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Lung Ultrasound-Implemented Diagnosis of Acute Decompensated Heart Failure in the ED

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BACKGROUND

Lung ultrasonography (LUS) has emerged as a noninvasive tool for the differential diagnosis of pulmonary diseases. However, its use for the diagnosis of acute decompensated heart failure (ADHF) still raises some concerns. We tested the hypothesis that an integrated approach implementing LUS with clinical assessment would have higher diagnostic accuracy than a standard workup in differentiating ADHF from noncardiogenic dyspnea in the ED.

METHODS

We conducted a multicenter, prospective cohort study in seven Italian EDs. For patients presenting with acute dyspnea, the emergency physician was asked to categorize the diagnosis as ADHF or noncardiogenic dyspnea after (1) the initial clinical assessment and (2) after performing LUS ("LUS-implemented" diagnosis). All patients also underwent chest radiography. After discharge, the cause of each patient's dyspnea was determined by independent review of the entire medical record. The diagnostic accuracy of the different approaches was then compared.

RESULTS

The study enrolled 1,005 patients. The LUS-implemented approach had a significantly higher accuracy (sensitivity, 97% [95% CI, 95%-98.3%]; specificity, 97.4% [95% CI, 95.7%-98.6%]) in differentiating ADHF from noncardiac causes of acute dyspnea than the initial clinical workup (sensitivity, 85.3% [95% CI, 81.8%-88.4%]; specificity, 90% [95% CI, 87.2%-92.4%]), chest radiography alone (sensitivity, 69.5% [95% CI, 65.1%-73.7%]; specificity, 82.1% [95% CI, 78.6%-85.2%]), and natriuretic peptides (sensitivity, 85% [95% CI, 80.3%-89%]; specificity, 61.7% [95% CI, 54.6%-68.3%]; n = 486). Net reclassification index of the LUS-implemented approach compared with standard workup was 19.1%.

CONCLUSIONS

The implementation of LUS with the clinical evaluation may improve accuracy of ADHF diagnosis in patients presenting to the ED.

TRIAL REGISTRY

Clinicaltrials.gov; No.: NCT01287429; URL: www.clinicaltrials.gov

ABBREVIATIONS

- ADHF, acute decompensated heart failure;
- AUC, area under the curve;
- BNP, brain natriuretic peptide;
- CXR, chest radiography;
- IQR, interquartile range;
- IS, interstitial syndrome;
- LUS, lung ultrasonography;

- NRI, net reclassification improvement;
- NT-pro-BNP, N-terminal pro-brain natriuretic peptide;
- ROC, receiver operating characteristic

Missed or delayed diagnosis of acute decompensated heart failure (ADHF) in the ED is associated with prolonged hospital stay, higher rates of ICU admission, higher mortality, and increased costs.[1, 2 and 3] However, although the worldwide incidence of heart failure is reaching epidemic proportions,[4] the initial diagnostic workup of ADHF has remained fundamentally unchanged over decades[4, 5 and 6] and may be heavily undermined by several factors, such as the poor sensitivity of the physical examination, ECG inaccuracy, and unreliability of chest radiography (CXR) findings.[1, 7 and 8]

Lung ultrasonography (LUS) has emerged as a rapid, noninvasive, bedside tool for the diagnosis of several pulmonary and pleural diseases.[9, 10, 11, 12, 13, 14, 15, 16 and 17] LUS detection of multiple and diffuse reverberation artifacts (B-lines) has been correlated with extravascular lung water content[18, 19 and 20] and with surrogate markers of pulmonary edema,[21 and 22] leading a consensus conference to recommend LUS for the diagnosis of ADHF.[15] However, LUS accuracy may be limited by its low specificity (as low as 54% in some studies), since B-lines may be detected in lung diseases with diffuse interstitial involvement other than ADHF.[10, 15, 18, 21 and 23] Furthermore, conflicting results on the correlation of B-lines with pulmonary artery wedge pressure have been published,[19, 24 and 25] which led some authors to raise concerns on LUS use for ADHF diagnosis.[19, 23 and 24] In this study, we evaluated the performance of a diagnostic approach implementing LUS with the clinical assessment in differentiating ADHF from noncardiac causes of acute dyspnea in the ED.

