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ORIGINAL SCIENTIFIC PAPER
Heart Failure and Cardiomyopathies

Association between B-lines on lung ultrasound, invasive haemodynamics, and prognosis in acute heart failure patients

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Aims Increased left atrial pressure leads to pulmonary congestion. Although the B-lines in lung ultrasound (LUS) are useful in detecting pulmonary congestion, data regarding the association between B-lines and invasive haemodynamics are inconsistent. This study aimed to explore the correlation of the B-line count by LUS with pulmonary capillary wedge pressure (PCWP) stratified for preserved and reduced ejection fraction (EF) in acute heart failure patients.

Methods and results We performed a prospective observational study on 116 hospitalized patients with acute heart failure (mean age, 75.2 ± 10.3 years), who underwent right heart catheterization before discharge. LUS was performed in eight zones within 4 h of right heart catheterization and compared with PCWP separately in each EF group. Cardiac events were recorded 1 year after discharge. PCWP revealed a clear pivot point at which the B-lines began to increase in the overall cohort and each EF. Specific thresholds of the increase in B-lines were identified at 19 and 25 mmHg for preserved and reduced EF, respectively. Residual congestion at discharge was defined as the presence of ≥6 B-lines. Patients with residual congestion had a higher risk for cardiac events than those without residual congestion (hazard ratio, 12.6; 95% confidence interval, 4.71–33.7; log-rank, $P < 0.0001$).

Conclusion A clear pivot point was associated with increased B-lines count in PCWP at 19 and 25 mmHg for preserved and reduced EF, respectively. Moreover, the increased B-line count above the defined cut-off used to quantify residual congestion was associated with significantly worse outcomes.

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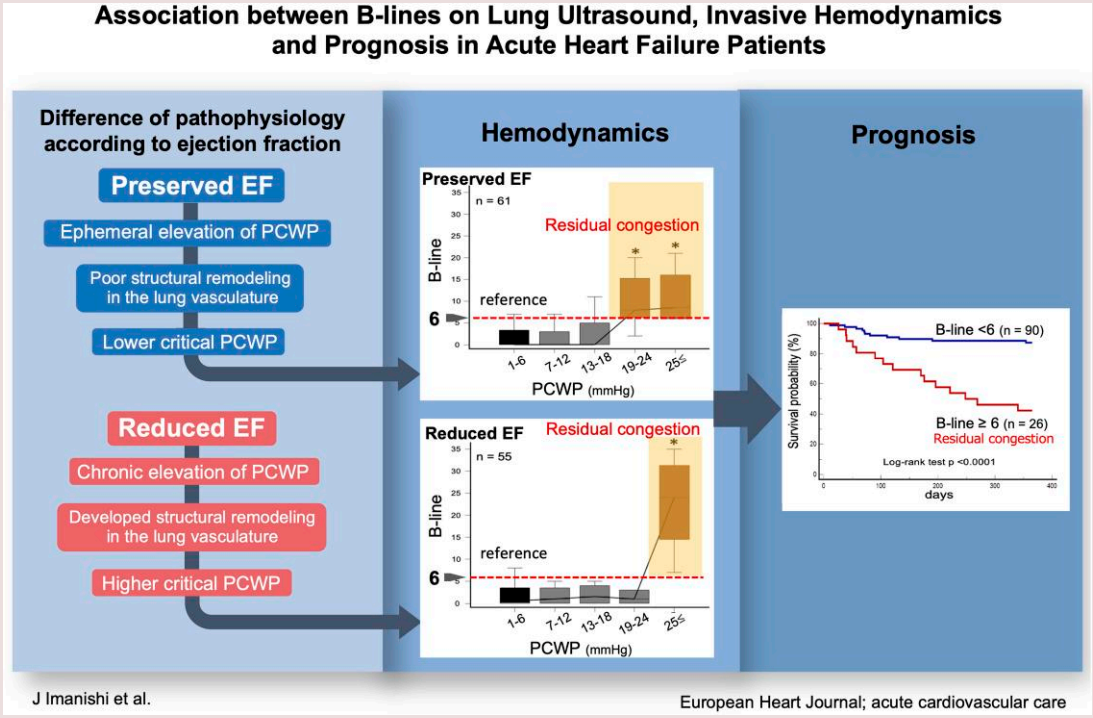
Graphical Abstract



Pulmonary capillary wedge pressure (PCWP) revealed distinctive pivot points of the increased number of B-lines by EF categories. We proposed that ≥6 B-lines (red dashed line) at discharge showed the best discriminating value for residual congestive patients at event risk. EF, ejection fraction.

Keywords Heart failure • Pulmonary congestion • Lung ultrasound • Invasive haemodynamics

Introduction

Heart failure (HF) is a growing public health problem owing to its high mortality and readmission rates and high national healthcare expenditures.[1] In addition, the number of patients newly diagnosed with HF is increasing as the population ages.[2] A haemodynamic hallmark of HF is elevated left ventricular (LV) filling pressure; therefore, its assessment is of great importance in the clinical management of patients with HF.[3] Thus, a non-invasive method of estimating LV filling pressure is valuable for the clinical management of patients with HF. Echocardiography is the first-line tool for both diagnosis and follow-up of patients with HF.[4] The latest echocardiographic guidelines propose a series of algorithms to estimate elevated LV filling pressure using multiple indices.[3] Although its clinical utility is getting recognition, there may be situations in which the algorithms are not applicable.[3]

