

Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial

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Aims

Although acute decompensated heart failure (ADHF) is a common cause of dyspnoea, its diagnosis still represents a challenge. Lung ultrasound (LUS) is an emerging point-of-care diagnostic tool, but its diagnostic performance for ADHF has not been evaluated in randomized studies. We evaluated, in patients with acute dyspnoea, accuracy and clinical usefulness of combining LUS with clinical assessment compared to the use of chest radiography (CXR) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in conjunction with clinical evaluation.

Methods and results

This was a randomized trial conducted in two emergency departments. After initial clinical evaluation, patients with acute dyspnoea were classified by the treating physician according to presumptive aetiology (ADHF or non-ADHF). Patients were subsequently randomized to continue with either LUS or CXR/NT-proBNP. A new diagnosis, integrating the results of both initial assessment and the newly obtained findings, was then recorded. Diagnostic accuracy and clinical usefulness of LUS and CXR/NT-proBNP approaches were calculated. A total of 518 patients were randomized. Addition of LUS had higher accuracy [area under the receiver operating characteristic curve (AUC) 0.95] than clinical evaluation alone (AUC 0.88) in identifying ADHF ($P < 0.01$). In contrast, use of CXR/NT-proBNP did not significantly increase the accuracy of clinical evaluation alone (AUC 0.87 and 0.85, respectively; $P > 0.05$). The diagnostic accuracy of the LUS-integrated approach was higher than that of the CXR/NT-proBNP-integrated approach (AUC 0.95 vs. 0.87, $p < 0.01$). Combining LUS with the clinical evaluation reduced diagnostic errors by 7.98 cases/100 patients, as compared to 2.42 cases/100 patients in the CXR/NT-proBNP group.

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Conclusion

Integration of LUS with clinical assessment for the diagnosis of ADHF in the emergency department seems to be more accurate than the current diagnostic approach based on CXR and NT-proBNP.

Keywords

Acute dyspnoea • Diagnosis • Lung ultrasound • Heart failure

Introduction

Dyspnoea is a common symptom in acute care medicine, accounting for almost 4 million visits per year in the U.S. emergency departments (EDs).¹ However, the identification of the cause of acute dyspnoea is complex and often inaccurate. Differential diagnosis includes multiple conditions, with acute decompensated heart failure (ADHF), pneumonia, obstructive pulmonary diseases, pulmonary embolism and asthma among the most common.^{2–4} In elderly patients, the prevalence of ADHF ranges between 45% and 55%.^{5,6} In patients with acute dyspnoea, particularly when caused by ADHF,^{7,8} erroneous or delayed diagnoses are known to increase the risk of prolonged hospital stay and intensive care unit admission, and are associated with higher costs and mortality.⁹ Therefore, a rapid and accurate diagnostic work-up is critical to the establishment of specific and effective treatment, especially in elderly patients with multiple co-morbidities.^{2,3} Current guidelines for ADHF diagnosis in the acute care setting recommend a work-up that includes detailed patient history, vital signs, physical examination, electrocardiogram (ECG), and chest radiography (CXR).⁶ However, this diagnostic approach is often unreliable,^{8,10,11} leading to 'uncertain' diagnosis in up to 44% of patients¹² and it is inconsistent with the final diagnosis in approximately one out of four cases.^{4,13–15} The addition of natriuretic peptide measurement, recommended in all patients with suspected ADHF,⁶ improves diagnostic accuracy,^{12,16} but the misclassification rate remains unacceptably high.^{10,17–19}

Over the past two decades, lung ultrasound (LUS) has emerged as a rapid and reliable tool that can be used in the bedside evaluation of patients with acute dyspnoea. Several observational studies and a recent meta-analysis have suggested that LUS has higher diagnostic accuracy for ADHF than standard clinical work-up, CXR, and natriuretic peptides.^{5,20–24} To date, no randomized studies comparing the diagnostic performance of LUS vs. current standard of care for ADHF diagnosis have been published.^{6,25} Here, we present the results of the first to our knowledge randomized trial aimed at evaluating, in patients presenting with acute dyspnoea to the ED, the accuracy of a diagnostic approach combining LUS and clinical assessment as compared to the traditional ADHF diagnostic work-up (clinical evaluation with CXR and natriuretic peptide measurement).