Materials and Methods

Study Design

This was a prospective, observational, multicenter, cohort study conducted in seven Italian EDs (two academic, one university-affiliated, and four community hospitals). Patients were enrolled from October 2010 to September 2012; each center recruited for a 6-month period. The protocol was approved by the institutional review board of the "Città della Salute e della Scienza di Torino" Hospital (project approval number 2CEI-105/0068893) and by the institutional review boards of the other participant hospitals. All patients gave informed written consent to participate. All patient data, after enrollment, were deidentified. The study was conducted in accordance with the principles of the Declaration of Helsinki for clinical research involving human subjects and registered on ClinicalTrials.gov (Identifier: NCT01287429).

Participants

We considered eligible all adult subjects (age > 18 years) presenting to the ED with acute dyspnea, defined as either sudden onset of shortness of breath or increase in the severity of chronic dyspnea in the last 48 h. We excluded patients with dyspnea obviously not due to ADHF (eg, traumatic injury), and those already invasively ventilated at the time of evaluation. The presence of an emergency physician with expertise in LUS (training performed according to Italian Society of Emergency Medicine [SIMEU] guidelines; > 40 examinations completed) was required for patient enrollment.

Study Protocol

After the initial standard workup, which included past medical history, history of the present illness, physical examination, ECG, and arterial blood gas analysis,[6] the emergency physician responsible for patient care was asked to categorize the diagnosis as ADHF or noncardiogenic dyspnea. The diagnosis of ADHF was based on the most updated guidelines available.[6 and 26] In a pragmatic "real world" approach, we decided not to define a strict diagnostic protocol nor to reinforce existing guidelines for the diagnosis of ADHF in the recruiting centers. Immediately after clinical workup, the same physician performed LUS, and the new

presumptive etiology, based on the results of both clinical assessment and LUS findings, was recorded ("LUS-implemented" diagnosis).

After hospital discharge, an expert emergency physician and a cardiologist, blinded to LUS results, independently reviewed the entire medical record and indicated the cause of patient's acute dyspnea ("final diagnosis"). In case of disagreement, a third expert emergency physician reviewed the medical records and adjudicated the case.

The etiology of dyspnea was categorized as a dichotomous variable (ADHF or noncardiogenic). If both etiologies were concomitantly present, the reviewers were asked to indicate the one they considered more relevant in determining patient's acute dyspnea.

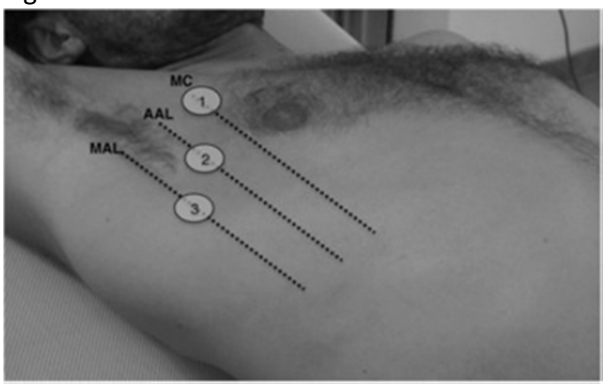
For all patients, a CXR report interpreted by a radiologist was available. To evaluate CXR accuracy, mention of pulmonary venous congestion and/or of bilateral interstitial and/or alveolar edema was considered diagnostic for ADHF.

