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## **Accuracy of several lung ultrasound methods for the diagnosis of acute heart failure in the emergency department: A multicenter prospective study**

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## **ABSTRACT**

### **Background**

Early appropriate diagnosis of acute heart failure (AHF) is recommended by international guidelines. This study assessed the value of several lung ultrasound (LUS) strategies for identifying AHF in the emergency department (ED).

### **Methods**

This prospective study, conducted in four EDs, included patients with diagnostic uncertainty based on initial clinical judgment. A clinical diagnosis score for AHF (Brest score) was quantified, followed by an extensive LUS examination performed according to the 4- (BLUE protocol), 6-, 8- and 28-point methods. The primary outcome was AHF discharge diagnosis adjudicated by 2 senior physicians blinded for LUS measurements. C-index was used to quantify discrimination.

### **Results**

Among the 117 included patients, AHF (N=69) was identified in 27.4%, 56.2%, 54.8% and 76.7% of patients with the 4-point (2 bilateral positive points), 6-point, 8-point ( $\geq 1$  bilateral positive point) and 28-point (B-line count  $\geq 30$ ) methods, respectively.

The C-index of the Brest score was 72.8 (65.3-80.3) whereas the C-index of the 4-, 6-, 8- and 28-point methods were respectively 63.7 (58.5-68.8), 72.4 (65.0-79.8), 74.0 (67.1-80.9) and 72.4 (63.9-80.9). The highest increase in C-index on top of the BREST score was observed with the 8-point method in the whole population (6.9 (1.6-12.2),  $p=0.010$ ) and in the population with intermediate Brest Score, followed by the 6-point method.

### **Conclusions**

In patients with diagnostic uncertainty, 6-point/8-point LUS method (using the 1 bilateral positive point threshold) improves AHF diagnosis accuracy on top of the BREST score.

**Clinical Trial Registration:** NCT03194243

## INTRODUCTION

Dyspnea is one of the most frequent causes of admission in the emergency department (ED)<sup>1</sup> and represents a significant diagnostic challenge for emergency physicians (EP). Acute heart failure (AHF) is one of the most common etiologies of acute dyspnea<sup>2</sup>. Guidelines recommend that diagnosis should be made as soon as possible in order to promptly begin appropriate early treatment<sup>3,4</sup>. Prognosis is related to initiation time of specific therapies<sup>5</sup>. In-hospital mortality is typically reported to be greater than 10%<sup>6</sup> and has remained stable in the last 30 years.

Diagnostic approaches include clinical evaluation, chest X-ray, biological tests and specific biomarkers. Nevertheless, diagnosis remains difficult, especially in ED patients, many of whom feature atypical clinical presentation due to several prior comorbidities and mixed/concomitant etiologies of acute dyspnea<sup>2</sup>. Recently, Basset et al. developed the Brest score for the diagnosis of AHF in ED patients<sup>7</sup>. However, this score classified 50% of cases in the intermediate probability group<sup>7</sup>, hence supporting the importance of developing and promoting “new tools”<sup>8</sup> which are complimentary to clinical scores in order to achieve quick diagnosis of AHF in patients admitted for acute dyspnea in the ED.

Ultrasound has gained widespread use in recent years and is now a highly valuable tool in the ED. Lung ultrasound (LUS) is a quick, reliable and easy-to-use exam that can improve the diagnostic accuracy for dyspneic patients<sup>9,10</sup>. Lichtenstein et al. furthermore highlighted its advantages in intensive care units for the evaluation of patients with respiratory distress (i.e. BLUE protocol)<sup>11</sup>. Several methods have been secondarily proposed to assess pulmonary congestion, using different analysis points, interpretation thresholds and various assessment conditions<sup>12-14</sup>. However, all of these studies focused on patients outside of the ED.

In light of the above, the present study aimed to evaluate and compare the diagnostic performance of currently available ultrasound protocols for pulmonary congestion assessment (i.e. the 4- (BLUE protocol), 6-, 8- and 28-point methods) in patients admitted for acute dyspnea in the ED. The study furthermore aimed to evaluate the diagnostic performance of these methods in patients with intermediate Brest scores (namely 4–8).

## **METHODS**

### **Study protocol and design**

This study is a part of the prospective PURPLE study (NCT 03194243, CNIL DR-2017-098). Patients admitted to the ED in four different hospitals including a university hospital over a 3-month period were included. All patients over 50 years old admitted for acute dyspnea for whom the treating physician had diagnostic uncertainty based on his/her initial clinical evaluation were included. Exclusion criteria consisted in traumatic dyspnea and systolic blood pressure < 70 mmHg.

For each patient, the Brest score was calculated<sup>7</sup> and a standardized LUS was performed. All clinical and ultrasound analysis data were collected by the EPs and entered in the Clinical Research Form of the study.

### **Ultrasound methods**

Ultrasounds were performed by ultrasound-certified EPs. Twenty-eight-point LUS were performed in all patients: for each point, a B-line grading from 0 to 10 was used. Using the data of this 28-point method, patients were able to be classified according to four published methods (Figure 1)<sup>11-13,15</sup>.

#### Four-point method (BLUE protocol)<sup>11</sup>

- Two scanning sites on each hemithorax:
  - o Second intercostal space, mid-clavicular line
  - o Fourth intercostal space, anterior axillary line
- A positive point was defined as the presence of at least three B-lines.
- A positive exam was defined, according to the seminal publication<sup>16</sup>, by the presence of at least three B-lines on each scanning site.