Methods

This was a randomized, multicentre, parallel group trial conducted in two Italian academic hospitals ('Città della Salute e della Scienza di Torino' University Hospital, Turin, and 'Careggi' University Hospital, Florence). The protocol was approved by the institutional review

boards of the two hospitals. All patients or their legally authorized representatives provided written informed consent and all data were de-identified immediately afterwards.

The primary aim of the study was the comparison of the accuracy and the clinical usefulness of two integrated diagnostic approaches [clinical examination plus LUS or plus CXR and level of N-terminal pro-B-type natriuretic peptide (NT-proBNP)] for the diagnosis of ADHF among patients suffering from acute dyspnoea in the ED.

The secondary aim was the assessment of the time needed for defining the integrated evaluation in both arms.

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 number NCT02105207).

Patients

We considered eligible all adult patients (age ≥ 18 years) who presented to the ED with acute dyspnoea, defined as either sudden onset of shortness of breath or increase in the severity of chronic dyspnoea in the previous 48 h.⁵ We excluded patients already mechanically ventilated with positive pressure (either invasively or non-invasively) at the time of first evaluation, or patients presenting with acute dyspnoea in the context of trauma.

The presence of an emergency physician with expertise in LUS (i.e. who completed LUS training in accordance with the Italian Society of Emergency Medicine standards²⁶ and performed and interpreted at least 40 LUS examinations⁵) was required for patient enrolment.

Study protocol

Immediately after the initial clinical evaluation [including past medical history, history of present illness, physical examination, arterial blood gas analysis (ABG) and ECG], the physician responsible for the care of the patient was asked to indicate the presumptive aetiology of dyspnoea, categorized as a dichotomous variable (ADHF or non-ADHF). If both aetiologies were concomitantly present, he/she was asked to record the one considered most relevant.

Afterwards, using computerized permuted blocks of random sizes, patients were randomized in a 1:1 ratio to continue the diagnostic work-up with performance of either CXR and level of NT-proBNP (CXR/NT-proBNP group) or LUS (LUS group). A new presumptive aetiological diagnosis, combining the results of both initial clinical assessment and the newly obtained findings, was then recorded.

Thereafter, CXR and NT-proBNP measurement were also performed in all patients in the LUS group, but their results were made available to the treating physician only after the new LUS-implemented presumptive diagnosis was recorded. Similarly, LUS could be performed, at physician's discretion, in patients enrolled in the standard of care group, but only after the CXR/NT-proBNP-implemented diagnosis was recorded. In other words, the treating physician had access, during patient's ED stay, to all available test results but, for study data collection, his/her opinion on the cause of dyspnoea was recorded,

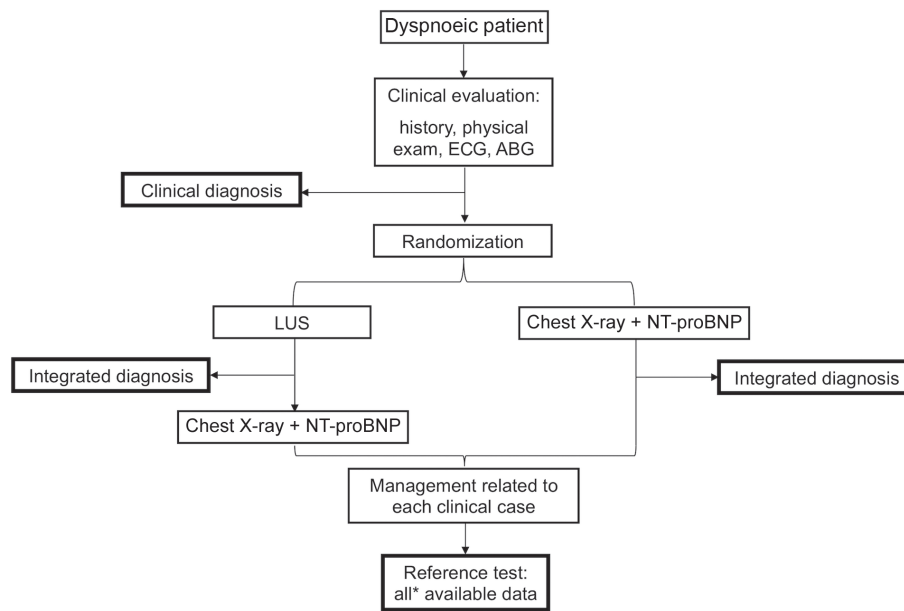


Figure 1 Management of individual patients enrolled in the study. ABG, arterial blood gas analysis; ECG, electrocardiogram; LUS, lung ultrasound; NT-proBNP, N-terminal pro-B-type natriuretic peptide. (*As reported in the Study protocol paragraph, this includes the complete medical record except for the lung ultrasound results).

