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Research paper

Lung ultrasound in congestion assessment of patients with advanced heart failure referred for heart transplant: Correlations with right heart catheterization findings

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ARTICLE INFO

Keywords:

Heart failure
 Advanced heart failure
 Pulmonary congestion
 Lung ultrasound

ABSTRACT

Background: In advanced heart failure (HF), diagnostic performance of physical exam may be poor. Physical examination associated with lung ultrasound (LUS) may be an important tool to facilitate congestion screening. **Objective:** To evaluate performance of LUS for congestion screening in advanced HF referred for transplant, as compared to findings of right heart catheterization (RHC).

Methods: Prospective study of 23 subjects with advanced HF referred for RHC. LUS was performed in association with clinical congestion score (CCS), analogue-visual dyspnea scale (AVDS) and presence of crepitation/bendopnea prior to catheterization. Congestion was assessed by the number of B-lines in the LUS, and by findings of physical examination as well as by NT-proBNP serum values.

Results: Congestion was present in 43.4 % of patients by LUS (B-lines ≥ 15), as compared to 21.7 % by CCS (score greater than or equal to 5), 56.5 % by NT-proBNP (>1000 pg/ml), and 60.8 % by pulmonary capillary wedge pressure (PCWP) (>15 mm Hg). The number of B-lines was correlated to cardiac index (CI) ($\rho = -0.619$; $p = 0.002$), but not with PCWP ($\rho = 0.190$; $p = 0.386$), RAP ($\rho = -0.244$; $p = 0.262$), CCS ($\rho = 0.198$; $p = 0.36$) and neither with NT-proBNP ($\rho = 0.282$; $p = 0.193$). Otherwise, NT-proBNP was correlated with PCWP ($\rho = 0.636$; $p = 0.001$) and with CI ($\rho = -0.667$; $p = 0.001$).

Conclusions: In advanced HF patients referred for transplant, number of B-lines in LUS was not correlated with PCWP or RAP. Advanced HF patients seem to have increased filling pressures, but no interstitial pulmonary congestion that LUS could detect.

1. Background

Heart failure (HF) is a serious condition that affects >26 million people worldwide [1], but epidemiological data on advanced HF (stage D) are scarce [2]. Findings from the ADHERE (Acute Decompensated Heart Failure National Registry) suggest that 5 % of all HF patients have terminal illness with refractory symptoms despite optimized therapy, estimating that this entity affects 250,000 to 500,000 people in the United States [3].

The signs and symptoms of pulmonary congestion in HF are very important tools to guide the diagnosis [4]. The accuracy of the clinical diagnosis of HF can be improved by organizing the signs and symptoms

in an integrated and hierarchical way, making clinical assessment more consistent [5]. One of these tools is the clinical congestion score (CCS), which is a scoring system that assesses the presence or absence of congestive signs and symptoms [6]. However, to correctly identify congestion in patients with advanced HF can be at the same time challenging and crucial for their management. Biomarkers, imaging methods and invasive evaluation are used in order to improve the accuracy to detect congestion in this setting. NT-proBNP is a powerful neuro-hormonal predictor of prognosis in HF [7] and can be used to titrate therapy [8]. Right heart catheterization (RHC) is considered the gold-standard to evaluate congestion, although it is an invasive diagnostic method and, therefore, performed in selected cases [9].

Abbreviations: HF, heart failure; AHF, advanced heart failure; LUS, lung ultrasound.

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<https://doi.org/10.1016/j.ahjo.2023.100250>

Received 1 November 2022; Received in revised form 3 January 2023; Accepted 3 January 2023

Available online 5 January 2023

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In the last two decades, lung ultrasound (LUS) has been presented as an alternative for the detection of interstitial pulmonary edema. This method is simple to perform and has shown good accuracy for the diagnosis of pulmonary congestion [10]. When associated with clinical history, physical examination, and some complementary tests (among them echocardiogram and NT-proBNP), LUS can be even more accurate in differentiation with several pulmonary pathological conditions [11]. However, in patients with advanced HF referred for heart transplant in which pulmonary lymphatic drainage is chronically adapted, the accuracy of LUS to assess pulmonary congestion in comparison to hemodynamic data should be evaluated. We therefore evaluated the performance of LUS in comparison with right heart catheterization for congestion detection in patients with advanced HF referred for evaluation for heart transplantation.