#### Six-point method<sup>12</sup>

- Three scanning sites on each hemithorax:
  - o Second intercostal space, mid-clavicular line
  - o Fourth intercostal space, anterior axillary line
  - o Fifth intercostal space, mid-axillary line
- A positive point was defined as the presence of at least three B-lines in a given scanning site.
- A positive exam was defined, according to the seminal publication<sup>12</sup>, by the presence of at least three B-lines on 2 scanning sites on each hemithorax.

#### Eight-point method<sup>13</sup>

- Four scanning sites on each hemithorax:
  - o Two anterior points, between the sternum and the anterior axillary line, comprised of 2 scanning sites
  - o Two lateral points between the anterior and the posterior axillary line, comprised of 2 scanning sites
- A positive point was defined as the presence of at least 3 B-lines in a given scanning site.

#### Twenty-eight-point method<sup>15,17</sup>

- Sixteen points on the right-side and 12 points on the left as described in Figure 1

- This exam was used both as a continuous count of overall B-lines as well as in the form of dichotomous variables ( $\geq 15$  or  $\geq 30$ ).

A positive point was defined as the presence of at least three B-lines in a given scanning site. The exams were then categorized according to the presence and number of bilateral positive point. We considered two definitions of positive exams: a positive exam was either defined as at least one positive zone bilaterally (i.e. at least one on the right lung and at least one on the left lung) or as at least two positive zones bilaterally. The presence of two positive points on each hemithorax, irrespectively of their locations (p.e. positive points on the superior part of the right thorax and on the inferior part of the left thorax), qualified for being considered as having “ $\geq 2$  bilateral positive points”.

### **Outcome**

Diagnostic outcome was the final diagnosis at discharge collected from the patients’ medical records. The final diagnosis of the hospital stay was adjudicated by 2 senior physicians blinded (Emergency Physician and Cardiologist) to the LUS measurements.

### **Sample size**

A random sample of 120 patients (60 with AHF and 60 without) was necessary, when the sample C-index was equal to 80%, to achieve a two-sided 95% confidence interval width of 16% (i.e. with a lower limit equal to 72% and a upper limit equal to 88%) by using the Hanley and McNeil's method. This setting also allows to have a confidence interval width of less than 0.18 for an C-index equal to 75% and a confidence interval width of 0.14 for an C-index of 0.85.

### **Statistical analysis**

All analyses were performed using R software (the R foundation for Statistical Computation). The two-tailed significance level was set at  $p < 0.05$ .

Baseline characteristics are described as mean  $\pm$  standard deviation or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Comparison of baseline characteristics according to AHF and non-AHF groups were carried out using the non-parametric Wilcoxon test for continuous variables and chi-square or Fisher’s exact tests for categorical variables.

Associations between LUS measurements and AHF were assessed using logistic regression. Odds-ratios (ORs) with 95% confidence intervals (CIs) are reported. For certain variables, quasi-complete separation was detected. ORs with CIs were therefore estimated using a logistic regression model with Firth’s penalized likelihood. This method provides a solution to the phenomenon of monotone likelihood which causes parameter estimates of the usual logistic regression model to diverge, with infinite standard errors.

Individual performance of LUS measurements for diagnosing AHF was assessed by the calculation of C-index which is very similar to the area under the curve (AUC) of the receiver operating characteristic (ROC) used on univariable data. In addition, the increase in C-index was calculated to assess the additional value of LUS measurements on top of the Brest score for the diagnosis of AHF.

## RESULTS

One hundred and seventeen patients were included, 62% of whom had a hospital discharge diagnosis of AHF (n=73) although only 54% (n=63) had an AHF diagnosis in the ED (3 patients with AHF at the ED had a non-AHF discharge diagnosis and 13 had an AHF diagnosis at discharge but not in the ED) (Table 1). The population was elderly (mean age =79.6 ± 11.8), mainly female (56%) and frequently had comorbidities. The majority of patients were hospitalized subsequent to ED admission (96%, n = 112), primarily in medical wards (n=68, 58%), while 25% (n=29) were admitted to intensive care units and only 13% (n=15) were admitted in a cardiology ward (Table 1). A majority of patients had an intermediate Brest score (64%, n=75) both in the AHF group (67%, n=49) and in the non-AHF group (59%, n=26).

### Diagnostic performances in the overall study population

In a first instance, the Brest score had a good diagnostic value when considered as a continuous variable (C-index=81.8, 95% CI [74.2-89.4]), which subsequently decreased when using BREST score categories (C-index=72.8, 95% CI [65.3-80.3]).

Among the LUS methods, the 4-point method (2 bilateral positive points) had the lowest C-index (63.7(95% CI [58.5 - 68.8]) whereas the other methods had very similar C-index (6-point method for  $\geq 1$  bilateral positive point, 72.4 (95% CI [65.0 - 79.8]); 8-point method for  $\geq 1$  bilateral positive point, 74.0 (95% CI [67.1 - 80.9]) and 28-point method for B-lines  $\geq 30$ , 72.4 (95% CI [63.9-80.9]).

The 6-point method ( $\geq 1$  bilateral positive point) had a specificity near 90% with a relatively low sensitivity (56.2%, 41.1-67.8%). The 8-point method ( $\geq 1$  bilateral positive point) had a higher specificity (93.2%, 81.3-98.6%) and similar sensitivity (54.8%, 42.7-66.5%). In contrast, the 28-point method had high sensitivity (B-lines  $\geq 15$ , 89.0 (79.5 - 95.1) and B-lines  $\geq 30$ , 76.7 (65.4 - 85.8)) but low specificity (B-lines  $\geq 15$ , 43.2 (28.3 - 59.0) and B-lines  $\geq 30$ , 68.2 (52.4 - 81.4)).