B-lines are linear artefacts that are observed during lung ultrasonography (LUS), reflecting extravascular lung water.[5] Recently, the number of B-line was reported to correlate with cardiac catheterization-derived LV filling pressure, making it a valuable adjunct to echocardiography and clinical variables in the management of patients with HF.[6] Although the concept is quite reasonable considering the pathophysiologic consequence of elevated LV filling pressure, some authors advocated the lack of correlation between the number of B-lines and an increase in LV filling pressure.[7] Essentially, not only might patients with a relatively normal left atrial pressure (LAP) have radiographic and symptoms of pulmonary congestion, but patients with chronically elevated LAP might have no evidence of pulmonary congestion. The threshold, which began to develop lung congestion, is not fully investigated according to the clinical settings. We assumed that patients with reduced ejection fraction (EF) have chronic structural remodelling for adaptation of sustained LAP and may be more resistant to the development of lung congestion as the capillary pressure rises. Accordingly, this study aimed to elucidate the correlation of lung congestion assessed by B-lines with pulmonary capillary wedge pressure (PCWP) stratified according to EF values and examine the effect of residual pulmonary congestion defined as the number of B-lines on clinical outcomes.

Methods

Study population

We prospectively included 147 patients (aged ≥18 years) admitted for acute HF who underwent right heart catheterization (RHC) a median of 3 days before discharge from August 2020 to July 2021. Attending physicians provided case-specific optimized therapy to the patients and decided the discharge according to established guidelines.[8] Of all the hospitalized patients for acute HF, those requiring haemodynamic invasive measurements because of clinically indeterminate volume at the discretion of the attending physicians were consecutively enrolled in the study. Of all patients with adequate quality data from standardized transthoracic echocardiography and lung ultrasound (LUS) examinations, we classified 61 patients with HF with preserved EF (LVEF ≥50%) and 55 patients with HF with reduced EF (LVEF <50%). Patients with known pulmonary fibrosis, pneumonia, active lung cancer, dialysis, a history of recent chest trauma, pleural effusion that would interfere with image acquisition, or COVID-19 were excluded.[9] Patients

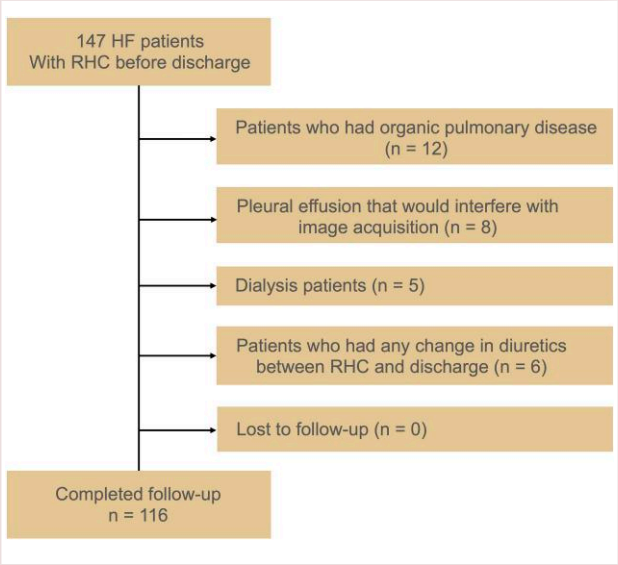


Figure 1 Study flowchart. Protocol used for the enrolment of patients with heart failure in this study. RHC = right heart catheterization.

who had any change in diuretic treatment between the day of RHC and discharge were also excluded. Of the 147 patients who underwent RHC before discharge, 12 (8%) had organic pulmonary disease and 19 met the other exclusion criteria, leaving a total of 116 patients for this study (*Figure 1*). From the point of view of the duration of HF, patients were also stratified by history of HF hospitalization, comparing patients never hospitalized to those with a prior hospitalization. On the day of RHC, none of the patients was admitted to the intensive care unit nor received intravascular vasodilators and inotropes.

This single-centre, prospective cohort study was approved by the Ethics Review Board of the Awaji Medical Center (approval no. 20–35). The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and all patients provided written informed consent to participate in the study.

Lung ultrasound

LUS examinations were performed at the end of the standard two-dimensional echocardiography with the patient in the supine position.[9,10] According to a recent consensus guideline, the ultrasound scanning of four sites in each hemithorax was obtained with the same probe used for the echocardiographic study, with the transducer orientation parallel to the ribs, at an imaging depth of 10–14 cm.[9,10] For each intercostal space, 3-s clips were recorded, and the number of B-lines was analysed in real time. Loops were recorded to maximize the number of B-lines for each zone by adjusting the gain to allow for optimal visualization of the pleural line and B-lines. The scanning lasted <3 min. The sum of B-lines recorded at each scanning site yielded a score ranging from 0 to 35, which denoted the extent of extravascular fluid in the lung. B-lines were defined as discrete, laser-like vertical hyperechoic reverberation artefacts arising from the pleural line, extending to the bottom of the screen without fading, and moving synchronously with lung sliding. All exams were performed by a single operator (J.I.), unaware of laboratory data, who took no part in the clinical management or in the final decision to discharge the patient. The intra- and inter-observer variability for the B-lines score were assessed by two independent observers in a set of 20 random cases and were 0.90 (0.77–0.96) and 0.94 (0.86–0.98), respectively.

Echocardiography

All echocardiographic studies were performed within 4 h of catheterization using a commercially available echocardiography system (Vivid S60N; GE Healthcare, Milwaukee, WI, USA) equipped with a 3.0-MHz transducer. Interpretation was blinded from haemodynamic data. All measurements were performed according to the American Society of Echocardiography.[11] If the patient was presenting with an irregular rhythm, such as atrial fibrillation, five consecutive cycles and the average of these five E-waves and e′ were registered.