2. Methods

2.1. Study design and population

This was a cross-sectional, prospective data collection study that evaluated the performance of LUS associated with the detailed physical examination in comparison to RHC to determine the presence of congestion in patients with advanced HF referred for evaluation for heart transplantation.

The study population consisted of patients followed up by the Heart Failure and Transplant Team of the Hospital de Clínicas de Porto Alegre. Inclusion criteria were: 1) age between 18 and 75 years; 2) HF with reduction ejection fraction functional class III or IV; 3) patients who are being referred for evaluation for heart transplantation by the HF and Transplant Team, or who are already on the transplant list, needing to repeat the RHC. Exclusion criteria were: 1) cardiogenic shock secondary to acute coronary syndrome; 2) patients under sedation and mechanical ventilation. The patients evaluated were both outpatient and inpatient, but the latter were stable and able to cooperate with the requested maneuvers of the physical examination. There were no restrictions on the etiology of HF. The protocol was reviewed and approved by the Human Research Ethics Committee from the study institution and all participants provided written informed consent.

2.2. Clinical assessment

All patients were evaluated by a trained professional who was blinded to the LUS data. Detailed anamnesis and physical examination were performed with objective and standardized survey of bendopnea and trepopnea and application of the CCS. The latter was calculated by summing up the values obtained in the clinical assessment of HF signs and symptoms, consisting of the following: pulmonary rales (0 to 4), central venous pressure elevation (0 to 4), peripheral edema (0 to 4), third heart sound (0 to 1) and orthopnea (0 to 4), ranging in total from 0 to 17. Patients with ≥ 5 points were considered as clinically congestive [6].

2.3. Natriuretic peptide analysis

NT-proBNP levels were determined using the electrochemiluminescence technique using a Cobas E602 device (Roche Diagnostics, Mannheim, Germany), following the specifications provided by the manufacturer. An NT-proBNP > 1000 pg/ml was considered a cutoff marker for presence of congestion.

2.4. Lung ultrasound

After the anamnesis and the detailed physical examination and immediately before the RHC, LUS was performed by a trained professional to assess the presence of B-lines in a sagittal orientation at 15 cm imaging depth using a convex transducer C60xi (2–5 MHz; Sonosite M-

Turbo). The examination was performed in four areas of each hemithorax with the patient in the supine or near-to-supine position, as recommended by a consensus guideline [12].

We analyzed the anterior and lateral hemithorax, along the parasternal border, hemiclavicular line, anterior axillary, medial axillary, from the second to the fifth intercostal space in the right hemithorax and from the second to the fourth intercostal space in the left hemithorax, performing the scanning scheme in eight zones. We analyzed each zone by longitudinal scans, moving probe over the thorax wall in a sliding movement. During this analysis, we noted the number of B-lines identified in each zone. Furthermore, the sum of the total number of B-lines resulted in the B-line score grouped into grades of severity: "mild" with 5–14 B-lines; "moderate" with 15–29 B-lines and "severe" with >30 B-line [13]. For some analyses, LUS data was divided in two groups of >15 B-lines or <15 B-lines based on previous work showing best congestion diagnostic accuracy with the cut-off point of 15 B-lines or more [14].

The examiner responsible for LUS was blinded to NT-proBNP levels and to the clinical variables as well as the attending physicians of these were also not aware of the ultrasound results until the end of the evaluation.

2.5. Hemodynamic assessments

Finally, all the individuals enrolled were submitted to the RHC according to the heart transplant assessment protocol. Interventional cardiologists who were unaware of the clinical evaluation results performed RHC.