For the 6-point and 8-point methods, the use of the  $\geq 1$  bilateral positive point threshold yielded higher C-index as well as a better sensitivity (13 and 6%) and moderately lower specificity (- 4 and - 11%).

Each method provided significant added value to the Brest score as assessed by changes in C-index. However, the highest increase in C-index were observed for the 6-point method (6.7 (95% CI [0.9-12.5], p = 0.024) and the 8-point method (6.9 (95% CI [1.6-12.2], p = 0.010) (Figure 2 and Table 3).

### Diagnostic performances with intermediate Brest scores

In patients (n = 75) with intermediate Brest scores (4–8), the 4-point method (2 positive points bilaterally) had a C-index of 61.2 (95% CI [55.3 - 67.1]) and an added value to the Brest score of less than 5 as measured by an increase in C-index. In contrast, the 6-point and 8-point methods had a C-index greater than 70 when considering  $\geq 1$  positive point bilaterally (respectively 71.8 (95% CI [62.4 - 81.2]) and 72.7 (95% CI [63.9 - 81.5])).

Similarly, to the results in the overall population, the 6-point and 8-point methods ( $\geq 1$  bilateral positive point) had a specificity near 90% and a sensitivity near 50%. For the 8-point method, the use of the  $\geq 1$  bilateral positive point threshold yielded a higher C-index as well as better sensitivity (14% increase) and moderately lower specificity (4% decrease).

A significant increase in C-index over the BREST score was only identified for the 8-point method (Increase in C-index = 10.7 (95% CI [1.7-19.7],  $p = 0.020$ ). However, the increase in C-index with the 6-point method had a very similar point estimate (Increase in C-index = 8.9 (95% CI [-0.2-17.9],  $p = 0.054$ ). Importantly, the 28-point method had a lower increase in C-index of 6.8 (95% CI [-2.6-16.1]) which was not statistically significant ( $p = 0.16$ ) (Figure 2 and Table 3).

## DISCUSSION

In the present study, the 6-point and 8-point methods were found to be the most relevant LUS methods for establishing AHF diagnosis in the ED. This result was furthermore confirmed among patients with intermediate Brest scores. In addition, all ultrasound methods (particularly the 6-point and 8-point methods) provided a diagnostic added value on top of the Brest score, both in the whole population (Increase in C-index 8-point method = 6.9, 95% CI [1.6-12.2],  $p=0.010$ ) and in patients with intermediate Brest scores (Increase in C-index 8-point method = 10.7, 95% CI [1.7-19.7],  $p=0.020$ ). The main results and techniques used as summarized in Figure 2.

Importantly, we identified a somewhat lower C-index for the diagnosis of AHF than that previously reported in a recent metanalysis<sup>18</sup> in which AHF identified on LUS proved to be a diagnostic variable with discriminatory value (positive LR 7.4, 95% CI = 4.2 to 12.8; negative LR 0.16, 95% CI = 0.05 to 0.51) and for which the authors acknowledged the high statistical heterogeneity for these pooled estimates ( $I^2 = 78\%$  and  $I^2 = 99\%$ , respectively). However, contrary to the above studies, the present analysis was conducted in the specific setting of “real-life” patients admitted to the ED for whom the treating physician had *diagnostic uncertainty* based on his/her initial clinical evaluation. Our results can be synthesized as in figure 3.

### Brest Score and AHF

Brest score is a clinical score recently developed for AHF diagnosis, with three probability categories: low, intermediate and high. Our study confirmed its good diagnostic capacity when considered as a continuous value analysis, although was decreased (C-index 72.8, 95% CI [65.3–80.3]) when dichotomized as risk categories. Indeed, the Brest score efficiently rules out AHF diagnosis for scores  $< 4$  and affirms the diagnosis for scores  $> 9$ . However, for patients with an intermediate score (4–8), other complementary tools (biomarkers and/or LUS)<sup>9</sup> seemingly appear necessary to improve diagnostic accuracy<sup>19</sup>.

### Lung ultrasound methods using 6 scanning sites or more

LUS is recommended by international guidelines<sup>4</sup>. It is reliable, reproducible, quick and easy-to-use, which prompted its increasing use in patients with acute dyspnea. Its diagnostic performance has been reported to be excellent in a large meta-analysis (sensitivity: 94.1%, 95% CI [81.3–98.3], specificity: 92.4%, 95% CI [84.2–96.4] for AHF diagnosis)<sup>20</sup>. In addition, Zanobetti et al. reported that the diagnostic accuracy of LUS is better for AHF than for other etiologies of acute dyspnea<sup>21</sup> and that 30 minutes of training is sufficient to provide a good expertise<sup>22,23</sup>. However, in these previous studies, a number of LUS methods were used, such that the indicated method in the aforementioned meta-analysis is unclear. Moreover, a head-to-head comparison of each



available method for AHF diagnosis was not conducted. In addition, previous studies typically did not specify if the clinical setting of the patients required the use of LUS. Indeed, it is likely that in patients with very unequivocal clinical pictures, the added value of LUS is moderate. Importantly, to the best of our knowledge, its added value on top of the Brest score, a recent and powerful clinical diagnostic tool, has not been previously assessed.

In the present study, the 6-point and 8-point methods were the most discriminative LUS tools for identifying AHF in elderly (mean age 79.6) patients in whom the ED physicians perceived diagnostic uncertainty. Importantly, in our study, uncertainty was purely physician-driven; This explains why only 2/3 of the population would qualify for uncertainty (i.e. intermediate risk of HF) using the Brest score. In this “real-life” clinical setting, the 6-point or 8-point method significantly increased the discrimination for AHF diagnosis on top of the Brest score (Table 3) along with an isolated C-index (i.e. not taking into account clinical features) greater than 70. In addition, the diagnostic performance of LUS was maintained in patients with intermediate BREST scores, which further strengthens the ability of LUS to correctly identify AHF in patients with the most clinical uncertainty.