In a subgroup of patients, brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP) levels were measured, although it was not expressly required by the study protocol. The cutoff values for diagnosing ADHF were set at 400 pg/mL for BNP,[27] and at 450, 900, and 1,800 pg/mL for patients < 50 years old, between 50 and 75 years old, and > 75 years of age, respectively, for NT-pro-BNP.[28] Finally, two emergency physicians with limited LUS training (< 10 examinations performed) and a physician expert in LUS blindly reviewed LUS images from 200 randomly selected patients, and both intra- and interobserver variability were evaluated.

Lung Ultrasonography

Patients were examined using a curvilinear transducer (5-3 MHz), according to a previously described, six-zone scanning protocol (Fig 1).[29] Diffuse interstitial syndrome (IS) was defined as the bilateral presence of two or more zones showing the presence of at least three B-lines: vertical, hyperechoic reverberation artifacts extending from the pleural line to the bottom of the screen.[9 and 15] The accuracy of LUS alone was determined by reanalyzing, a posteriori, the sonographic images; the presence of diffuse IS was considered diagnostic for ADHF.

Figure 1.



Six-zone scanning protocol used for lung ultrasonography evaluation. The anterior chest wall was divided into three zones. Two zones were located anteriorly, in the second intercostal space on the mid-clavicular line, and in the fourth intercostal space on the anterior axillary line, respectively. The third zone was located laterally in the fifth intercostal space on the mid-axillary line. An additional scan was performed on the posterior axillary line at the base of the lungs to assess for the presence of pleural effusion. AAL = anterior axillary line; MAL = mid-axillary line; MC = mid-clavicular line. (The patient provided written consent for the use of this photograph.)

Statistical Analysis

The sample size calculation assumed a prevalence of ADHF ranging from 45% to 55%, with sensitivity and specificity of the clinical assessment alone ranging from 70% to 85% and from 75% to 85%, respectively.[1, 3 and 30] We estimated that a sample size of 915 patients could achieve a power of 90% to test an absolute difference of 10% in both sensitivity and specificity between clinical and LUS-implemented evaluation, with 5% α error (two-sided test). Descriptive data are presented as mean (± SD) or median (with interquartile range [IQR]) for continuous variables, and as numbers and percentages for categorical variables.

The accuracy of each diagnostic tool is expressed as sensitivity, specificity, predictive values, and likelihood ratios obtained using 2 × 2 tables. For each test, "positive" and "negative" results were considered the diagnosis of ADHF or noncardiac dyspnea, respectively. Receiver operating characteristic (ROC) and area under the curve (AUC) statistics[31 and 32] are also shown.

We used the McNemar test for paired data[33] to compare the accuracy in the detection of ADHF of the different diagnostic tests. Diagnostic improvement obtained with LUS implementation to the initial standard workup was assessed by the net reclassification improvement (NRI), which estimates the percentage of subjects moving from one clinical diagnosis to the other.[34] Intra- and interobserver agreement was assessed using Cohen κ with associated 95% CI. Data were collected in a Microsoft Excel (Microsoft Inc) spreadsheet, and statistical analyses were conducted using Stata 11.0/SE (Stata Corp).

Results

Patients

Of 1,007 patients eligible for this study, two denied consent to enrollment; therefore, 1,005 patients were included in the analyses. Of these, 544 (54.1%) were enrolled in community hospitals and 461 (45.9%) in academic or university-affiliated centers. Sixty-two emergency physicians participated in the study, each enrolling a median number of 44 patients (IQR, 22).

Final diagnosis was ADHF for 463 patients (46%) and noncardiac dyspnea for 542 (54%). Interrater agreement between the two expert physicians adjudicating the final diagnosis of ADHF was very high (κ, 0.93; 95% CI, 0.91–0.95; $P < .01$). Of the 35 discordant cases, 16 were categorized as ADHF by the third expert.

Admissions were 821 (81.7%), 176 patients were discharged home, and eight patients died in the ED. Among admitted patients, 602 were admitted to general internal medicine/cardiology units, 175 to ICU or high-dependency units, 12 to surgical units, and 32 to short-stay units (with five patients subsequently admitted to internal medicine units, and 27 discharged home).