2.6. Complementary examinations

The information about ventricular function and objective values in the cardiopulmonary test were obtained through the patients' charts, considering only the exams performed in the last 3 months.

2.7. Statistical analysis

Continuous variables are expressed as mean \pm SD or median (25th, 75th percentiles), as appropriate. Categorical variables are presented as counts and percentages. Univariate comparisons were made by chi-square or 2-sample Student *t*-test, as appropriate. Shapiro-Wilk was used to assess normal distribution of all continuous variables. The comparison of groups with and without congestion was performed by Student *t*-test for the quantitative variables and by the chi-square test for the categorical variables. Correlation test (Person or Spearman) was used to calculate the correlation between B-lines and hemodynamic and physical examination findings.

Considering that congestion is present in about half of patients with advanced HF, and that LUS has been shown to have a positive correlation with PCWP in the RHC with R around 0.6, 19 patients would be necessary to detect this correlation [14].

Statistics analysis was performed using the software IBM SPSS statistics version 21.0.0.

3. Results

3.1. Clinical characteristics

The main characteristics of the patients are listed in Table 1. Most subjects were white, female, 55 ± 9 years, and New York Heart Association (NYHA) functional class III, with a very low left ventricular ejection fraction. All subjects were in current use of beta-blocker and diuretics (furosemide), and around 95 % were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The mean daily dose of furosemide was 123 mg. Idiopathic and ischemic were the most common etiologies.

Table 1
Baseline characteristics of included patients.

	n = 23
Age, years	55 ± 8.7
Female	13 (56.5)
White	18 (78.3)
Body-mass index, kg/m ²	29.5 ± 5.5
Left ventricular ejection fraction, %	28.7 ± 8.2
Heart disease etiology	
Idiopathic	10 (43.5)
Post-ischemic	9 (39.1)
Valvar	2 (8.7)
Familial	1 (4.3)
Hypertension	1 (4.3)
NYHA functional class	
I	0
II	8 (34.7)
III	13 (56.5)
IV	2 (8.6)
Medical history	
Hypertension	14 (60.9)
Smoking	10 (43.5)
Diabetes	7 (30.4)
Hypothyroidism	7 (30.4)
Current medication	
Beta-blocker	23 (100)
ACE inhibitor or angiotensin II receptor blockers	22 (95.7)
Aldosterone antagonist	18 (78.3)
Digoxin	14 (60.9)
Aspirin	10 (43.5)
Thiazide	2 (8.7)
Furosemide	23 (100)
Nitrates	9 (39.1)
Hydralazine	7 (30.4)
Furosemide dose, mg	123 ± 52
Laboratory values	
Creatinine level, mg/dl	1.2 ± 0.5
Hemoglobin level, g/dl	13 ± 1.4
Clinical congestion on CCS, points	3.0 ± 1.9
Analogue-visual dyspnea scale, mm	44 ± 29
Cardiopulmonary test	
VO ₂ peak, ml/kg/min	15.7 ± 3.8
VO ₂ peak, %	61.6 ± 17.2
VE/VCO ₂ (slope)	43.2 ± 13.2
Hypotensive response, n (%)	2 (8.7)
Periodic ventilation, n (%)	7 (30.4)

Values are mean ± standard deviation or number (%).

NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; CCS = clinical congestion score; VO₂ = oxygen uptake; VE/VCO₂ slope = regression slope relating minute ventilation to carbon dioxide output.

3.2. Evaluation of congestion and hemodynamic parameters

Pulmonary and systemic congestion was measured through symptoms, physical examination findings (including CCS), NT-proBNP, LUS and hemodynamic findings. As shown in Fig. 1, 10 patients (43.7 %) had moderate to severe congestion, and the mean of B-lines was 16.3.