While the present study reports less evocative C-index than in previous reports<sup>18,24</sup>, it should be emphasized that only patients with true diagnostic uncertainty were considered in the present analysis, which could have decreased the diagnostic performance of LUS. In this particular setting, an isolated C-index of 70% or greater together with a significant increase of 6 to 10% in C-index suggest a strong and clinically relevant improvement in diagnostic accuracy for AHF in actual clinical settings focusing on the most difficult cases. These results further confirm the strong diagnostic ability of LUS.

#### **Lung ultrasound methods using 4 scanning sites**

The BLUE protocol technique, developed in an intensive care unit by Lichtenstein et al, is the most widely used and taught LUS technique<sup>11</sup>. However, in the present study, the diagnostic ability of a 4-point LUS technique for diagnosing AHF was somewhat less than that of other methods which rely on a greater number of scanning points (6 to 28). The BLUE protocol, relying on 4 anterior scanning sites to identify AHF, may be less effective in ED patients due to the lower severity of patients with dyspnea (and subsequent pulmonary features/lesions) admitted in the ED comparatively to patients admitted in intensive care units. Patients admitted in the ED are likely to exhibit less extensive pulmonary abnormalities than patients admitted in the ICU and may therefore benefit from LUS techniques involving 6 scanning sites or more.

#### **Perspectives**

LUS is a new helpful tool in the ED as well as in the pre-hospital setting. While echocardiography can assess cardiac dysfunction and filling pressures, the latter requires trained practitioners and can be difficult to perform in the setting of acute dyspnea. Our results show that LUS using a 6- or 8-point method, as in other reports<sup>25</sup>, improves the diagnostic accuracy of AHF in the ED. Notwithstanding, while the specificity of LUS using either a 6-point or 8-point method herein was similar to other reports, the sensitivity documented in our study was only about 50%, which is much lower than the 90.5% (87.4- 93) reported by Pivetta et al.<sup>26</sup> However, this previous study was performed by an ED group with extensive experience in LUS, which may have resulted in its higher diagnostic performance. In addition, the differences in diagnostic performance could also be partly related to the absence of identification of lung sliding and condensation in the present study. In addition, LUS

alone may not be sufficient to fully identify AHF in patients with high diagnostic uncertainty. Nazerian et al. showed a good diagnostic performance of a simplified echocardiography performed by emergency physicians for AHF diagnosis<sup>27</sup>. Other studies also suggest that using the size and collapsibility of the inferior vena cava, or other markers can improve diagnostic accuracy in dyspneic patients<sup>28,29,30</sup>. Furthermore, Laursen et al. showed that an algorithm using cardiac, vascular and lung ultrasound resulted in an improved early diagnostic accuracy<sup>31</sup>. Thus, the use of an ultrasound-based algorithm rather than a LUS-centered algorithm may be needed to further improve AHF diagnosis accuracy. Importantly, studies advocating a multimodal ultrasound approach for improving early diagnostic accuracy<sup>31</sup> do not provide a precise algorithm. We believe that such an algorithm should be validated. It is the hope that the EMERALD-US study will be able to provide reliable evidence regarding an integrated ultrasound algorithm in the field of acute dyspnea admitted in the ED (NCT: NCT03691857).

## LIMITATIONS

The present prospective multicenter study has certain limitations. First, various ultrasound devices were used as well as various patient positions<sup>32</sup> (it is however likely that most patients were in semi-seated position) which could have resulted in some heterogeneity. However, given that LUS is likely to occupy an increasing place in emergency settings, including with various ultrasound devices, in various positions, pragmatic studies such as the present study more aptly reflect this intrinsic heterogeneity.

Uncertainty was an inclusion criteria but was purely physician-driven. This could have introduced some heterogeneity in the data as the perception of uncertain situations might vary across physicians.

The adjudicated diagnosis used for the current analysis was based on the hospitalization report extracted from the medical record. This diagnosis could have been influenced by the LUS results. However, the final diagnosis was adjudicated by 2 senior physicians blinded to the LUS measurements.

## CONCLUSION

The present study suggests that LUS using the 8-point/6-point method improves AHF diagnosis on top of the BREST score, especially in patients with intermediate BREST scores. Validated algorithms centered not only on the positive diagnosis of AHF, but also on the competing diagnosis of dyspnea (e.g. pneumonia) using LUS, vascular ultrasound and simplified echocardiography could further improve LUS diagnostic accuracy in the ED.

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	<b>Population (n=117)</b>		<b>No-AHF (n=44)</b>		<b>AHF (n=73)</b>		<b>p</b>
	<b>N</b>	<b>Mean ± SD n (%)</b>	<b>N</b>	<b>Mean ± SD n (%)</b>	<b>N</b>	<b>Mean ± DS n (%)</b>	
<b>Clinical Characteristics</b>							
Age (years)	117	79.6 ± 11.8	44	77.0 ± 13.6	73	81.2 ± 10.3	0.088