Table 1 shows patient demographic and clinical data. Table 2 reports symptoms associated with dyspnea and findings detected during the initial clinical assessment.

TABLE 1. Demographic Characteristics and Medications of Patients Enrolled

Characteristics	ADHF (n = 463)	Noncardiac Dyspnea (n = 542)	All Patients (N = 1,005)	*P* Value[a]
Age, median (IQR), y	78 (11)	76 (13)	77 (13)	< .01
Women	248 (53.6)	216 (39.8)	464 (46.2)	< .01
Baseline characteristics				
Tobacco use[b]	166 (35.8)	254 (46.9)	420 (41.8)	< .01
COPD	125 (27.2)	284 (52.2)	409 (40.7)	< .01
Asthma	3 (0.7)	35 (6.5)	38 (3.8)	< .01
Interstitial lung disease	19 (4.1)	38 (7)	57 (5.7)	< .05
Hypertension[c]	335 (72.4)	303 (55.9)	638 (63.5)	< .01
Congestive heart failure[c]	148 (32)	55 (10.2)	203 (20.2)	< .01
Ischemic cardiomyopathy/CAD	155 (33.5)	104 (19.2)	259 (25.8)	< .01
Other cardiomyopathies	169 (36.5)	71 (13.1)	240 (23.9)	< .01
Diabetes[c]	169 (36.5)	112 (20.7)	281 (27.9)	< .01
Arrhythmia[d]	161 (34.8)	106 (19.6)	267 (26.5)	< .01
Dyslipidemia[c]	100 (21.6)	60 (11.1)	160 (15.9)	< .01
Cerebrovascular accident[c]	37 (8)	42 (7.8)	79 (7.9)	> .05
CKD/chronic dialysis[e]	108 (23.3)	61 (11.3)	169 (16.8)	< .01
Neoplastic disease[c]	42 (9.1)	90 (16.6)	132 (13.1)	< .01
Thromboembolic disorder	11 (2.4)	27 (5)	38 (3.8)	> .05
Medications				
Diuretics	314 (67.8)	234 (43.2)	548 (54.5)	< .01
β-Blockers	206 (44.5)	91 (16.8)	297 (29.5)	< .01
ACE inhibitors	248 (53.6)	184 (33.9)	432 (43)	< .01
Antiplatelet agents[f]	206 (44.5)	182 (33.6)	388 (38.6)	< .01
Anticoagulants[g]	106 (22.9)	68 (12.5)	174 (17.3)	< .01
Bronchodilators	92 (19.9)	270 (49.8)	362 (36)	< .01
Antidiabetic agents/insulin	161 (34.8)	111 (20.5)	272 (27.1)	< .01
Steroids	39 (8.4)	98 (18.1)	137 (13.6)	< .01
Antiarrhythmic agents	101 (21.8)	66 (12.2)	167 (16.6)	< .01
Home oxygen	38 (8.2)	80 (14.8)	118 (11.7)	< .01

Data given as No. (%) unless otherwise indicated. ACE = angiotensin-converting-enzyme; ADHF = acute decompensated heart failure; CAD = coronary artery disease; CKD = chronic kidney disease; IQR = interquartile range. a: χ^2 test for categorical variables, or Mann-Whitney *U* test for continuous variables. b: Current or remote use. c: Any type and/or grade of disorder/disease. d: Any type of cardiac rhythm disorders (eg, atrial fibrillation, paroxysmal, persistent or permanent; atrial flutter; sick sinus syndrome; atrioventricular blocks; supraventricular paroxysmal tachycardia). e: CKD defined as chronic renal failure with creatinine level > 2 mg/dL (177 μmol/L). f: Acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, tirofiban, and dypiridamole. g: Warfarin, acenocoumarol, any type of heparin, fondaparinux.