in the LUS group, before CXR and NT-proBNP results were made available, and, in the CXR/NT-proBNP group, before performance of LUS. Therefore, although the results of those subsequent tests could have potentially changed his/her final diagnostic judgment and patient's management, the diagnoses recorded immediately after LUS and CXR/NT-proBNP, respectively, were not affected.

Lung ultrasound was performed by the physician responsible for patient enrolment and care. We used a curvilinear probe (5–2 MHz) and a previously described eight-zone scanning protocol.²⁷ Patients were evaluated in a sitting or semi-recumbent position.^{5,27} The presence of three or more B-lines/intercostal space represented a positive region of increased lung density (i.e. interstitial syndrome). B-lines are defined as laser-like, vertical, hyperechoic artefacts that arise from the pleural line, extend to the bottom of the screen without fading, and move synchronously with lung sliding.²⁷ Bilateral presence of three or more B-lines in two or more zones was considered diagnostic for diffuse interstitial syndrome. The presence of pleural effusions was also evaluated.

All LUS evaluations were performed using intermediate-size ultrasound devices equipped with three probes (Esaote MyLab5, Esaote MyLab30 Gold, Esaote MyLab Alpha, and Philips HD7).

NT-proBNP levels were measured using a commercially available electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics, Mannheim, Germany).

After the assessment of the integrated diagnosis, the management of the patient was independent of the arm allocation, and the responsible physician based diagnostic and therapeutic decisions on the patient's clinical needs.

After hospital discharge or death, two expert intensivists/emergency physicians (A.G. and E.L.), blinded to LUS results and to initial group assignment, independently reviewed patients' complete medical records, including summaries with discharge diagnoses. The

adjudication of ADHF was based on the 2012 European Society of Cardiology guidelines for heart failure²⁸ (i.e. presence of typical symptoms and signs of heart failure resulting from an abnormality of cardiac structure or function). In case of disagreement, a cardiologist (D.C.) reviewed the entire medical records and adjudicated the case (Figure 1).

The time needed to convey the integrated diagnosis (clinical evaluation plus LUS or clinical evaluation plus CXR/NT-proBNP) was also measured and compared in the two groups.

Analysis of data

Descriptive results are presented as numbers and percentages for categorical variables and mean (\pm standard deviation, SD) or median (25th–75th percentiles) for continuous variables. The distributions of continuous variables are compared by means of the Wilcoxon–Mann–Whitney test.²⁹

The outcome of our experimental study is a measure of accuracy of the two combined diagnostic approaches for ADHF diagnosis. In particular, we estimated sensitivity (SE), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), likelihood ratios, and area under the receiver operating characteristic curve (AUC ROC).³⁰ 'Positive' and 'negative' results were considered the diagnosis of ADHF and non-ADHF, respectively. We compared the within group difference in accuracy by using the McNemar test for paired data³¹ and the between group difference in accuracy by using the chi-square test.³²

In addition, the clinical usefulness of each approach was also evaluated by category-based net reclassification index (NRI), reclassification tables,³³ and net benefit (NB), using decision curve analysis.³⁴ NRI quantifies how many times the diagnosis changes by virtue of a new test result. It assesses the diagnostic improvement provided by each combined diagnostic approach in relation to the initial clinical