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Sex (men)	117	52 (44 %)	44	16 (36 %)	73	36 (49 %)	0.19
Chronic heart failure	117	19 (16 %)	44	3 (7 %)	73	16 (22 %)	0.039
Chronic pulmonary disease	117	38 (33 %)	44	18 (41 %)	73	20 (27 %)	0.16
SBP (mmHg)	117	137.1 ± 25.0	44	131.8 ± 21.2	73	140.3 ± 26.7	0.11
DBP (mmHg)	117	73.1 ± 15.5	44	70.6 ± 12.7	73	74.6 ± 16.9	0.18
Heart rate (bpm)	117	93.6 ± 24.6	44	95.8 ± 21.2	73	92.2 ± 26.5	0.25
Respiratory rate (bpm)	106	27.3 ± 8.6	39	28.6 ± 10.6	67	26.6 ± 7.3	0.54
SpO <sub>2</sub> (%)	117	93.5 ± 5.8	44	91.7 ± 8.2	73	94.6 ± 3.4	0.045
<b>NYHA score</b>	117						
NYHA III		51 (44 %)		20 (45 %)		31 (42 %)	
NYHA IV		59 (50 %)		22 (50 %)		37 (50 %)	
Jugular venous distension	117	19 (16 %)	44	1 (2 %)	73	18 (24 %)	0.0001
Hepato-jugular reflux	117	19 (16 %)	44	3 (7%)	73	16 (22 %)	0.039
Peripheral edema	117	64 (54 %)	44	18 (41%)	73	46 (63 %)	0.026
Lungs auscultation	117		44		73		<0.0001
Crackles		52 (44 %)		4 (9 %)		48 (66 %)	
Focal auscultatory findings		18 (15 %)		12 (27 %)		6 (8 %)	
Rhonchi		23 (20 %)		13 (29.5 %)		10 (13 %)	
Wheezing		8 (7 %)		7 (16 %)		1 (1 %)	
<b>Biology</b>							
eGFR MDRD (mL/min/1.73m <sup>2</sup> )	116	60.1 ± 27.5	44	71.6 ± 26.7	72	53.1 ± 25.7	0.0004
Natremia (mmol/L)	115	135.9 ± 5.6	44	135.7 ± 5.9	71	136.0 ± 5.4	0.81
BNP (pg/mL)	86	946 ± 1017	27	274 ± 281	59	1254 ± 1083	<0.0001
NT-proBNP (pg/mL)	15	2815 ± 3741	5	575 ± 448	10	3936 ± 4183	0.13
Hemoglobin (g/dL)	117	12.4 ± 2.0	44	13.2 ± 1.9	73	11.9 ± 2.0	0.0004
Hematocrit (%)	113	38.6 ± 5.8	43	40.8 ± 5.4	70	37.2 ± 5.6	0.0008
<b>Radiology</b>							
Cardiomegaly	117	68 (58 %)	44	13 (29 %)	73	55 (75 %)	<0.0001
Pulmonary congestion	117	59 (50 %)	44	7 (16 %)	73	52 (71 %)	<0.0001
Pleural effusion	117	35 (30 %)	44	12 (27 %)	73	23 (3 %)	0.68
Pulmonary infection	117	39 (33 %)	44	22 (50 %)	73	17 (23 %)	0.004
<b>Brest score</b>	117		44		73		
Continuous		5.9 ± 2.7		4.1 ± 2.0		7.0 ± 2.4	<0.0001
0-3		22 (19 %)		17 (38 %)		5 (7 %)	<0.0001
Categorized 4-8		75 (64 %)		26 (59 %)		49 (67 %)	
9-15		20 (17 %)		1 (2 %)		19 (26 %)	
<b>Diagnosis: AHF</b>							
Emergency Department	117	63 (54 %)	44	3 (7 %)	73	60 (82 %)	<0.0001
At hospitalization discharge	117	73 (62 %)	44	0 (0 %)	73	73 (100 %)	<0.0001
<b>Lung Ultrasound</b>							
Ultrasound quality	115	7.1 ± 1.6	43	6.9 ± 1.7	72	7.3 ± 1.5	0.21
<b>4- point method</b>	117		44		73		
B-line count		8.4 ± 8.9		3.6 ± 3.9		11.3 ± 9.8	<0.0001
≥1 bilateral positive point		40 (34 %)		5 (11 %)		35 (47 %)	<0.0001
≥2 bilateral positive points		20 (17 %)		0 (0 %)		20 (27 %)	<0.0001
<b>6-point method</b>	117		44		73		
B-line count		12.6 ± 12.8		5.2 ± 5.4		17.0 ± 13.8	<0.0001
≥1 bilateral positive point		46 (39 %)		5 (11 %)		41 (56 %)	<0.0001
≥2 bilateral positive points		29 (25%)		0 (0 %)		29 (39 %)	<0.0001
<b>8-point method (superomedial point)</b>	117		44		73		
B-line count		15.5 ± 16.6		5.3 ± 5.8		21.6 ± 18.0	<0.0001
≥1 bilateral positive point		43 (37 %)		3 (7 %)		40 (54 %)	<0.0001
≥2 bilateral positive points		31 (26 %)		1 (2 %)		30 (41 %)	<0.0001
<b>28-point method</b>	117		44		73		
B-line count		57.3 ± 58.6		22.0 ± 21.3		78.5 ± 63.6	<0.0001
B-lines ≥ 15		90 (77 %)		25 (57 %)		65 (89 %)	<0.0001
B-lines ≥ 30		70 (60 %)		14 (32 %)		56 (78 %)	<0.0001
<b>Hospitalization</b>	117	112 (95 %)	44	40 (91 %)	73	72 (98 %)	0.009
Medical Ward		68 (58 %)		32 (73 %)		36 (49 %)	
Intensive Care Unit		29 (24 %)		7 (16 %)		22 (30 %)	
Cardiology ward		15 (12 %)		1 (2 %)		14 (19 %)	

Table 1: Characteristics of the study population

SBP/DPB: systolic/diastolic blood pressure; SpO<sub>2</sub>: blood oxygen saturation; NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; MDRD: Modification of diet in renal disease; BNP: Brain natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; AHF; acute heart failure