Haemodynamic data

RHC was performed using 6-Fr fluid-filled balloon-tipped catheters. After calibration with the zero point at the midthoracic line, the catheters were inserted into the pulmonary artery, and waveforms of PCWP, main pulmonary artery pressure, and right atrial pressure were recorded at end of resting expiration. The mean pressures on the PCWP and right atrial pressure waveforms were measured. All measurements were obtained from three consecutive beats, and the averaged values were used for the final analysis.

Follow-up and endpoints

Patients were followed up after discharge by their primary care physician or our HF outpatient clinic. The pre-specified primary endpoint was the composite of cardiac death or re-hospitalization for the treatment of HF. Cardiac events were recorded 1 year after discharge. We defined cardiac death as any death due to an evident cardiac cause, any death related to congestive HF or myocardial infarction, or unwitnessed death. Re-hospitalization for the treatment of HF was defined as a stay in hospital for >24 h mainly as a result of signs and/or symptoms of worsening HF. Outcome data were collected by follow-up phone calls, contact with patients' primary care physician or cardiologist, and review of electronic medical records. All pre-specified primary endpoints were adjudicated by two cardiologists (blinded to the LUS data) who independently reviewed medical records of patients. The LUS results were concealed to the primary care physicians/cardiologist caring for the patient, and the frequency of follow-up visits was left to their discretion.

Statistical analysis

For the main analysis, patients were divided into two groups based on EF as described earlier. Continuous variables were expressed as mean values ± standard deviation or percentages for normal distribution. Non-normally distributed data are shown as the median and interquartile ranges. Between-group comparisons were examined for baseline characteristics using an unpaired *t*-test or a Mann–Whitney test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables, as appropriate. To evaluate the number of B-lines associated with each PCWP group, we compared each PCWP group against the lowest PCWP group, which serves as the reference value, by separately analysing patients with preserved and reduced EF. Two-way analysis of variance (ANOVA) was used to analyse interactions in the number of B-lines due to EF and PCWP groups. The cut-off values of the number of B-lines for identifying residual pulmonary congestion were estimated using the receiver operating characteristic (ROC) curve. The Kaplan–Meier curve was constructed to assess cardiovascular event-free survival during the follow-up period, and event rates were compared by means of the log-rank test. For both univariate and multivariate analyses, the associations of parameters with cardiovascular events were identified by the Cox proportional-hazards model. In the selection of univariate variables, all the established prognostic markers were selected as dependent variables regardless of the results of the group comparisons. Variables with a univariate value of $P < 0.10$ were incorporated into the stepwise selection, whereas age, estimated glomerular filtration rate (eGFR), and albumin were forced into the multivariate analysis regardless of their association on the univariate analysis. Moreover, competing risk proportional hazards regression analysis was applied according to the method of Fine and Gray for the end point re-hospitalization of HF with death as a competing risk. For all steps, a *P*-value of 0.05 was considered significant. MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium) was used for all statistical analyses.

Results

Patient characteristics

Of 116 patients enrolled, the mean age was 75.2 ± 10.3 years, and 43 (37%) were women. A history of hypertension (54%), dyslipidaemia

Table 1 Characteristics of the overall population and of different subgroups

	Total patients ($n = 116$)	EF ≥ 50% ($n = 61$)	EF < 50% ($n = 55$)	*P* value
Demographics				
Age (years)	75.2 ± 10.3	76.1 ± 10.6	74.2 ± 10.0	0.310
Female (%)	43 (37)	29 (48)	14 (25)	0.014
Body mass index (kg/m^2)	22.1 ± 3.8	22.4 ± 3.9	21.8 ± 3.6	0.393
Length of hospital stay (days)	18 ± 11	15 ± 10	20 ± 12	0.015
Days from RHC to discharge (days)	3 (1–7)	2 (1–5)	5 (1–8)	0.083
Medical history, *n* (%)				
Hypertension	63 (54)	40 (66)	23 (42)	0.010
Diabetes mellitus	33 (28)	19 (31)	14 (26)	0.499
Dyslipidaemia	46 (40)	23 (38)	23 (42)	0.653
Atrial fibrillation	37 (32)	15 (25)	22 (40)	0.077
Coronary artery disease	25 (22)	9 (15)	16 (29)	0.062
Previous CABG	16 (14)	10 (16)	6 (11)	0.394
Prior heart failure hospitalization	23 (20)	15 (24)	8 (15)	0.177
Medications, *n* (%)				
ACE-I/ARB	82 (70)	36 (59)	46 (84)	0.004
β-blocker	79 (68)	33 (54)	46 (84)	<0.001
Diuretic	78 (67)	38 (62)	40 (73)	0.234
Spironolactone	52 (45)	25 (41)	27 (49)	0.383
Laboratory results				
BNP (pg/mL)	717 ± 949	516 ± 876	943 ± 984	0.015
eGFR (mL/min/1.73 m^2)	48.0 ± 26.2	48.2 ± 28.2	47.8 ± 24.0	0.927
Haemoglobin (g/dL)	12.8 ± 1.9	12.3 ± 1.8	13.3 ± 1.9	0.003
Haematocrit (g/dL)	39.5 ± 5.8	37.9 ± 5.5	41.3 ± 5.8	0.002
Albumin (g/dL)	3.6 ± 0.5	3.6 ± 0.5	3.7 ± 0.4	0.082
Ultrasound parameters				
LV end-diastolic dimension (mm)	49 ± 9	44 ± 7	54 ± 8	<0.001
LV end-systolic dimension (mm)	37 ± 12	28 ± 6	46 ± 9	<0.001
LV ejection fraction (%)	49 ± 19	65 ± 8	32 ± 11	<0.001
LV mass index (g/m^2)	115 ± 34	108 ± 33	123 ± 33	0.014
Left atrial volume index (mL/m^2)	59 ± 23	57 ± 27	61 ± 18	0.303
E wave velocity (cm/s)	71 ± 31	75 ± 36	66 ± 24	0.166
E wave deceleration time (ms)	201 ± 74	226 ± 83	171 ± 49	<0.001
LV e′ velocity (cm/s)	4.4 ± 1.8	4.7 ± 2.1	4.1 ± 1.5	0.081
E/e′ ratio	18.5 ± 11.2	18.5 ± 12.0	18.6 ± 10.4	0.965
TAPSE (mm)	19 ± 4	20 ± 4	17 ± 4	<0.001
Lung ultrasound measures				
B-line range (median, IQR)	2 (0–5)	2 (0–6)	2 (0–5)	0.284
≥ 3 B-lines (*n*, %)	53 (46)	28 (46)	25 (45)	0.962
Haemodynamic data at time of right heart catheterization				
Systolic blood pressure (mmHg)	131 ± 28	138 ± 30	123 ± 24	0.005
Diastolic blood pressure (mmHg)	62 ± 13	61 ± 14	64 ± 13	0.201
Right atrial pressure (mmHg)	5.6 ± 4.9	5.6 ± 5.2	5.6 ± 4.6	0.942
PA systolic pressure (mmHg)	30.5 ± 12.2	29.1 ± 10.7	32.1 ± 13.6	0.190
PA diastolic pressure (mmHg)	14.6 ± 7.6	12.9 ± 7.0	16.4 ± 7.9	0.011
Mean PA pressure (mmHg)	21.1 ± 8.9	20.0 ± 7.8	22.8 ± 9.8	0.049