Table 2 describes all congestion parameters. Bendopnea was present in 60.9 % of patients, and CCS indicated congestion in 21,7 % of them. On hemodynamic evaluation, PCWP ≥ 18 mm Hg was present in 56.5 % of patients and RAP ≥ 10 mm Hg was present in 34.7 % (cut-off values reported in the literature) [15]. The mean of NT-proBNP was 1581 pg/ml, and 56.5 % had values ≥ 1000 pg/ml.

3.3. Hemodynamic findings and pulmonary congestion patterns, stratified by number of B-lines

When comparing patients with or without congestion as defined by B-lines in LUS, there was no difference in PCWP or RAP, as well as in clinical examination findings or NT-proBNP values (Table 3). Interestingly, patients with B-lines ≥15 had lower cardiac index (CI) than subjects with B-lines <15.

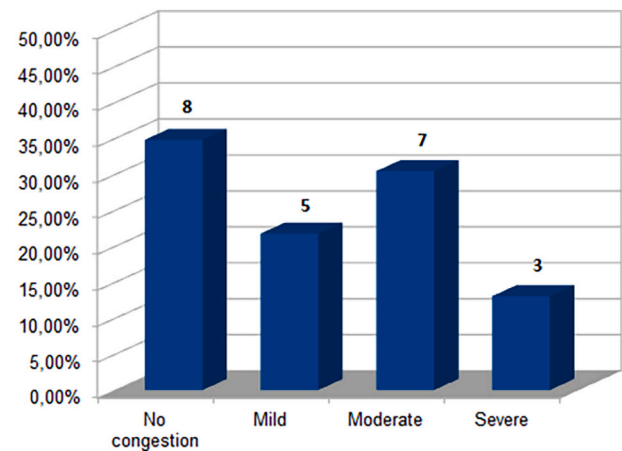


Fig. 1. Degree of congestion severity according to the number of B-lines on LUS: No congestion: <5 lines; mild: 5–14 lines; moderate: 15–30 lines; severe: >30 lines.

Table 2
Congestion parameters.

Signs and symptoms of congestion, no (%)	
Jugular distension	6 (26)
Hepatojugular reflux	9 (39.1)
Peripheral edema	10 (43.4)
Third heart sound	2 (8.7)
Rales	4 (17.3)
Orthopnea	20 (86.9)
Bendopnea	14 (60.9)
Trepopnea	10 (43.5)
No signs of congestion	2 (34.6)
CCS ≥ 5, no (%)	5 (21.7)
B-lines, no (%)	
<15	13 (56.3)
≥15	10 (43.7)
Hemodynamic findings	
PCWP, mm Hg	18.3 ± 8
RAP, mm Hg	7.7 ± 3.9
Cardiac index, l/min/m ²	2.3 ± 0.6
Transpulmonary gradient, mm Hg	9.8 ± 7.9
PVR, Woods units	2.6 ± 2.5
NT-proBNP, pg/ml	1581 (115–6468)

Values are no (%), mean ± SD or no (min–max).

CCS = clinical congestion score; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; PVR = pulmonary vascular resistance; NT-proBNP = amino-terminal portion of B-type natriuretic peptide.

3.4. Correlation among LUS, NT-proBNP, and hemodynamic findings

Fig. 2A shows there is no correlation between NT-proBNP and LUS-B-lines number. Fig. 2B and C shows that LUS B-lines number had no correlation with PCWP, but an inverse, significant correlation with CI, respectively. NT-proBNP had a positive correlation with PCWP and also a negative correlation with CI (Fig. 2D and E, respectively).

3.5. Comparison of several parameters to evaluate congestion

We further explored whether all parameters commonly used to access congestion would provide additive information. In a Venn diagram (Fig. 3) we depicted these findings and observed that 18 patients (78,3 %) showed signs of congestion by any of the three parameters included (LUS, NT-pro BNP and CCS). In this diagram we could also notice that only three patients had congestion detected by the three methods simultaneously. 13 subjects (56.5 %) had NT-proBNP>1000, but only 6 of them had clinical or ultrasonographic findings of congestion.