TABLE 2. Symptoms Associated With Acute Dyspnea and Clinical Findings Detected at the Time of Patient Presentation in the ED

Symptoms/Findings	ADHF (n = 463)	Noncardiac Dyspnea (n = 542)	All Patients (N = 1,005)	*P* Value[a]
Associated symptoms				
Fever[b]	28 (6.1)	164 (30.3)	192 (19.1)	< .01
Dry and/or productive cough	77 (16.6)	278 (51.3)	355 (35.3)	< .01
Chest pain	54 (11.7)	49 (9)	103 (10.3)	> .05
Palpitation	18 (3.9)	10 (1.9)	28 (2.8)	.05
Physical examination findings, mean (SD)				
Heart rate, beats/min	95.2 (22.7)	98 (21.4)	96.7 (22)	< .05
Systolic BP, mm Hg	147.6 (26.8)	138.6 (24.2)	142.6 (25.8)	< .01
Diastolic BP, mm Hg	81.3 (15.4)	77.8 (13.7)	79.4 (14.6)	< .01
Pao_2/Fio_2 ratio[c]	271.5 (72.8)	283.4 (84.5)	278 (79.6)	< .05
Respiratory rate, breaths/min	28.3 (7.9)	28.3 (8.1)	28.3 (7.9)	> .05
Temperature, °C	36.3 (0.6)	36.9 (1.4)	36.6 (1.2)	< .01
Wheezing	97 (21)	210 (38.8)	307 (30.6)	< .01
Rales	375 (81)	286 (52.8)	661 (65.8)	< .01
Peripheral edema	253 (54.6)	117 (21.6)	370 (36.8)	< .01
Noninvasive mechanical ventilation[d] in the ED	97 (20.9)	48 (8.9)	145 (14.4)	< .01

Data given as No. (%) unless otherwise indicated. See Table 1 legend for expansion of abbreviations. A: χ^2 test for categorical variables, Mann-Whitney *U* test, or Student *t* test for continuous variables. B: Tympanic temperature > 38.3°C. c: The ratio of Pao_2 and Fio_2 was calculated using Pao_2 (mm Hg) measured at the time of the first arterial blood gas analysis and Fio_2 provided, as reported in the case report form. In 83.1% of cases, the blood gas analysis was performed with patients breathing room air (Fio_2, 0.21). d: Any type of noninvasive mechanical ventilation.

Outcomes

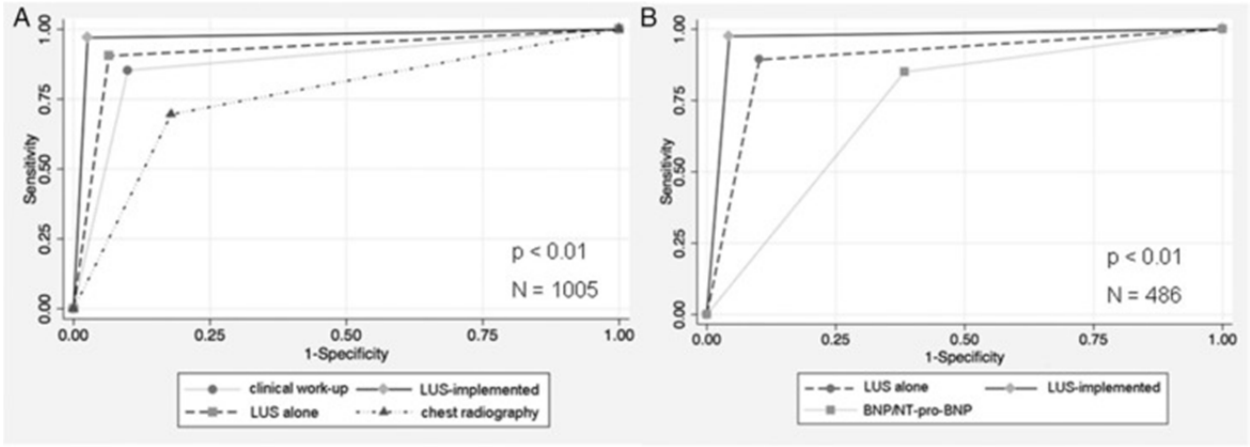
Figure 2 and Figure 3 show accuracy, ROC, and AUC of the different diagnostic approaches evaluated. Clinical workup and LUS alone had relatively high accuracy in the identification of ADHF, whereas CXR showed only moderate accuracy. Sensitivity and specificity were significantly higher for LUS alone compared with CXR ($P < .01$). The LUS-implemented protocol had the highest accuracy, with a significant increase in sensitivity and specificity in comparison with clinical workup alone ($P < .01$) (Fig 2). The NRI of LUS-implemented approach compared with standard clinical workup was 19.1% (95% CI, 14.6%-23.6%; $P < .01$) (Table 3). The accuracy of BNP/NT-pro-BNP values, available in a subgroup of 486 patients, was significantly lower than that of the LUS-implemented approach ($P < .01$) (Fig 2).