Continued

Table 1 *Continued*

	Total patients ($n = 116$)	EF ≥ 50% ($n = 61$)	EF < 50% ($n = 55$)	*P* value
PCWP (mmHg)	13.7 ± 7.8	12.3 ± 6.6	15.1 ± 8.7	0.053
Cardiac output (L/min)	4.1 ± 1.3	4.4 ± 1.3	3.7 ± 1.1	0.002
Cardiac index (L/min/m^2)	2.6 ± 0.7	2.9 ± 0.7	2.3 ± 0.6	<0.001
Pulmonary vascular resistance index	248 ± 161	217 ± 142	280 ± 173	0.042
Diastolic pulmonary gradient (mmHg)	2.0 ± 3.1	1.8 ± 3.1	2.3 ± 3.1	0.382
Clinical follow-up, *n*, (%)				
Cardiac death	3 (3)	2 (3)	1 (2)	1.000
Re-hospitalization for AHF	23 (20)	9 (15)	14 (25)	0.151
Composite endpoint	26 (22)	11 (18)	15 (27)	0.235

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or *n* (%).
AHF, acute heart failure; ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; E/e′, ratio of early diastolic transmitral filling velocity (E) and early diastolic mitral annular tissue velocity (e′); eGFR, estimated glomerular filtration rate; LV, left ventricular; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; TAPSE, tricuspid annual plane systolic excursion.

(40%), and atrial fibrillation (32%) were common. Overall, the sum of B-lines in eight zones ranged from 0 to 35 [median 2, interquartile range (IQR) 0–5]. The main characteristics of the study population are presented in *Table 1*. We divided the overall population into patients with reduced EF (n = 55) and preserved EF ($n = 61$). The number of B-lines was not significantly different in both reduced and preserved EF: median 2 (IQR 0–5) vs. 2 (IQR 0–6), $P = 0.284$. The percentage of patients with ≥3 B-lines was also not significantly different between the two groups. Patients with preserved EF were more likely to be female, have a history of hypertension and lower brain natriuretic peptide (BNP) levels at discharge. By contrast, eGFR and albumin levels did not show significant differences between the two groups. Although no significant differences were found in e′, E/e′, and left atrial volume index between the two groups, patients with reduced EF had higher LV mass index and LV end-diastolic and systolic dimensions. Patients with reduced EF tended to have higher pulmonary artery diastolic pressure, mean pulmonary artery pressure, pulmonary vascular resistance index, as well as lower cardiac output. No significant difference was noted in the PCWP between patients with preserved EF and reduced EF. During the 12-month follow-up period, a total of 26 events (22%) occurred: 3 (3%) cardiac deaths and 23 (20%) re-hospitalizations for acute HF. No difference was found in the cardiac event rates between the two groups.