	Univariable association		Adjusted on Brest score (continuous)	
	OR (CI 95%)	p	OR (CI 95%)	p
<b>4-point method</b>				
B-line count	1.20 (1.09 - 1.31)	<0.0001	1.22 (1.10 - 1.36)	0.0003
≥1 bilateral positive point	7.18 (2.54 - 20.29)	0.0002	7.49 (2.29 - 24.53)	0.0009
≥2 bilateral positive points	34.10 (4.46 - 4381.20)	<0.0001	23.96 (2.57 - 3248.84)	0.002
<b>6-point method</b>				
B-line count	1.14 (1.07 - 1.22)		1.17 (1.08 - 1.26)	0.0002
≥1 bilateral positive point	9.99 (3.53 - 28.26)		12.08 (3.51 - 41.53)	<0.0001
≥2 bilateral positive points	59.00 (7.84 - 7559.37)	<0.0001	51.15 (6.08 - 6740.40)	<0.0001
<b>8-point method</b>				
B-line count	1.15 (1.08 - 1.23)	<0.0001	1.15 (1.07 - 1.24)	<0.0001
≥1 bilateral positive point	16.57 (4.70 - 58.38)	<0.0001	15.68 (3.87 - 63.48)	0.0001
≥2 bilateral positive points	30.00 (3.91 - 229.96)	0.001	38.75 (4.19 - 358.43)	0.001

*Table 2: Association between the different lung ultrasound techniques and AHF diagnosis (in univariable analysis and after adjustment on the Brest score)*

	Performance		Diagnostic value of LUS techniques in addition to the Brest score				
	C-index value of the considered parameter (CI 95 %)	Specificity (CI 95%)	Sensitivity (CI 95%)	C-index value of Brest Score and considered parameter (CI 95 %)	P	C-index increase in addition to the Brest score (CI 95 %)	p
<b>Overall Population</b>							
<b>Brest score</b>							
Continuous	81.8 (74.2 - 89.4)						
Categories (0-3, 4-8, 9-15)	72.8 (65.3 - 80.3)						
<b>4- point method</b>							
B-line count	76.7 (68.2 - 85.1)			88.1 (82.0 to 94.1)	<0.0001	6.3 (1.0 to 11.6)	0.020
≥1 bilateral positive point	68.3 (60.8 - 75.8)	88.6 (75.4 - 96.2)	47.9 (36.1 - 60.0)	86.6 (80.1 to 93.1)	<0.0001	4.8 (-0.1 to 9.6)	0.053
≥2 bilateral positive points	63.7 (58.5 - 68.8)	100.0 (92.0 - 100.0)	27.4 (17.6 - 39.1)	85.3 (78.6 to 91.9)	<0.0001	3.5 (0.4 to 6.5)	0.026
<b>6-point method</b>							
B-line count	78.2 (70.1 - 86.4)			89.1 (83.3 to 94.8)	<0.0001	7.3 (1.7 to 12.8)	0.010
≥1 bilateral positive point	72.4 (65.0 - 79.8)	88.6 (75.4 - 96.2)	56.2 (44.1 - 67.8)	88.5 (82.5 to 94.5)	<0.0001	6.7 (0.9 to 12.5)	0.024
≥2 bilateral positive points	69.9 (64.2 - 75.5)	100.0 (92.0 - 100.0)	39.7 (28.5 - 51.9)	88.4 (82.6 to 94.2)	<0.0001	6.6 (2.3 to 10.8)	0.002
<b>8-point method</b>							
B-line count	81.8 (74.3 - 89.3)			90.6 (85.2 to 96.0)	<0.0001	8.8 (2.8 to 14.7)	0.004
≥1 bilateral positive point	74.0 (67.1 - 80.9)	93.2 (81.3 - 98.6)	54.8 (42.7 - 66.5)	88.7 (82.9 to 94.6)	<0.0001	6.9 (1.6 to 12.2)	0.010
≥2 bilateral positive points	69.4 (63.3 - 75.5)	97.7 (88.0 - 99.9)	41.1 (29.7 - 53.2)	88.7 (82.8 to 94.7)	<0.0001	6.9 (1.7 to 12.1)	0.009
<b>Patients with intermediate Brest score</b>							
<b>Brest score</b>							
Continuous	71.7 (59.9 - 83.6)			N/A			
<b>4-point method</b>							
B-line count	75.9 (65.0 - 86.8)			81.6 (71.7 to 91.5)	<0.0001	9.9 (0.1 to 19.6)	0.047
≥1 bilateral positive point	68.7 (59.3 - 78.2)	88.5 (69.8 - 97.6)	49.0 (34.4 - 63.7)	78.5 (67.8 to 89.2)	<0.0001	6.8 (-2.1 to 15.7)	0.13
≥2 bilateral positive points	61.2 (55.3 - 67.1)	100.0 (86.8 - 100.0)	22.4 (11.8 - 36.6)	76.5 (65.9 to 87.1)	<0.0001	4.8 (0.3 to 9.3)	0.037
<b>6-point method</b>							
B-line count	78.4 (68.0 - 88.7)			83.4 (74.0 to 92.7)	<0.0001	11.6 (1.9 to 21.4)	0.020
≥1 bilateral positive point	71.8 (62.4 - 81.2)	88.5 (69.8 - 97.6)	49.0 (34.4 - 63.7)	80.6 (70.4 to 90.8)	<0.0001	8.9 (-0.2 to 17.9)	0.054
≥2 bilateral positive points	69.4 (62.5 - 76.3)	100.0 (86.8 - 100.0)	22.4 (11.8 - 36.6)	81.4 (71.9 to 90.8)	<0.0001	9.6 (3.1 to 16.1)	0.004
<b>8-point method</b>							