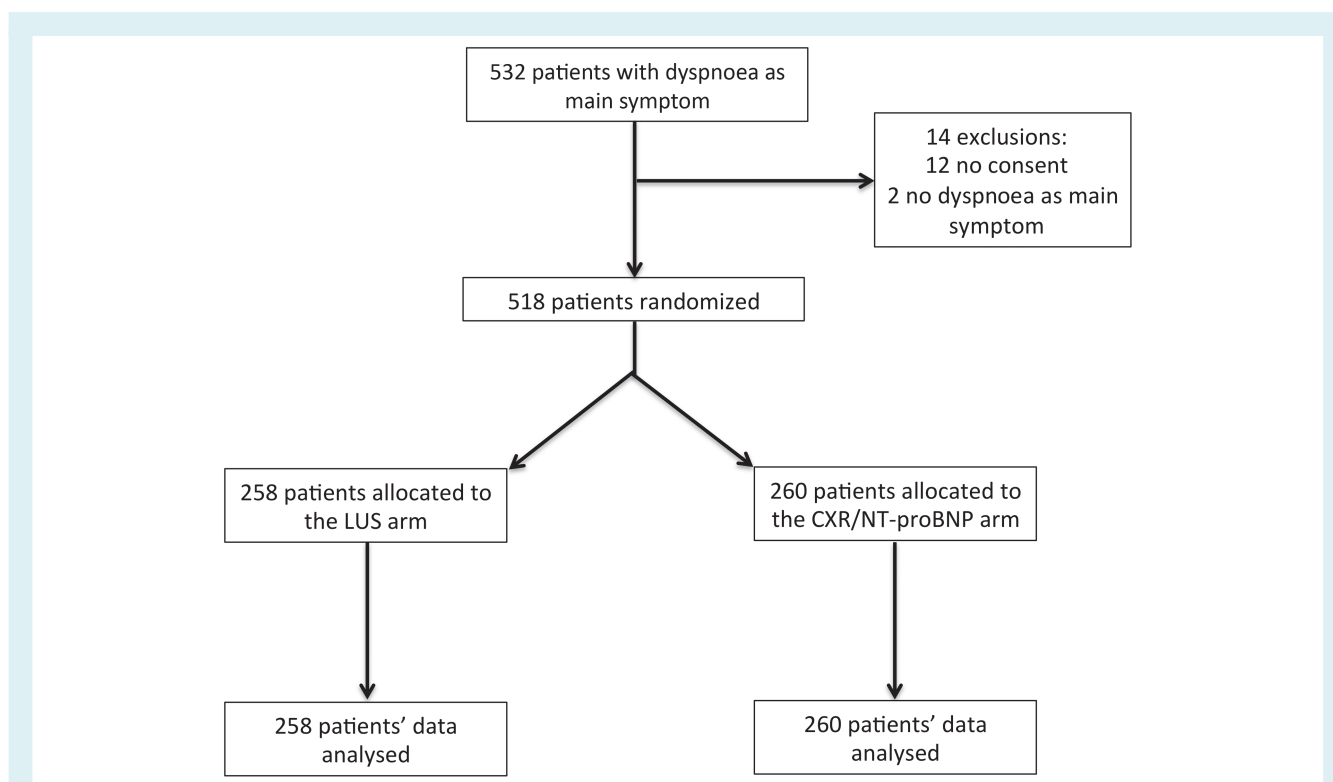


Figure 2 Consolidated Standards of Reporting Trials (CONSORT) diagram. CXR, chest radiography; LUS, lung ultrasound; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

assessment by estimating the percentage of subjects shifting from ADHF to non-ADHF or vice versa.³³ Computation of the NB, as for other decision analytic methods, has been proposed to evaluate diagnostic tests in terms of their real clinical consequences. The NB quantifies the possible diagnostic gain by putting on the same scale right and wrong diagnoses, and is defined as the benefit (of a true positive compared to a false negative) minus the harm (of a false positive compared to a true negative) for a given threshold probability of ADHF (typically, its prevalence). The decision curve shows the NB for all possible values of the prevalence.^{34,35}

Agreement between the reviewers for defining the most likely cause of acute dyspnoea was calculated by using the Cohen's kappa.³⁶

Assuming a sensitivity of the LUS approach of approximately 95%, as reported in a previous multicentre study,⁵ 80% power and a 5% alpha error, we estimated that a sample size of 258 patients/group would be sufficient to test a 10% sensitivity difference.

Statistical analyses were conducted using STATA software, version 13.1 (Stata Corp., College Station, TX, USA).

Results

Patients

From January 2014 to March 2015, we identified 532 eligible patients. Of these, 518 were enrolled (411 at the 'Città della Salute e della Scienza di Torino' University Hospital) and underwent randomization, 260 to the CXR/NT-proBNP group and 258 to the LUS group (Figure 2).