Lung ultrasound findings and pulmonary capillary wedge pressure

As shown in *Figure 2A*, a clear transition was seen in the relationship between PCWP and the number of B-lines in the overall cohort. In particular, for PCWP in patients with preserved EF (*Figure 2B*), a clear pivot point at 19 mmHg was associated with a remarkable increase in the number of B-lines (from 0 in the 13–18 mmHg group to 8 in the 19–24 mmHg group). Above this threshold, there was a continuous increase in the number of B-lines. This pattern was similar for PCWP in patients with reduced EF (*Figure 2C*), where a clear threshold was higher than those in patients with preserved EF. In patients with reduced EF, the number of B-lines increased from 1 in the 19–24 mmHg group to 24 in the ≥25 mmHg group. Based on two-way ANOVA, significant interactions between reduced EF and preserved EF were observed in the higher PCWP group for the number of B-lines (P for interaction < 0.001). Residual pulmonary congestion at discharge was defined as the presence of B-lines above the pivot point at which the number of B-lines begins to increase following decompensation. The cut-off number of B-lines above a pivot point in patients with reduced EF (≥25 mmHg) was 6, with an area under the curve of 0.998, sensitivity of 100%, and specificity of 98%. Similarly, in patients with preserved EF and the overall cohort, the cut-off number of B-lines above a pivot point (≥19 mmHg) was also 6, with an area under the curve of 0.940 and 0.867, the sensitivity of 87% and 73%, and specificity of 94% and 95%. Thus, residual pulmonary congestion at discharge was defined as the presence of ≥6 B-lines in the overall cohort and each EF group. *Figure 3* compares patients as having a prior HF hospitalization or not. In both groups, a clear transition was seen in the relationship between PCWP and the number of B-lines, but there was no difference in the pivot point for PCWP.

Differences in lung and heart ultrasonography variables with and without residual pulmonary congestion

Table 2 compares the demographic data according to the presence of residual pulmonary congestion at discharge (B-lines ≥6). No significant difference was found in both groups concerning age, sex, and medications. The standard echocardiographic parameters of the LV filling pressure such as the E wave velocity and E/e′ of patients with residual pulmonary congestion were significantly higher and tricuspid annual plane systolic excursion (TAPSE) of patients with residual pulmonary congestion was significantly lower than for those without residual pulmonary congestion. Both groups showed similar values for LV diameter, LV EF, and LV mass index.

Prognostic effect of residual pulmonary congestion at discharge

The event-free survival curves showed significantly better outcomes for patients without residual pulmonary congestion than for those with residual pulmonary congestion in both the overall population and each EF group (*Figure 4*). Among the parameters, univariate analyses revealed that TAPSE, log BNP, and number of B-lines were significant predictors of cardiac events (*Table 3*). Even after adjustment for clinical variables, including age, eGFR, and albumin, the number of B-lines remained associated with the risk of cardiac events. The association between the

number of B-lines and outcomes was comparable for patients with reduced EF [univariate hazard ratio (HR) 1.051 (1.008–1.097), $P = 0.012$; multivariable HR 1.053 (1.011–1.096), $P = 0.013$] and preserved EF [univariate HR 1.101 (1.019–1.190), $P = 0.015$; multivariable HR 1.124 (1.033–1.224), $P = 0.007$]. Cox proportional hazards model was performed to assess the effect of B-line to predict time-to-first rehospitalization after discharge. Death was treated as a competing risk, and the model was adjusted for age, eGFR, and Albumin. The adjusted HR for the number of B-lines was 1.07 (95% confidence interval: 1.03–1.10).

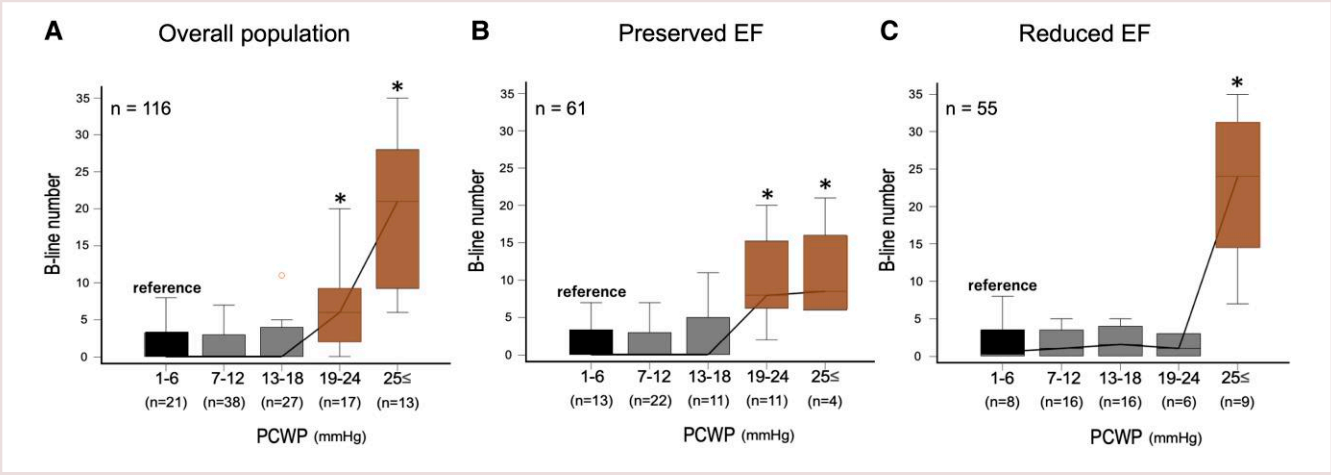


Figure 2 Association of B-line number with pulmonary capillary wedge pressure according to ejection fraction. The values of B-lines for each group were shown in *Figure 2*. (*A*). A clear transition was seen in the relationship between pulmonary capillary wedge pressure and the number of B-lines in overall cohort. (*B*). Association of pulmonary capillary wedge pressure with B-line number in the preserved ejection fraction group. The B-line number increased significantly at pulmonary capillary wedge pressure above the 19–24 mmHg group compared with the 1–6 mmHg group. (*C*). Association of pulmonary capillary wedge pressure with B-line number in the reduced ejection fraction group. The B-line number was significantly increased at pulmonary capillary wedge pressure above the 25 mmHg group compared with the 1–6 mmHg group. The significance for each B-line number is denoted by $*P < 0.05$ in comparison with the reference group.