B-line count	81.0 (71.2 - 90.8)			85.4 (76.4 to 94.3)	<0.0001	13.6 (3.4 to 23.8)	0.009
≥1 bilateral positive point	72.7 (63.9 - 81.5)	92.3 (74.9 - 99.1)	53.1 (38.3 - 67.5)	82.4 (72.6 to 92.2)	<0.0001	10.7 (1.7 to 19.7)	0.020
≥2 bilateral positive points	67.5 (59.6 - 75.3)	96.2 (80.4 - 99.9)	38.8 (25.2 - 53.8)	80.4 (70.3 to 90.4)	<0.0001	8.6 (0.9 to 16.4)	0.029

*Table 3. Diagnostic performance of the various lung ultrasound techniques in conjunction with the Brest score for pulmonary congestion assessment*

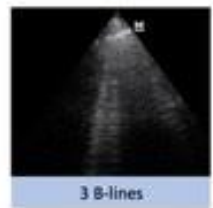
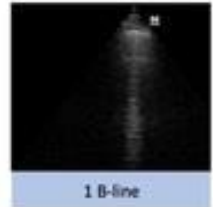
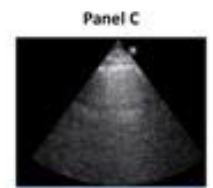
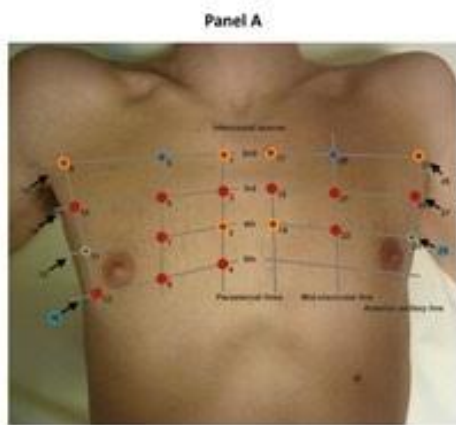


Supplementary table 1: Association between 28-point method and AHF diagnosis (in univariable analysis and after adjustment on the Brest score)

	Univariable association		Adjusted on Brest score (continuous)	
	OR (CI 95%)	p	OR (CI 95%)	p
<b>28-point method</b>				
B-line count	1.04 (1.02 - 1.06)	<0.0001	1.04 (1.02 - 1.06)	<0.0001
B-lines $\geq 15$	6.17 (2.40 - 15.90)	0.0008	4.92 (1.68 - 14.44)	0.004
B-lines $\geq 30$	7.06 (3.06 - 16.27)	<0.0001	6.97 (2.58 - 18.79)	0.0001

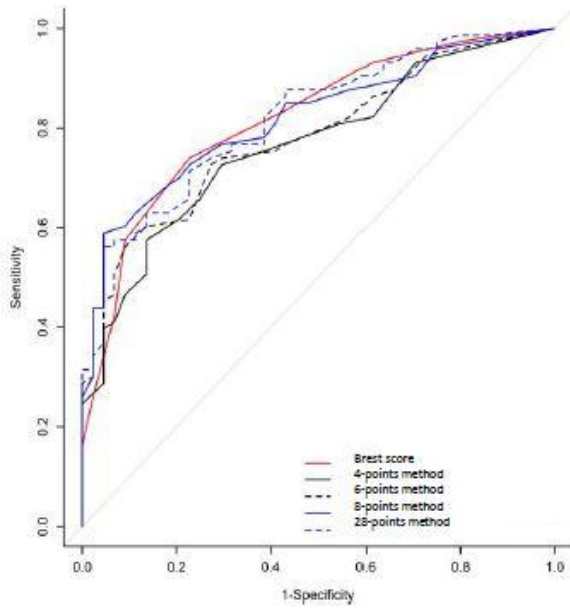
Supplementary table 2: Performances for AHF with the 28-points method

	Performances			Increased level of evidence added by the LUS techniques in addition to the Brest score (continuous)			
	C-index value of the considered parameter (CI 95 %)	Specificity (CI 95%)	Sensitivity (CI 95%)	C-index value of Brest Score and considered parameter (CI 95 %)	P	C-index increase in addition to the Brest score (CI 95 %)	p
<b>Overall Population</b>							
<b>28-points method</b>							
B-line count	82.1 (74.7 - 89.6)			90.5 (85.0 to 95.9)	<0.0001	8.7 (2.6 to 14.7)	0.005
B-lines $\geq 15$	66.1 (57.9 - 74.3)	43.2 (28.3 - 59.0)	89.0 (79.5 - 95.1)	85.0 (78.0 to 92.0)	<0.0001	3.2 (-0.7 to 7.1)	0.11
B-lines $\geq 30$	72.4 (63.9 - 80.9)	68.2 (52.4 - 81.4)	76.7 (65.4 - 85.8)	86.7 (80.1 to 93.2)	<0.0001	4.8 (-0.6 to 10.3)	0.082
<b>Patients with intermediate Brest score</b>							
<b>28-points method</b>							
B-line count	80.1 (70.1 - 90.1)			84.3 (75.0 to 93.6)	<0.0001	12.6 (2.5 to 22.6)	0.014
B-lines $\geq 15$	64.0 (53.1 - 74.9)	42.3 (23.4 - 63.1)	85.7 (72.8 - 94.1)	78.3 (67.6 to 89.0)	<0.0001	6.6 (-2.5 to 15.7)	0.16
B-lines $\geq 30$	68.5 (57.2 - 79.8)	61.5 (40.6 - 79.8)	75.5 (61.1 - 86.7)	78.5 (67.4 to 89.6)	<0.0001	6.8 (-2.6 to 16.1)	0.16