Figure 2.

		Sensitivity	Specificity	PPV	NPV	LR+	LR-	p	
No. = 1005	Clinical work-up	85.3% (81.8-88.4)	90% (87.2-92.4)	88% (84.6-90.8)	87.8% (84.8-90.4)	8.6	0.2	< .01	
	LUS-implemented	97% (95-98.3)	97.4% (95.7-98.6)	97% (95-98.3)	97.4% (95.7-98.6)	37.5	0.03		
	LUS-alone	90.5% (87.4-93)	93.5% (91.1-95.5)	92.3% (89.4-94.6)	92% (89.4-94.1)	14	0.1	< .01	
	Chest radiography	69.5% (65.1-73.7)	82.1% (78.6-85.2)	76.8% (72.5-80.8)	75.9% (72.5-79.3)	3.9	0.4		
No.= 486	LUS-implemented	97.5% (94.9-99)	95.6% (91.9-98)	96.8% (94-98.5)	96.6% (93.1-98.6)	22.3	0.02	< .01	
	BNP/NT-pro-BNP	85% (80.3-89)	61.7% (54.6-68.3)	75.1% (69.9-79.7)	75.1% (67.9-81.5)	2.2	0.2		< .01
	LUS-alone	89.3% (85.1-92.7)	89.8% (84.8-93.6)	92.3% (88.4-95.1)	86% (80.7-90.4)	8.8	0.11		

Diagnostic accuracy of the different approaches to acute dyspnea in the ED. BNP = brain natriuretic peptide; LR^- = negative likelihood ratio; LR^+ = positive likelihood ratio; LUS = lung ultrasonography; NPV = negative predictive value; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; PPV = positive predictive value.

Figure 3.



	Area under curve (AUC)	
Clinical work-up	0.876	p < 0.01
LUS-implemented	0.972	
LUS-alone	0.920	p < 0.01
Chest radiography	0.758	

	Area under curve (AUC)	
LUS-implemented	0.966	
LUS-alone	0.895	p < 0.01
BNP/NT-pro-BNP	0.733	

A, Receiver operating characteristic (ROC) curve comparing accuracy of clinical workup, LUS-implemented diagnosis, LUS alone, and chest radiography. B, ROC curve comparing accuracy of clinical workup, LUS-implemented diagnosis, LUS alone, and BNP/NT-pro-BNP levels. See Figure 2 legend for expansion of other abbreviations.

TABLE 3. Net Reclassification Improvement[a]

Patient With ADHF		LUS-Implemented (Post-LUS)			Patients With Noncardiac Dyspnea		LUS-Implemented (Post-LUS)		
		Noncardiac Dyspnea	ADHF		Total	Noncardiac Dyspnea		ADHF	Total
Clinical workup (pre-LUS)	Noncardiac dyspnea	5	63	68	Clinical workup (pre-LUS)	Noncardiac dyspnea	481	7	488
	ADHF	9	386	395		ADHF	47	7	54
	Total	14	449	463		Total	528	14	542

LUS = lung ultrasonography. See Table 1 legend for expansion of other abbreviation. A: Net reclassification improvement was calculated as ([63 / 463] − [9 / 463]) + ([47 / 542] − [7 / 542]) = 19.1% (95% CI, 14.6%-23.6%; *P* < .01).