Table 3

Hemodynamics findings and pulmonary congestion patterns according to the pattern of B-lines.

Characteristics	B-lines ≥ 15 (n = 10)	B-lines < 15 (n = 13)	p value
Hemodynamics findings			
RAP, mm Hg	6.5 (4; 9.75)	9 (5; 10.5)	0.769
sPAP, mm Hg	48 (29.5; 62.5)	34 (28; 56)	0.369
dPAP, mm Hg	21 (10.75; 31.25)	20 (12.5; 25)	0.584
mPAP, mm Hg	31 (16.25; 41.5)	28 (17.5; 35.5)	0.616
PCWP, mm Hg	19 (10.5; 28.5)	18 (12.5; 22)	0.686
Transpulmonary gradient, mm Hg	10 (2.75; 17.5)	7 (3.5; 10.5)	0.376
CI, l/min/m ²	1.95 (1.72; 2.18)	2.62 (2.15; 3.21)	0.02
PVR, woods unit	3 (0.57; 4.37)	1.6 (1.0; 2.42)	0.376
Physical examination findings			
CCS	3 (2; 5.5)	3 (1; 4)	0.923
AVDS	2.5 (1.0; 7.25)	5 (2.7; 7.5)	0.407
Bendopnea	4 (28.6)	10 (71.4)	0.079
Trepopnea	3 (30)	7 (70)	0.263
NT-proBNP	1090.5 (484.1; 3275)	1060 (339.9; 2118)	0.563

Values are median (25th; 75th) or n (%).

RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; CCS, Clinical Congestion Score; AVDS, Analogue-Visual Dyspnea Scale; NT-proBNP, amino-terminal portion of B-type natriuretic peptide.

4. Discussion

This study showed that in a group of patients with advanced HF referred for evaluation for heart transplantation, the number of B-lines was not correlated to PCWP or RAP in RHC, but it was inversely correlated to CI. Moreover, our findings showed that NT-proBNP was not correlated to the number of B-lines, but was correlated to PCWP and CI, demonstrating its direct relation both to high filling pressures and to the prognosis of HF.

In the 1990s, LUS was first proposed to detect acute pulmonary edema in critically ill patients [16]. However, it was only in 2004 that this test was used in combination with Doppler echocardiography to identify pulmonary congestion in patients with HF admitted to a cardiologic ward [17]. Thus, LUS has been incorporated into clinical practice as an important tool in the evaluation of pulmonary congestion in patients with HF, and its accuracy in this purpose has also been much studied in the last two decades, proving to be superior to physical examination and to radiography for the diagnosis of congestion [18].

LUS was also shown to add value to the natriuretic peptides (BNP and NT-proBNP) both for diagnosis and prognosis and for the treatment of patients with decompensated HF. According to an earlier study in a scenario of congestion assessment in outpatients, positive correlations between LUS data and natriuretic peptide levels were reported, showing that the cut-off point of 15 B-lines or more showed the best accuracy when the reference for HF decompensation was the combined approach of NT-proBNP >1000 pg/ml and/or E/e' greater than or equal to 15 [14]. Another author, using LUS in the emergency scenario, reported that bilaterally identifying multiple B-lines was a sensitive but not specific predictor of BNP elevation >500 pg/ml [19]. The latter was the first published study to show that the presence of B-lines correlated with higher levels of BNP.

In the present study, less than half of the patients showed B-lines ≥ 15 and only half of them showed elevated filling pressures. We also did not detect correlation between the number of B-lines and NT-proBNP values. Otherwise, NT-proBNP was correlated to PCWP and CI, and these findings are consistent with those of previous works, showing that natriuretic peptides identify hemodynamic congestion, a condition that precedes pulmonary congestion, which is identified by B-lines

[14,20,21]. Furthermore, according to literature, NT-proBNP is also a predictor of prognosis in HF [7], which is apparently poor in this sample.