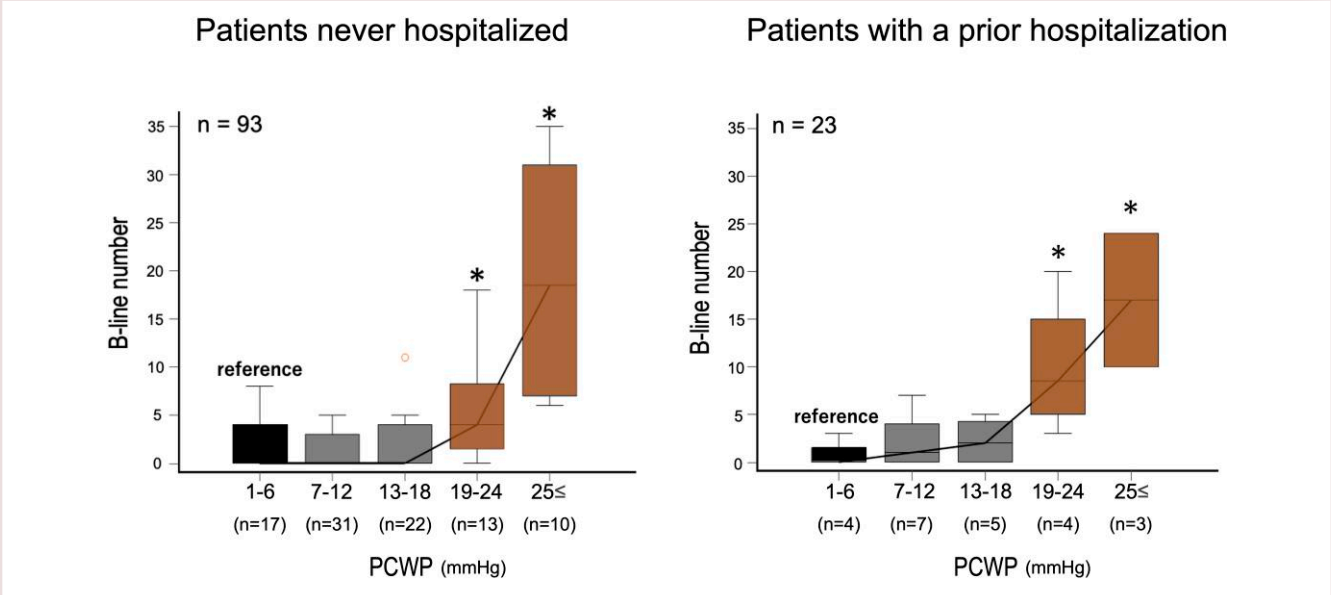


Figure 3 Association of B-line number with pulmonary capillary wedge pressure according to history of heart failure hospitalization. A clear transition was seen in the relationship between pulmonary capillary wedge pressure and the number of B-lines in patients with and without a history of heart failure hospitalization. Still, there was no difference in the pivot point for pulmonary capillary wedge pressure. The significance for each B-line number is denoted by $*P < 0.05$ in comparison with the reference group.

Table 2 Characteristics of patients with and without lung ultrasound-guided subclinical pulmonary congestion at discharge

	Residual pulmonary congestion		*P* value
	Yes (B-line ≥6, *n* = 26)	No (B-line <6, *n* = 90)	
Demographics			
Age (years)	75.9 ± 10.2	75.0 ± 10.3	0.682
Female (%)	8 (31)	35 (39)	0.452
Body mass index (kg/m^2)	22.4 ± 3.7	22.0 ± 3.8	0.624
Length of hospital stay (days)	20 ± 10	17 ± 11	0.265
Days from RHC to discharge (days)	3 (1–7)	3 (1–7)	0.814
Laboratory results			
BNP (pg/mL)	877 ± 1168	672 ± 881	0.342
eGFR (mL/min/1.73m^2)	40.1 ± 30.8	50.4 ± 24.4	0.080
Haemoglobin (g/dL)	12.0 ± 1.9	13.0 ± 1.9	0.019
Albumin (g/dL)	3.6 ± 0.4	3.6 ± 0.5	0.342
Medical history, *n* (%)			
Hypertension	13 (50)	50 (56)	0.618
Diabetes mellitus	13 (50)	20 (22)	0.006
Dyslipidaemia	12 (46)	34 (38)	0.444
Atrial fibrillation	11 (42)	26 (29)	0.198
Coronary artery disease	7 (27)	18 (20)	0.452
Previous CABG	6 (23)	10 (11)	0.121
Prior HF hospitalization	7 (27)	16 (18)	0.305
Medications, *n* (%)			
ACE-I/ARB	19 (73)	63 (70)	0.762
β-blocker	18 (69)	61 (68)	0.889
Diuretic	17 (65)	61 (68)	0.820
Spironolactone	9 (35)	43 (48)	0.237
Ultrasound parameters			
LV end-diastolic dimension (mm)	48 ± 8	49 ± 10	0.452
LV ejection fraction (%)	52 ± 18	49 ± 20	0.419
LV mass index (g/m^2)	107 ± 37	117 ± 33	0.179
Left atrium volume index (mL/m^2)	57 ± 18	59 ± 24	0.669
E wave velocity (cm/s)	88 ± 43	66 ± 25	0.001
E/e′ ratio	23.1 ± 12.8	17.2 ± 10.5	0.021
TAPSE	17 ± 5	20 ± 4	0.010

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or *n* (%). All abbreviations as in *Table 1*.