Median age was 79 years (25th–75th percentiles: 71–85 years); 243 women (47%) and 275 men (53%) were enrolled. Review of patients' complete medical records after hospital discharge or death identified 224 patients (43.2%) with final diagnosis of ADHF (38.5% and 48.1% in the CXR/NT-proBNP group and in the LUS group, respectively) and 294 patients of non-ADHF. The final diagnoses for the latter were chronic obstructive pulmonary disease (COPD) exacerbations (32.7%), pneumonia (32.4%), upper respiratory airway infections (13.6%), pleural effusion and/or atelectasis (5.7%), respiratory failure in metastatic cancer patients (4.7%), interstitial lung diseases (4.4%), asthma acute exacerbations (3.1%), pulmonary embolism (1.4%), and other less frequent aetiologies (i.e. myasthenia gravis, pneumothorax, interstitial pneumonia, pulmonary hypertension – 2%).

Cohen's kappa for agreement between the first two reviewers was 0.84 [95% confidence interval (CI) 0.79–0.88]. In 42 cases (8.1%), the third reviewer had to evaluate the medical records in order to solve the disagreement between the two other reviewers. At the end of ED evaluation, 48 patients (9.3%) were discharged home, 310 (59.9%) were admitted to an internal medicine or cardiology unit, 132 (25.5%) to an intensive care unit or high dependency unit, and 28 (5.4%) to short-stay observation unit (with 24 patients subsequently discharged home). Hospital mortality rate was 7.9% (41/518), with 24 patients who died in the CXR/NT-proBNP group and 17 in the LUS group.

Table 1 summarizes patients' baseline demographic and clinical data; Table 2 reports symptoms associated with acute dyspnoea,

Table 1 Demographic, baseline characteristics and home medications of enrolled patients, by study arm and final diagnosis

	Study arm		All patients (n = 518)	Final diagnosis	
	LUS (n = 258)	CXR/NT-proBNP (n = 260)		ADHF (n = 224)	Non-ADHF (n = 294)
Age, years, median (25th–75th percentiles)	79 (70–85)	79 (71–85)	79 (71–85)	81 (73–86)	77 (68–84)
Women, n (%)	112 (43.4)	131 (50.4)	241 (46.9)	107 (47.8)	136 (46.3)
Centre, Turin/Florence, n	205/53	206/54	411/107	185/39	226/68
Discharge from the ED/admission, n (%)	19/239 (7.4/92.6)	29/231 (11.2/88.8)	48/518 (9.3/100)	5/219 (2.2/97.8)	43/251 (14.6/85.4)
Length of stay for admitted patients, days, median (25th–75th percentiles)	9 (5–14)	10 (5–15)	9 (5–15)	9 (5–16)	9 (5–15)
Ejection fraction, %, median (25th–75th percentiles) ^a	52 (36–60)	50 (35–65)	50 (35–58)	44 (35–55)	55 (50–60)
Pleural effusion detected using LUS, n (%) ^b	116 (45)	43 (42.6)	159 (44.3)	110 (61.8)	49 (27.1)
Baseline characteristics, n (%)					
Tobacco use ^c	130 (50.4)	118 (45.4)	248 (47.9)	93 (41.5)	155 (52.7)
COPD	106 (41.1)	101 (38.9)	207 (40.0)	70 (31.3)	137 (46.6)
Asthma	13 (5.0)	14 (5.4)	27 (5.2)	5 (2.2)	22 (7.5)
Interstitial lung disease	12 (4.7)	8 (3.1)	20 (3.9)	3 (1.3)	17 (5.8)
Hypertension ^d	184 (71.3)	185 (71.2)	369 (71.2)	174 (77.7)	195 (66.3)
History of heart failure ^d	99 (38.4)	102 (39.2)	201 (38.8)	135 (60.3)	66 (22.5)
Ischaemic cardiomyopathy/CAD	89 (34.5)	82 (31.5)	171 (33.0)	94 (42.0)	77 (26.2)
Other cardiomyopathies	114 (44.2)	97 (37.3)	211 (40.7)	130 (58.0)	81 (27.6)
Diabetes ^d	80 (31.0)	76 (29.2)	156 (30.1)	78 (34.8)	78 (26.5)
Arrhythmia ^e	95 (36.8)	85 (32.7)	180 (34.8)	103 (46.0)	77 (26.2)
Dyslipidaemia ^d	72 (27.9)	66 (25.4)	138 (26.6)	76 (33.9)	62 (21.1)
Obesity ^f	52 (17.8)	44 (21.2)	96 (18.5)	44 (20.3)	52 (18.9)
Cerebrovascular accident ^d	64 (24.8)	56 (21.5)	120 (23.2)	49 (21.9)	71 (24.2)
CKD/chronic dialysis ^g	65 (25.2)	56 (21.5)	121 (23.4)	74 (33.0)	47 (16.0)
Neoplastic disease ^d	56 (21.7)	58 (22.3)	114 (22.0)	41 (18.3)	73 (24.8)
Thromboembolic disorder	13 (5.0)	14 (5.4)	27 (5.2)	14 (6.3)	13 (4.4)
Medications, n (%)					
Diuretics	151 (58.5)	145 (55.8)	296 (57.1)	148 (66.1)	148 (56.8)
Beta-blockers	105 (40.7)	94 (36.2)	199 (38.4)	126 (56.3)	73 (24.8)
ACE inhibitors	105 (40.7)	86 (33.1)	191 (36.9)	76 (34.0)	115 (39.1)
Antiplatelet agents ^a	120 (46.5)	123 (47.3)	243 (46.9)	109 (48.7)	134 (45.6)
Anticoagulants ^g	57 (22.1)	52 (20.0)	109 (21.0)	64 (28.6)	45 (15.3)
Bronchodilators	90 (34.9)	89 (34.2)	179 (34.6)	56 (25.0)	123 (41.8)
Antidiabetic agents	69 (26.7)	64 (24.6)	133 (25.7)	71 (31.7)	62 (21.1)
Steroids	72 (27.9)	75 (28.9)	147 (28.4)	41 (18.3)	106 (36.1)
Antiarrhythmic agents	39 (15.1)	34 (13.1)	73 (14.1)	42 (18.8)	31 (10.5)
Home oxygen	35 (13.6)	34 (13.1)	69 (13.3)	25 (11.2)	44 (15.0)