There are few studies comparing the number of B-lines with invasive hemodynamic measures in patients with advanced HF. In the HF scenario, RHC is considered the best diagnostic method for congestion assessment compared to clinical assessment, LUS, NT-proBNP, and Doppler echocardiography, although only LUS assesses interstitial edema directly. However, routine RHC for the management of HF is not justified, due to a neutral impact on overall mortality and hospitalization, besides being an invasive test with an increased risk of related complications [9]. On the other hand, it becomes mandatory in patients undergoing cardiac transplantation to assess pulmonary pressures, CI and filling pressures. Chakko et al. studied 52 patients with advanced chronic HF referred for evaluation for heart transplantation in order to establish a relationship between findings of clinical history, physical examination, chest X-ray and PCWP, but at the time of the study, LUS was not yet available [22]. As well as in the Chakko study, which compared radiological findings to PCWP, we have found no correlation between LUS B lines <15 and PCWP values. On the other hand, we have demonstrated that the number of B-lines was inversely correlated to CI, which may represent the actual severity of HF in this sample. Chakko et al. study and ours, confirms the notion that in patients with advanced heart failure referred for heart transplant evaluation, the lymphatic drainage may be increased so that the alveoli remain dry, despite high PCWP, and radiographic pulmonary edema and LUS detectable edema are absent [22].

In another scenario, a study evaluated 20 pre and post cardiac surgery patients with LUS, chest X-ray, pulmonary artery catheterization and the pulse contour cardiac output (PiCCO) system [23]. Positive linear correlations were found between number of B-lines and PCWP and between number of B-lines and systolic pulmonary pressure determined by pulmonary artery catheterization, but no significant correlations were observed between B-lines and CI, the latter going against our finding that number of B-lines was inversely correlated to CI. In 2009, Lichtenstein et al. evaluated 102 patients hospitalized in intensive care units (ICUs), all under mechanical ventilation and submitted to pulmonary artery catheterization, as a way of correlating pulmonary congestion identified with LUS (through B-lines) and PCWP [24]. With the results obtained it was possible to further validate the concept that B-lines derive from the excess fluid along the interlobular septa caused by the elevation of PCWP, with consequent hydrostatic pulmonary edema. A recent study evaluated 73 critically ill patients (admitted to ICUs) and concluded that B-lines allow good prediction of pulmonary congestion, but are of limited utility for the prediction of hemodynamic congestion indicated by PCWP [25]. These studies evaluated the presence of congestion in a setting of critically ill patients and pre and post cardiac surgery patients, however, none of them specifically evaluated patients with pulmonary congestion secondary to advanced HF referred for pre-transplant assessment, except for one in whom LUS was not yet available.

Through the venn diagram we were able to understand the absence of a specific method to detect congestion, since only three patients showed congestion in all evaluated methods (CCS, NT-proBNP and LUS) and only four patients in all methods when hemodynamic, LUS and NT-proBNP parameters were evaluated together. From this analysis and the evaluation of data from literature, we realized that the correct identification of congestion requires the integration of several methods: complete clinical evaluation, pulmonary congestion investigation in an invasive or ultrasound way, assessment of hemodynamic congestion through PCWP and measurement of natriuretic peptides [20,26]. Discordance between clinical, ultrasonographic, and hemodynamic findings leads us to realize that perhaps the LUS may not have the same validity in this group, since these patients may present only hemodynamic congestion without pulmonary edema, as we demonstrated by the evidence of high filling pressure rates in our sample (65 % of patients showed PCWP ≥ 15). Additional studies using lung ultrasound in this