Discussion

To the best of our knowledge, this is the first clinical study showing the substantial diagnostic capacity of B-lines to identify elevated PCWP and prognosis according to EF categories. This study has two major findings. First, we found that PCWP revealed a clear pivot point at which the number of B-lines began to increase in the overall cohort and each EF category, and specific thresholds of the increased number of B-lines were identified at 19 and 25 mmHg for preserved EF and reduced EF, respectively. Second, an increase in the number of B-lines above the pivot point used to quantify residual pulmonary congestion at discharge was linked to significantly worse outcomes.

Lung congestion and haemodynamics

We demonstrated that the increased number of B-lines is associated with elevated PCWP by RHC. In addition, PCWP revealed distinctive pivot points of the increased number of B-lines by EF categories. These results were in contrast to those of previous studies as regard the two points. First, some authors advocate an absence of correlation between PCWP and number of B-lines. Platz *et al.*[12] reported a fair association of the number of B-lines with right-sided haemodynamic variables, whereas no significant association was identified with PCWP. A study of 73 patients with a critical illness during simultaneous PCWP monitoring also found that B-line assessment has limited usefulness for the prediction of haemodynamic congestion indicated by PCWP.[7] The discrepancy in results between these studies and the present study could be due to the possible compensation mechanism for lung congestion by pulmonary vascular changes. While LV filling pressures were used to confirm an association between the number of B-lines and lung congestion, a uniform relationship is not expected. Specifically, pulmonary congestion reflects the integrated effects of capillary wall permeability, hydrostatic and oncotic pressures,[13] and rates of the active clearance of water from the alveolar space via alveolar epithelial cells[14] and from the interstitial space via the lymphatic system.[15] When the pulmonary capillary pressure remains elevated chronically, the lungs become even more resistant to pulmonary congestion because the lymph vessels expand greatly, increasing their capability to carry fluid away from the interstitial spaces perhaps as much as 20 times.[16] Thus, variability in pulmonary congestion for a given increase in wedge pressure reflects individual adaptations to HF. Moreover, we found that in patients with reduced EF, the high PCWP group had a significantly increased number of B lines compared to those with preserved EF, suggesting that the lymphatic drainage reserve in the reduced EF may be considerably poorer than the preserved EF. PCWP may not always be strongly correlated to the number of B-lines because of the heterogeneous study cohorts. Consequently, our study strengthens the case of LUS for the correct assessment of haemodynamics by EF categories. Second, in some studies showing the association between PCWP and number of B-lines, the obtained relationship was a linear correlation. However, considering the process of how congestion develops, it is doubtful that their observed relationship can be applied in all cohorts. Guyton et al. showed in animal models that pulmonary congestion develops when the LAP increases beyond a critical threshold, which is enough to overcome colloid osmotic pressure in the perialveolar interstitium.[17] The present study agreed with reports by Guyton *et al.*,[17] and it is reasonable pathophysiologically to consider that there was an abrupt transition in the relationship between pulmonary congestion and PCWP.

Spectrum of pulmonary congestion in patients with preserved and reduced ejection fraction

A previous study has reported a good association between the number of B-lines and LV filling pressure but did not stratify the analysis by EF.[6] This study shows a different threshold of PCWP for the increasing number of B-lines between patients with preserved EF and reduced EF. Indeed, patients with reduced EF had a higher PCWP threshold, possibly suggesting the difference in the vulnerability for haemodynamic burden according to preserved and reduced EF. In our data, patients