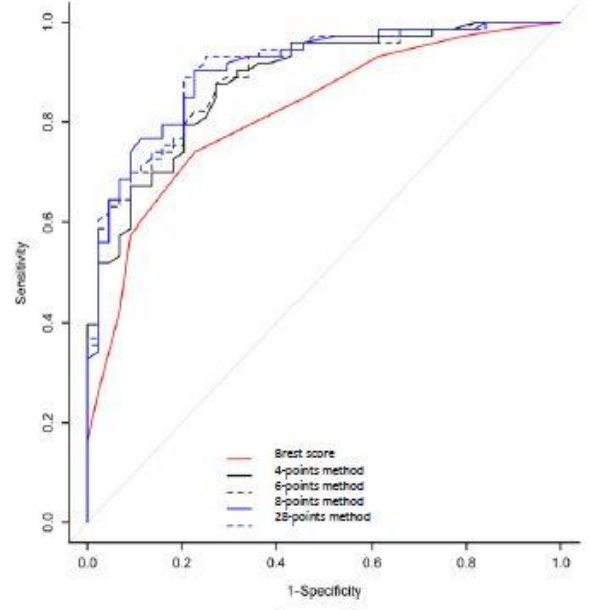


**Figure 1:** LUS methods: 4 to 28-point method described on a frontal (**panel A**) and lateral (**panel B**) view. Examples of LUS recordings showing 0 to 3 B-lines (**panel C**).

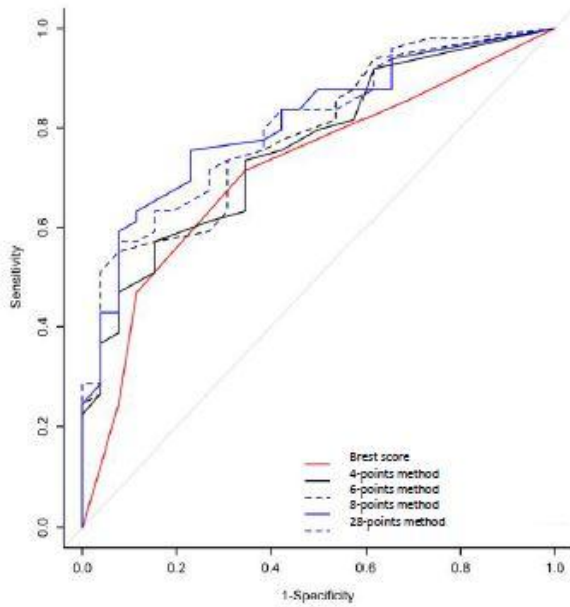
- 28-point method
- 8-point method
- 6-point method
- and ● 4-point method



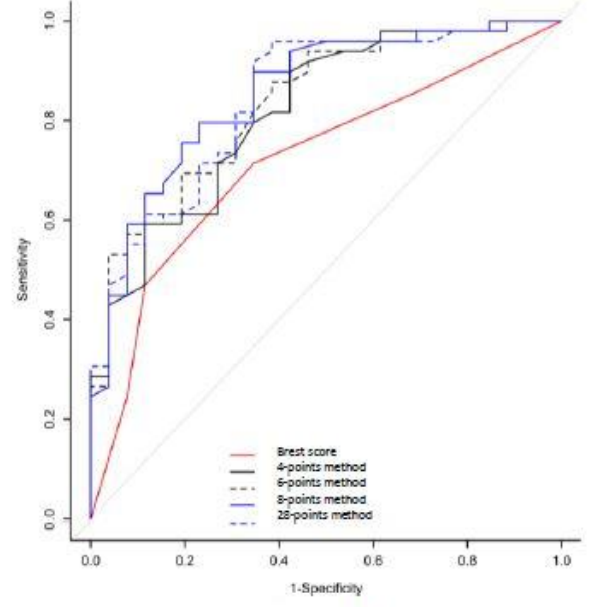
**Curve 1.a**



**Curve 1.b**



**Curve 2.a**






**Curve 2.b**

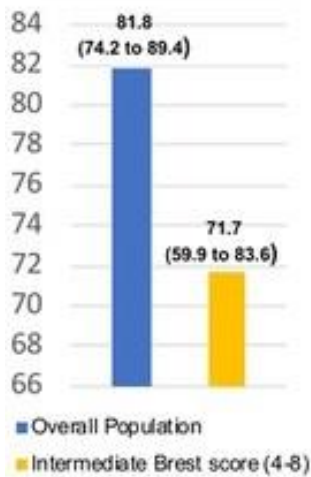
**Figure 2 : ROC curves for the AHF diagnostic (B-line count)**

1. Overall population
  - a. Brest score and LUS techniques
  - b. Brest score and LUS techniques + Brest score
2. Patients with Brest score  $\in [4 ; 8]$ 
  - a. Brest and LUS techniques
  - b. Brest score and LUS techniques + Brest score

# Diagnostic performance of the Brest score and LUS methods

<b>Brest Score</b>		<b>4-point LUS method</b>	<b>6-point LUS method</b>	<b>8-point LUS method</b>
<u>Variables</u>	<u>Points score</u>			
Age > 65 years	+2			
Sudden dyspnea	1			
Night outbreak	2			
Orthopnea	1			
Prior CHF episode	1			
COPD	2			
Myocardial infarction	-2			
Pulmonary crackles	1			
Pitting leg edema	2			
ST abnormalities	1			
Atrial fibrillation/flutter	1			
<b>Maximal score</b>	<b>15</b>			

**AUC for Brest score**



**IAUC by LUS methods in addition to the Brest score**