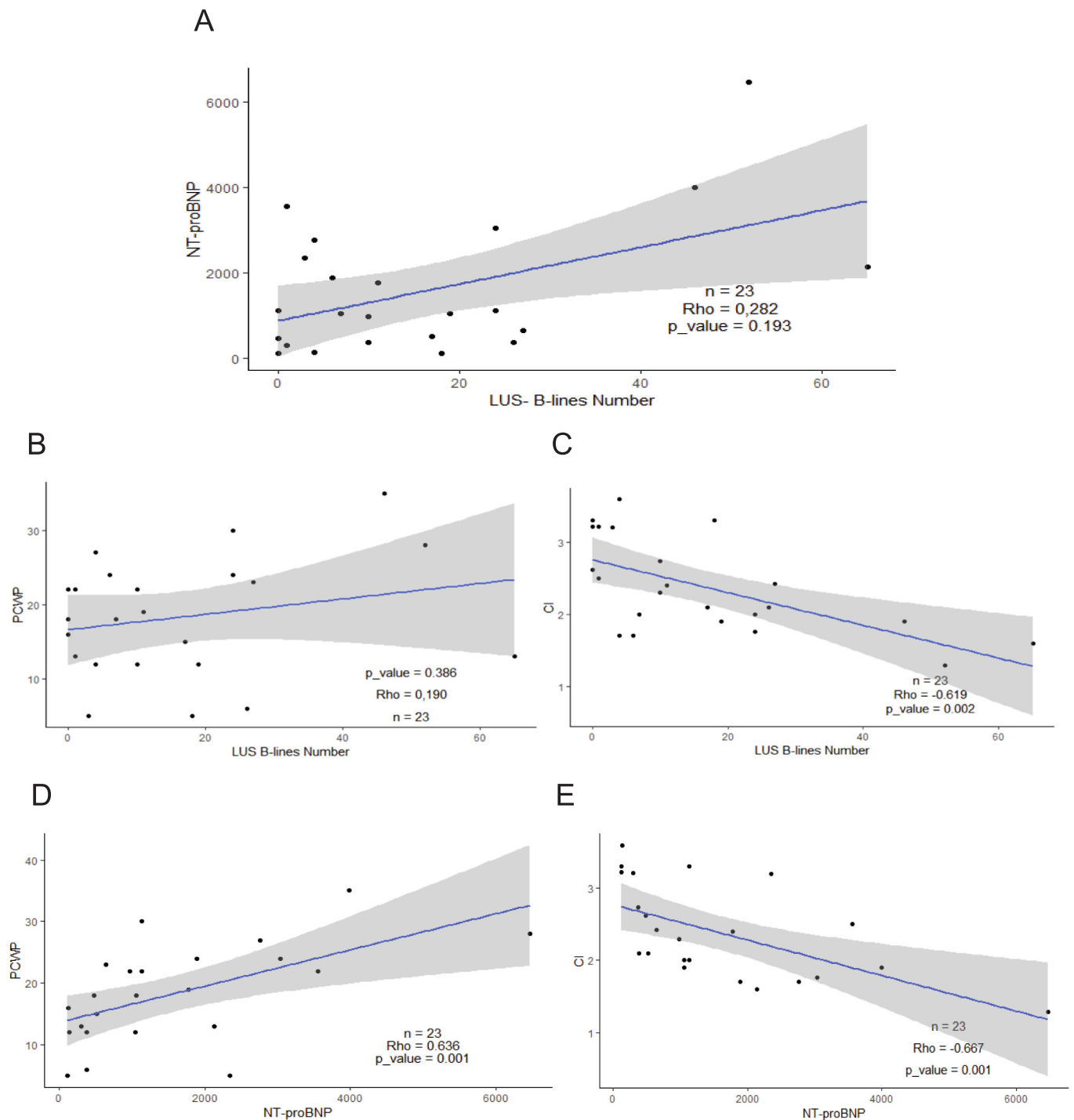


Fig. 2. Correlation between LUS B-lines number and NT-proBNP levels (A) and PCWP (B) and CI (C). Correlation between NT-proBNP and PCWP (D) and CI (E).

scenario are needed to confirm our findings.

