atrium.
Reference Category: a: ≤ 45 points; b: <III; c: <3 points; d: 30 mm; e: ≥300 m; f: <30; g: ≤40 ml/m^2; h: <15; i: ≤25 mm Hg; j: ≤20.5 mm Hg; k: ≤12.5 mm Hg; l: <2 radiological findings; m: ≤1000 pg/ml; n: ≤2020 pg/ml.
Multivariate Cox regression analysis were performed considering the information related to the MLHFQ, 6minWT distance, LUS – B-lines number and RA pressure using the positive likelihood ratio statistics interactive method of backward elimination (with probability for either entry or removal from the model equals to 0.05 and 0.1, respectively).
† Mahan formula.
‡ Henry formula.

patients with <15 B-lines, whereas all APE events occurred in presence of significant PC on LUS (≥15 B-lines). The occurrence of all events was also higher in the ≥30 B-lines group (Fig. 1).

A combined strategy added a discriminative value in determine patients at risk for APE, showing a worst outcome for those with LUS B-lines ≥ 30 and MLHFQ ≥ 45 points (HR 11.2 (95%CI: 4.3–29.3); p < 0.0001) and an average APE-free survival of 75 ± 10 days (95%CI: 56.1–94.9) (Fig. 1).

4. Discussion

This study assessed the prognostic value of LUS B-lines in a cohort of moderate-to-severe systolic HF outpatients, providing a comprehensive comparison of 28-region B-line scan with other diagnostic tools, such as clinical evaluation, CXR, echocardiography, and NT-proBNP. In summary: (i) Degree of PC measured by LUS at T0 can accurately predict 120-day HF-specific admission and all events; (ii) B-lines ≥ 30 identified a high-risk group for APE admission at 120 days, a better predictor than other commonly used diagnostic parameters; (iii) Patients free of significant PC by LUS (B-lines < 15) have an excellent 120-day event-free survival, despite other parameters evaluated; (iv) B-lines ≥ 30 combined with MLHFQ ≥ 45 points strategy maximize the prediction of 120-day HF-specific admission.

4.1. Pathophysiology and role of pulmonary congestion

The role of silent PC is relevant in HF outpatient outcomes. Recognition and quantification of PC are crucial in an evaluation of HF patients, because prompt adjustment of treatment can reduce morbidity and mortality. The vast majority of HF patients with reduced ejection fraction are hospitalized due to congestion rather than low cardiac output [24,25]. In the *congestion cascade*, increased LV filling pressure represents a phase of hemodynamic congestion which is different from pulmonary, systemic and clinical congestion [26]. PC refers specifically to the presence of extravascular lung water (EVLW) sonographically assessable by B-lines. Patients with the same LV filling pressures may have significantly different PC, from a complete absence of EVLW to alveolar pulmonary edema. Many pathophysiological events are involved and can explain these differences: (i) the integrity of alveolar-capillary membranes; (ii) systemic inflammation status influencing vascular permeability; (iii) hydrostatic and oncotic pressures; (iv) the speed of increase in LV filling pressures and duration of disease; (v) the efficacy of lymphatic drainage. Assessment of B-lines by LUS offers specific visualization of PC [27,28], allowing non-invasive semi-quantification of the degree of EVLW as an outpatient. This complements the hemodynamic congestion assessment that can also be non-invasively performed through echocardiography. This may explain why, in our study, E/e′ ratio has a different predictive value for APE compared to B-lines.

Natriuretic peptides, which are instrumental in the management of HF patients, reflect more hemodynamic than pulmonary congestion [3,5]. NT-proBNP and LUS evaluate different pathophysiological mechanisms, so they are somehow correlated in relatively large populations [9,10,29–31], but can provide different information in the single patient, one enhancing the value of the other, especially in gray-zone patients [30–32].

There is no standardized tool for evaluating PC in the clinical arena [26]. Although not recommended for outpatient follow-up, CXR is the most widely used method to establish the presence and degree of EVLW, allowing a visualization of the lungs in the context of the whole chest [15,33]. Nearly 20% of HF outpatients may have a normal CXR, limiting its overall sensitivity for detecting PC. Our results are consistent with these data, showing a suboptimal value of CXR for predicting outcomes in chronic HF outpatients [34]. Neither is clinical examination satisfactory, with its inherent insufficient sensitivity in recognizing congestion until significant decompensation develops. Interestingly, but not surprisingly, the 6MWT, dyspnea scale and Minnesota were predictive for adverse outcomes in our study. Regardless of not directly evaluating congestion, these tools assess the overall clinical status that somehow reflects the congestion process, and could improve the LUS predictive value in a combined strategy evaluation.