Finally, when two emergency physicians with limited LUS training (< 10 examinations performed) and a physician expert in LUS blindly reviewed LUS images from 200 randomly selected patients, the κ statistic for agreement for the diagnosis of IS was 0.94 (95% CI, 0.89-0.98; *P* < .01). Intraobserver agreement was 0.97 for the expert operator (95% CI, 0.95-0.99; *P* < .01) and 0.92 for the physicians with limited LUS training (95% CI, 0.88-0.96; *P* < .01).

Discussion

In this study, we found that, in adult subjects with acute dyspnea in the ED, a LUS-implemented approach had higher diagnostic accuracy than other commonly used diagnostic tools (ie, initial clinical workup, CXR, LUS alone, and BNP/NT-pro-BNP levels) in differentiating ADHF from noncardiac causes of acute dyspnea. To overcome LUS limitations in ADHF diagnosis,[1, 6, 35 and 36] we adopted an integrated approach that paired LUS with the pretest probability of the clinical assessment. Moreover, we strictly defined diffuse IS as the bilateral presence of two or more positive zones, to decrease false-positive diagnoses due to the appearance of B-lines in several primary lung diseases (eg, pneumonia, atelectasis). By using this strategy, we obtained sensitivity, specificity, and AUC values for the diagnosis of ADHF as high as 97.0%, 97.4%, and 0.972, respectively.

In agreement with previous data,[1, 3, 37 and 38] the accuracy of the initial clinical workup for ADHF diagnosis was only moderate. The LUS-implemented approach increased the sensitivity and specificity of clinical assessment by 11.7% and 7.4%, respectively, with an NRI of 19.1%, which shows a relevant diagnostic impact of LUS in this setting.

CXR is still considered a fundamental component of the initial assessment of a patient with suspected ADHF.[39] However, in our study, CXR sensitivity, although higher than that reported in other studies,[1 and 7] was as low as 69.5%, confirming that the absence of pulmonary venous congestion/interstitial edema/alveolar edema is not sufficient to exclude the diagnosis of ADHF.[1] The superiority of LUS in the detection of diffuse IS may be at least partially related to the more rapid sonographic detection of signs of pulmonary congestion, which have been shown in experimental studies to appear only 15 min after the induction of pulmonary injury and to even precede changes in Pao_2/Fio_2 ratio.[40]

The LUS-implemented approach resulted in absolute increases in sensitivity and specificity of 6.5% and 3.9%, respectively, when compared with LUS-alone, although, in our study, the sensitivity, specificity, and AUC of LUS alone were higher than in previous studies.[10, 11 and 41] This discrepancy may be related to the difference in clinical setting[21 and 41] or to the timing of LUS performance.[10]

In a subgroup of patients (486 of 1,005), we evaluated the diagnostic accuracy of serum concentrations of BNP/NT-pro-BNP, extensively studied biomarkers of ADHF.[1, 6 and 36] In agreement with previous studies,[6, 11,

[28 and 38] natriuretic peptides had higher sensitivity (85.0%) than specificity (61.7%), and a moderate AUC (0.733). It is known that this relatively low specificity is due to the increase of BNP/NT-pro-BNP levels in several other diseases, such as pulmonary embolism, left ventricle dysfunction without ADHF, atrial fibrillation, and cor pulmonale.[42, 43 and 44] In our study, both LUS-implemented approach and LUS alone outperformed BNP/NT-pro-BNP values in differentiating ADHF from noncardiac causes of dyspnea. Previously published studies reported results apparently not consistent with ours.[11, 35 and 41] However, the differences in the clinical setting, LUS timing, and/or BNP/NT-pro-BNP sampling may at least partially account for this discrepancy. Therefore, it can be hypothesized that detection of sonographic IS may be useful in recognizing those conditions where myocardial wall stress is increased but extravascular lung water content remains unchanged (eg, pulmonary embolism, atrial fibrillation, and cor pulmonale). In addition, LUS may be helpful in patients with only slightly elevated BNP/NT-pro-BNP levels ("grey zone"), or in situations where this analysis is not available in a timely manner (eg, remote areas, peripheral EDs, low-income countries).