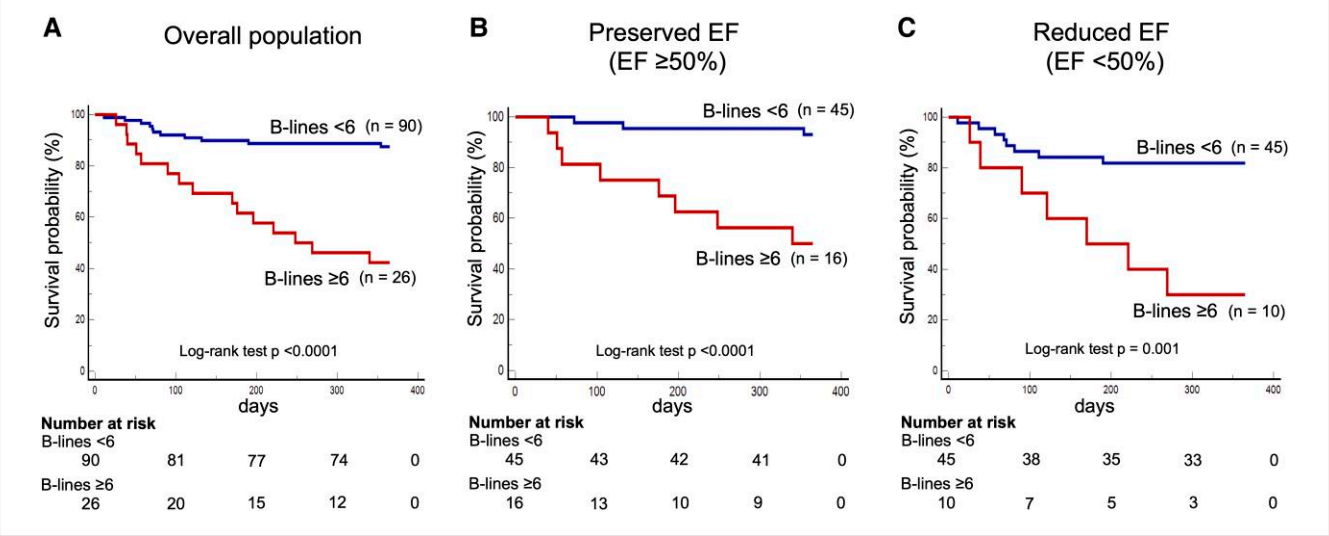


Figure 4 Kaplan–Meier analysis according to presence or absence of residual pulmonary congestion. Kaplan–Meier survival curves for the primary endpoint (cardiac death and hospitalization for acute heart failure) in the overall population (*A*), preserved ejection fraction group (*B*), and reduced group (*C*). Patients with B-lines ≥6 had significantly increased incidence of adverse events compared with patients with B-lines <6 in the overall population and two subgroups.

Table 3 Univariate and multivariate logistic regression analysis

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
E/e′	1.023	0.995–1.051	0.104			
E wave velocity	1.006	0.995–1.017	0.285			
TAPSE	0.903	0.827–0.986	0.024			
LAVI	1.004	0.989–1.019	0.644			
B-lines (per 1 increase)	1.070	1.033–1.108	0.002	1.093	1.045–1.143	0.001
Log BNP (per 1.0 log unit)	2.980	1.268–7.004	0.012			
History of coronary artery disease	1.478	0.621–3.518	0.377			

Adjusted by age, eGFR, albumin.
CI, confidential interval; HR, hazard ratio; LAVI, left atrial volume index; other abbreviations as in *Table 1*.

with reduced EF demonstrated little signs of pulmonary congestion despite having a high PCWP. The discrepancy in findings may be related to the presence or absence of adaptations that develop chronically in the lungs. While pulmonary congestion develops acutely with left atrial hypertension,[17] more sustained elevations may lead to structural remodelling in the lung vasculature, which dampens the elevation in pulmonary capillary pressure even as LAPs are high, while decreasing capillary permeability to reduce oedema formation.[18,19] In the present study, patients with preserved EF displayed a lower threshold of PCWP than those with reduced EF. This is because patients with preserved EF displayed normal or mild elevation in PCWP at rest, but marked elevations during exercise. With this ephemeral PCWP elevation, there may be less of a stimulus promoting capillary and vascular structural remodelling.[18,19,20]

Residual pulmonary congestion and prognosis

Previous studies have demonstrated that residual pulmonary congestion by LUS predicts adverse events in chronic HF.[21] However, a standardized definition for residual pulmonary congestion is not established yet. Previous authors have reported several cut-off numbers of B-lines with prognostic significance according to the LUS protocol performed and the clinical setting.[21,22] In many cases, they employed the area under the ROC curve to identify the best number to predict the adverse outcomes by applying the Youden criteria. In our study, as residual pulmonary congestion develops when LAP increases beyond a critical threshold, we employed the area under the ROC curve to identify the best number to predict above a pivot point of the increasing

number of B-lines. This finding is reasonable because residual pulmonary congestion should be derived from the degree of congestion. We proposed that ≥6 B-lines at discharge showed the best discriminating value for the event risk, and this interestingly coincides with the study of Bidaut *et al.*[21] in ambulatory patients, in which the cut-off value was derived from clinical outcomes.

Clinical implication

B-lines are an efficient marker of both elevated PCWP and residual pulmonary congestion. The absence of congestion on LUS might be a measure of treatment success associated with excellent outcomes and avoiding overtreatment, especially in patients with other causes of shortness of breath, such as chronic obstructive pulmonary disease. On the contrary, the persistence of residual pulmonary congestion might be a measure of inadequate treatment. Quantifying congestion by LUS might also help guide the intensity of diuretic use and decide on the frequency of follow-up appointments or determine when it might be appropriate to reassure patients and discharge them back to primary care.

Study limitations

This study has some limitations. First, this was a single-centre study with a moderate sample size; accordingly, additional studies with larger patient populations are needed to validate our findings. Second, the detection of B-lines does not necessarily imply a cardiogenic sign of pulmonary congestion. Pulmonary fibrosis and non-cardiogenic pulmonary oedema may result in the presence of B-lines. To avoid misinterpretation of this sign, the key is to contextualize B-lines in the clinical setting. When the 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 considered. Third, there is a potential for selection bias in favour of more complex clinical situations as RHC was performed in HF patients due to clinically indeterminate volume. Despite that, this study likely better reflects the utility of B-line in a 'real-world' HF population with a clinical indication for RHC. Finally, we cannot ascertain that more aggressive treatment to reduce the number of B-lines will improve outcomes. The prognostic value of B-lines should be tested in a larger, multi-centre, prospective trial to fully confirm its potential. We consider our study as hypothesis generating and acknowledge the need for validation in a prospective trial, especially with the calculated cut-off of six B-lines.

Conclusions

Quantifying B-lines, according to LVEF, provides pathophysiological insights into the haemodynamics and prognosis in patients with acute HF. PCWP revealed a clear pivot point at which the number of B-lines began to increase in each EF category, and specific thresholds of the increase in the number of B-lines were identified at 19 and 25 mmHg for preserved and reduced EF, respectively. In addition, residual pulmonary congestion at discharge, defined as the increase in the number of B-lines above the pivot point, was associated with worse outcomes in patients with acute HF.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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