4.2. Comparison with previous studies and clinical implications

Different scores and tools have been proposed to predict adverse outcomes in chronic HF outpatients [16,35,36]. However, they are

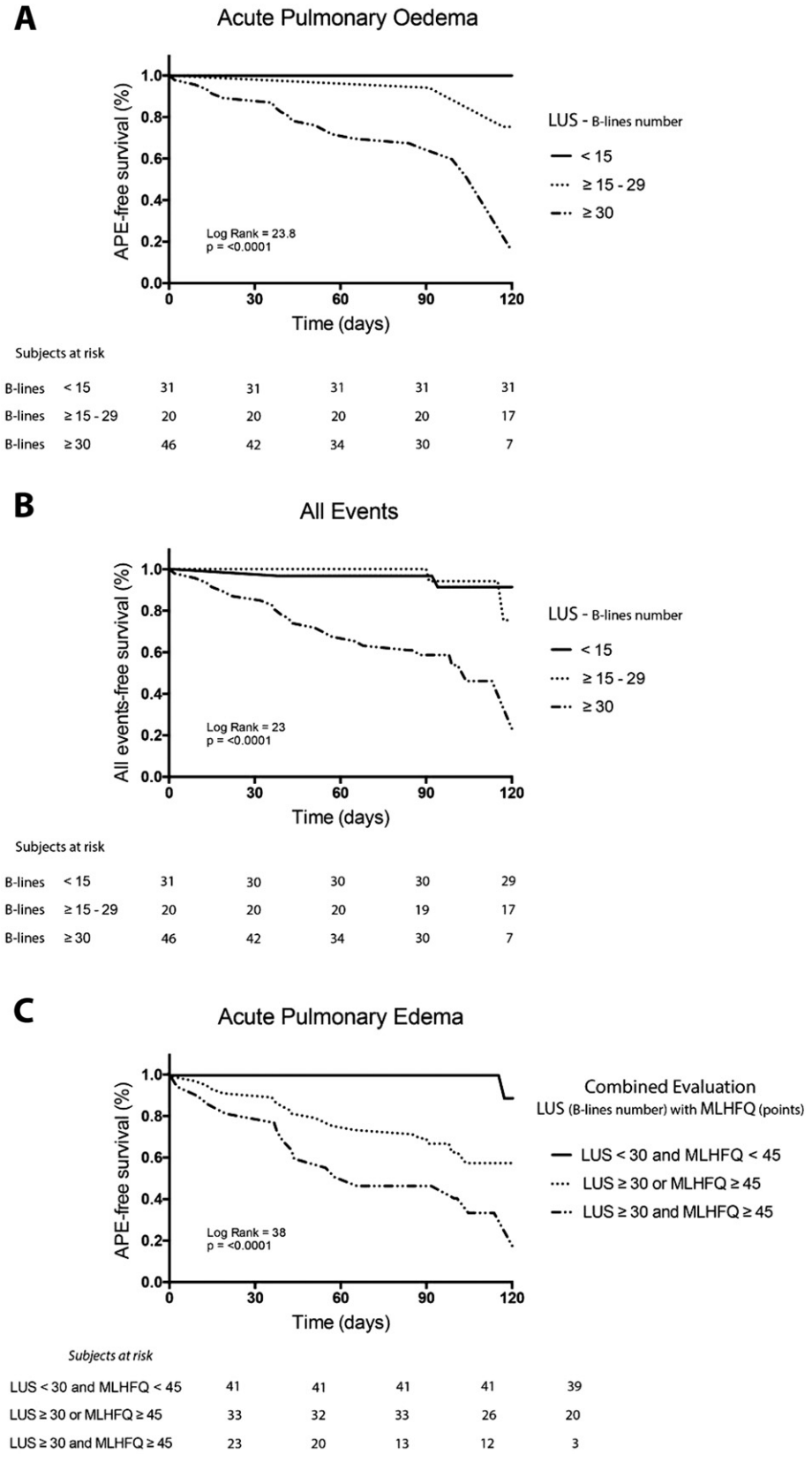

Fig. 1. Kaplan-Meier survival curves. A: LUS acute pulmonary edema event free survival; B: LUS all events free survival. C: Combined strategy acute pulmonary edema event free survival. LUS: lung ultrasound.

often limited by difficult routine application, and as yet none of them is currently implemented in the clinical practice.