A strength of our study may be considered the high degree of generalizability. We enrolled 1,005 patients with acute dyspnea in seven EDs, from both academic and community hospitals. As in previous similar studies,[7, 11 and 45] patients were usually elderly, with several comorbidities, and taking multiple medications chronically (Table 1). Pragmatically, the physicians were not limited by a strict diagnostic protocol, but were free to evaluate patients according to real-world practices. Moreover, they had heterogeneous clinical and LUS expertise, ranging from residents to experienced attending physicians.

Finally, we found a very good intra- and interobserver agreement between inexperienced operators and a physician expert in LUS when interpreting LUS images. These findings confirm previous results,[10, 11 and 29] indicating that LUS can be easily learned and its interpretation is highly reproducible.

These results are of particular interest when considering that echocardiography, the recommended test for the assessment of patients presenting with suspected ADHF and acute onset of symptoms, requires extensive training, especially to assess diastolic dysfunction. It also is often not readily available in emergency setting.[6]

Although we did not specifically collect data on the time elapsed between onset of symptoms and ED referral or between ED admission and LUS performance, LUS was performed within 40 min from presentation to the ED in the vast majority of patients enrolled in our study. LUS was delayed in 16 patients, due to lack of availability of the ultrasound system, but the time between ED admission and LUS performance was still < 1 h.

Several limits have to be taken into account in interpreting our results. First, we did not enroll consecutively all patients presenting to the ED with acute dyspnea. Moreover, patient enrollment required the presence of an emergency physician with expertise in LUS. Therefore, we cannot exclude a selection bias leading to an overestimation of LUS accuracy. However, patients' characteristics, consistent with previous studies, the number of centers and of physicians participating in the study, and the physicians' heterogeneous expertise in LUS make this possibility unlikely. Second, a common problem in studies on patients with ADHF is the lack of a standard criterion to determine the final diagnosis. As others have done,[11 and 38] we used the independent review of the medical records by two expert physicians, with a third physician reviewing discordant cases. Despite the clear limitation of such analysis, we observed a high interrater agreement. An additional limitation exists, since the same emergency physician performed both the initial clinical workup and LUS, and so was not blinded to the results of clinical workup. Therefore, LUS findings may have not been completely independent from the clinical diagnosis, and the diagnostic accuracy of the LUS-implemented approach could be subject to bias. Even the final diagnosis, although the reviewers were blinded to LUS results, may have been indirectly affected by this bias, since the therapeutic management of the patients may have been influenced by the LUS results. Additionally, in patients with multiple concomitant causes of dyspnea (eg, pneumonia and ADHF), we asked both investigators and reviewers to

indicate the one they considered more relevant in determining the patient's acute dyspnea. Therefore, we are not able to assess the diagnostic accuracy of the LUS-implemented approach in those patients with acute dyspnea with mixed etiology. Finally, the study protocol did not allow us to compare the accuracy of the LUS-implemented approach with a CXR-implemented approach, which is the standard diagnostic approach currently used. However, LUS alone was significantly more accurate than CXR; therefore, it is highly unlikely that a less accurate test would have outperformed a more accurate test when integrated with the clinical assessment. In conclusion, our study demonstrates that the implementation of LUS with the clinical assessment improves the diagnostic accuracy for ADHF and has a significant diagnostic impact in adult patients presenting to the ED with acute dyspnea.

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