ACE, angiotensin-converting-enzyme; ADHF, acute decompensated heart failure; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CXR, chest radiography; ED, emergency department; LUS, lung ultrasound; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

^aAcetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, tirofiban, and dipyridamole.

^bIn the CXR/NT-proBNP group, LUS was performed in 101 patients. In total, LUS was performed in 359 patients of whom 178 affected by ADHF.

^cCurrent or remote use.

^dAny type or grade of disorder/disease.

^eAny type of cardiac rhythm disorders.

^fPresence or absence of obesity as reported in the ED chart.

^gCKD defined as chronic renal failure with creatinine level > 2 mg/dL (> 177 mol/L).

^hWarfarin, acenocoumarol, any type of heparin, fondaparinux, apixaban, rivaroxaban, dabigatran.

Table 2 Symptoms associated with dyspnoea, and clinical and laboratory findings reported at presentation in the emergency department

	Study arm		All patients (n = 518)	Final diagnosis	
	LUS (n = 258)	CXR/NT-proBNP (n = 260)		ADHF (n = 224)	Non-ADHF (n = 294)
Associated symptoms, n (%)					
Fever ^a	57 (22.1)	70 (26.9)	127 (24.5)	17 (7.6)	110 (37.4)
Dry or productive cough	113 (43.8)	112 (43.1)	225 (43.4)	47 (21.0)	178 (60.5)
Chest pain	33 (12.8)	22 (8.5)	55 (10.6)	29 (13.0)	26 (8.8)
Palpitation	16 (6.2)	17 (6.5)	33 (6.4)	21 (9.4)	12 (4.1)
Physical examination findings, median (25th–75th percentiles) or n (%)					
Heart rate, b.p.m.	90 (80–110)	90 (76–105)	90 (79–110)	90 (74–110)	90 (80–108)
Systolic blood pressure, mmHg	135 (120–158)	140 (120–150)	135 (120–150)	140 (120–160)	135 (120–150)
Diastolic blood pressure, mmHg	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)
P _a O ₂ /FiO ₂ ratio ^b	257.1 (195.2–314.3)	257.1 (189.3–300)	257.1 (190.5–304.8)	266.7 (209.8–326.2)	242.9 (183.6–295.2)
Respiratory rate, /min	28 (22–32)	25 (20–30)	28 (22–30)	28 (24–32)	24.5 (20–30)
Temperature, °C	36.1 (36–37.3)	36.1 (36–37.1)	36.1 (36–37.1)	36 (36–36.2)	36.7 (36–37.6)
Wheezing	73 (28.3)	64 (24.6)	137 (26.5)	32 (14.3)	105 (35.7)
Rales	156 (60.5)	173 (66.5)	329 (63.5)	165 (73.7)	164 (55.8)
Peripheral oedema	104 (40.3)	104 (40)	208 (40.2)	133 (59.4)	75 (25.5)
Non-invasive mechanical ventilation ^b in the ED	34 (13.2)	30 (11.5)	64 (12.4)	43 (19.2)	21 (7.1)
Laboratory findings, median (25th–75th percentiles)					
White blood cells, 10 ⁶ cells/L	9150 (7100–12820)	9370 (7220–12530)	9310 (7145–12715)	9120 (6930–11890)	9580 (7260–13370)