The prognostic value of B-lines as an independent predictor of events has been demonstrated in previous studies in patients with acute HF [32,

37,38], chronic HF [13,39], acute coronary syndromes [40], hemodialysis [41,42] or acute dyspnea, and/or chest pain [43]. Our findings are consistent with those previous works, reinforcing the major role played by EVLW in predicting adverse outcome. In a recent study of chronic HF outpatients, Gustafsson et al. [13] showed that the presence of B-lines and pleural effusion assessed by handheld ultrasound device (in an isolated or combined way) independently increased the risk of death or hospitalization. The Authors considered the dichotomous presence or absence of sonographic PC and did not determine the best discriminative B-line number. More recently, Platz et al. found that presence of ≥3 B-lines in an 8 zone LUS examination carried the worst outcome in HF outpatients [39]. These data are very similar to our findings, although the B-line cut-off is significantly lower. This apparent discrepancy can be explained by the differences in study population (older and with more advanced HF in our cohort) and in the scanning scheme (which includes more sites in our protocol). It is important to underline that a few B-lines (i.e. <5 total B-lines), especially when found at the lung bases, should be considered a normal finding, as confirmed by several studies [7,9]; this is not in contrast with proposing a cut-off of ≥3 B-lines, which can be highly significant from a statistical point of view, but not applicable in the clinical arena. Moreover, it is not only the absolute number of B-lines that should be considered, but also their spatial distribution all over the chest: 1 or 2 B-lines in a single scanning site should not be considered a sign of significant PC. According to the 2012 International Evidence-Based Recommendations of Point-of-care LUS a single region should show at least 3 B-lines to be considered positive for pulmonary interstitial syndrome [7].

The short examination time, the 100% feasibility and simplicity of LUS evaluation (basic technology including pocket-sized devices) allows this technique to be easily performed during a routine outpatient visit as an extension of the physical examination [44]. In the setting of acute dyspnea, this high versatility has promoted LUS B-lines from a research tool to Recommendation papers in the time-span of about a decade [34,45,46].

While further large-scale randomized outcome studies are needed to understand whether a B-line-guided approach could contribute to reducing HF morbidity and mortality, the presence of severe PC may be taken as an alarm to promptly optimize outpatients' treatment and intensify the follow-up, with the aim of reducing the number of acute HF hospitalizations.

4.3. Study limitations

The present paper describes the same cohort of 97 patients already included in a previous study published in 2013 by ourselves [10]. However, that study described the cross-sectional clinical and functional correlates of B-lines, whereas the present study is focused on longitudinal mid-term prognostic value. The 2 aspects are separate and complementary in defining the diagnostic value (for identifying pulmonary congestion) and the prognostic yield (in outcome prediction of events).

Sample size is a limitation of this monocentric cohort and our series may not represent the average patient with HF. However, the number of patients enrolled was determined to be sufficient according to sample size calculation.

Our findings are based on counting B-lines, which can be debated. B-lines are substantially rough ultrasound artifacts, but by now many studies have shown the good correlations between the somehow "imprecise" number of B-lines and more established parameters of increased EVLW and decompensation [9,10,20,30,47]. However, in the clinical routine, eyeballing imaging of B-lines can be enough to get quick but meaningful information on the degree of PC. Like any other test, LUS should not be interpreted in isolation, but always contextualized in the overall clinical picture [48].

The used of a sectorial probe for LUS evaluation also could be discussed, as the convex or microconvex probes seem to be the most appropriate. However, the bias between probes is very low, and we believe that we should not give up the meaningful information we get in our everyday practice from lung ultrasound only because we do not have the perfect probe available [47,48].

The detection of B-lines does not necessarily imply a cardiogenic etiology. Pulmonary fibrosis and non-cardiogenic pulmonary edema may also result in the presence of B-lines, suggesting a differential diagnosis that was not present in our population [49,50]. This limitation is less relevant when B-lines are used to determine persistent pulmonary congestion in patients with a previously established diagnosis of HF. To avoid misinterpretation of this sign, the key is to contextualize B-lines in the clinical setting. When presence or persistence of B-lines is totally unrelated to the clinical picture, caution should be used and other causes of B-lines should be taken into account (pulmonary fibrosis in patients on amiodarone, non-cardiogenic pulmonary edema, interstitial lung disease). The characteristics of the pleural line seem also very helpful in aiding a differential diagnosis, when the clinical picture is still ambiguous [19].

We had 60% of our patients receiving diuretics. This percentage may seem to be low, since all our patients had documented heart failure with reduced ejection fraction. However, according to guidelines [15] the use of diuretics is usually indicated to reduce the signs and symptoms of congestion, and only 57% of the patients had evidence of congestion on the basis of the clinical congestion score. The evidence of pulmonary congestion was higher with B-lines (68% had >15 and 95% had >5 B-lines) but this information (whose validation was the objective of the study) was likely not used by the referring physician to change the prescription pattern.

5. Conclusion

In moderate-to-severe systolic HF outpatients, severe PC (B-lines ≥ 30) identifies a high-risk group for APE admission at 120 days. Absence of significant PC (B-lines < 15) identifies a subgroup at minimal risk for adverse outcomes.

Given its prognostic value, LUS could be considered a reliable tool for management of HF patients; it could be used as an extension of the physical examination, helping identify those patients who, though asymptomatic, show a significant number of B-lines and likely need more intense monitoring and therapy titration.

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Conflict of interest

The authors report no relationships or competing interests that could be construed as a conflict of interest.

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