4.1. Limitations of the study

Patients included in this study were a selected group of chronic HF patients referred for evaluation for cardiac transplantation. The findings cannot be applied to patients with acute HF, in whom the correlation between LUS and hemodynamic findings seems to be better. It is known that some patients with HF do not present clinical or radiographic signs of congestion, despite markedly high filling pressures and depressed cardiac output [22]. Although the small sample is a probable and

important limitation to demonstrate correlation between number of B-lines and PCWP, we could demonstrate inverse correlation between number of B-lines and CI, which might reflect that LUS could indicate the severity of the HF. Possibly, the evidence of congestion through B-lines is not as reliable in this group of patients or could be detected if we had a larger sample. However, even with this limitation, we were able to show positive correlation between NT-proBNP and PCWP, which is coincident with the literature.

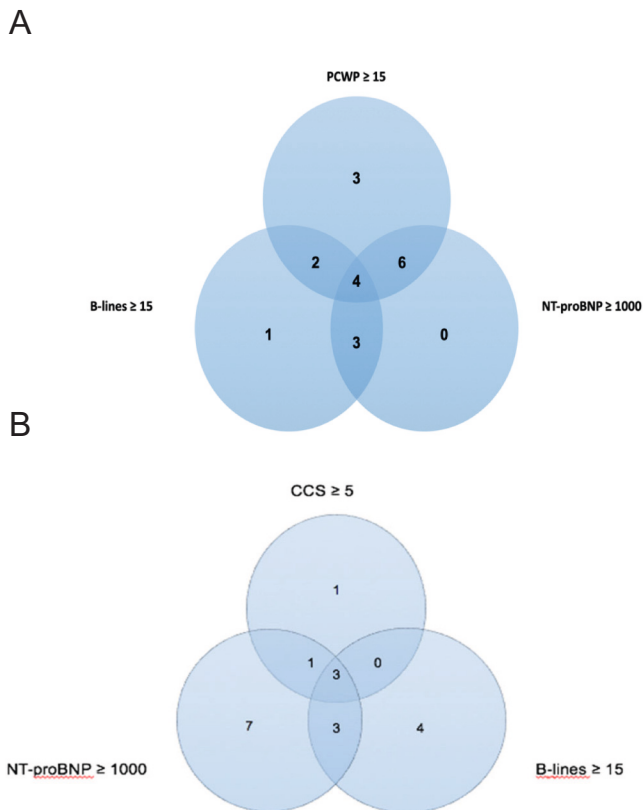


Fig. 3. Venn diagram demonstrating all patients with any positive parameter of congestion.

5. Conclusions

In this sample of patients with advanced HF referred for pre-transplant assessment, B-lines evaluated by LUS were not correlated with PCWP or RAP in RHC. Discordance between clinical, ultrasonographic, and hemodynamic findings leads us to realize that perhaps the LUS may not have the same performance in the group of patients as it has in acute HF patients. Advanced HF patients referred for pre-transplant assessment may present only hemodynamic congestion without pulmonary edema, as we demonstrated by the evidence of high filling pressure rates in our sample (65 % of patients showed PCWP ≥ 15). Additional studies using lung ultrasound in this scenario are needed to confirm our findings.

Funding sources

This study was partially funded by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Coordination for the Improvement of Higher Education Personnel; CAPES) - Brasil - Finance Code 001; and partially funded by Hospital de Clínicas de Porto Alegre (Fundo de Incentivo à Pesquisa e Eventos; FIPE/HCPA), No. 2017-0377.

Ethical statement

The protocol was reviewed and approved by the Human Research Ethics Committee from the study institution and all participants provided written informed consent.

CRedit authorship contribution statement

Fernanda Barth: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Luís Beck-da-Silva:**

Conceptualization, Writing – review & editing. **Eduarda Chiesa Ghisleni:** Methodology, Investigation. **Maurício Butzke:** Methodology, Investigation. **Fernando Luís Scolari:** Methodology, Investigation. **Bruno da Silva Matte:** Methodology, Investigation. **Andréia Biolo:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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