Haemoglobin, g/dL	12.5 (10.8–13.7)	12.5 (11–14.3)	12.5 (10.9–14.1)	11.9 (10.5–13.6)	13 (11.3–14.4)
Platelets, 10 ⁹ cells/L	237.5 (183–304.5)	232 (180–305)	235.5 (181–305)	232.5 (181–301)	236.5 (181.5–309.5)
Glucose, mg/dL	132.5 (110–175)	129 (109–168)	130 (109–171)	141 (113–192)	126 (106–160)
Creatinine, mg/dL	1.1 (0.8–1.5)	1 (0.8–1.5)	1.1 (0.8–1.5)	1.3 (0.9–1.7)	1 (0.8–1.3)
Sodium, mmol/L	138 (135–140)	138 (135–141)	138 (135–141)	139 (136–141)	138 (135–140)
Potassium, mmol/L	4.1 (3.8–4.5)	4.1 (3.8–4.5)	4.1 (3.8–4.5)	4.2 (3.9–4.4)	4.1 (3.7–4.4)
AST, IU/L	22 (17–32)	21 (17–29)	21 (17–31)	23 (17–33)	20 (17–28)
ALT, IU/L	21 (14–32)	20 (14–30)	20 (14–31)	21 (14–34.5)	20 (15–30)
Troponin, ng/mL	0.034 (0.016–0.058)	0.033 (0.016–0.070)	0.033 (0.016–0.063)	0.046 (0.023–0.076)	0.024 (0.011–0.049)
NT-proBNP, pg/mL	1993 (608–5295)	1686 (360–6005)	1903 (441–5408)	4237 (2011.5–8626.5)	695 (236–2305)
D-dimer, mg/L	0.7 (0.4–1.9)	0.9 (0.5–1.7)	0.8 (0.43–1.84)	0.92 (0.59–1.81)	0.77 (0.33–1.84)
CRP, mg/L	19.9 (7.3–60.2)	23.5 (7.1–63.3)	21.7 (7.3–62.2)	14.1 (5.3–28.8)	33.3 (11.3–97.9)
Lactates, mmol/L	1.4 (0.9–2.1)	1.4 (0.9–2)	1.4 (0.9–2.1)	1.5 (1–2.1)	1.3 (0.9–1.9)

ADHF, acute decompensated heart failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CXR, chest radiography; ED, emergency department; LUS, lung ultrasound; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P_aO₂/FiO₂, ratio of partial pressure of arterial oxygen and fraction of inspired oxygen.

^aTympanic temperature > 38.3°C (or > 101°F).

^bCalculated using P_aO₂ (mmHg) measured at the time of the first arterial blood gas analysis, and FiO₂ provided, as reported in the case report form.

^cAny type of non-invasive mechanical ventilation.

and clinical and laboratory findings detected during the initial clinical assessment.

Other commonly performed tests, either in the ED or during hospitalization (but always after collection of study data outcomes — i.e., presumptive aetiology of dyspnoea) were: echocardiography (performed in 69.9% of patients enrolled in the study), computed tomography (29%), coronary angiography (7.4%), and Doppler sonographic study of the limbs (7.8%).

The median number of positive lung zones among all enrolled patients was 3 (25th–75th percentiles: 1–6). In the ADHF final diagnosis group, the median number of positive zones was 6 (25th–75th percentiles: 4–7), in the non-ADHF final diagnosis group it was 1 (25th–75th percentiles: 0–3). Forty-six per cent of patients had zero, one or two positive zones, 6% had three

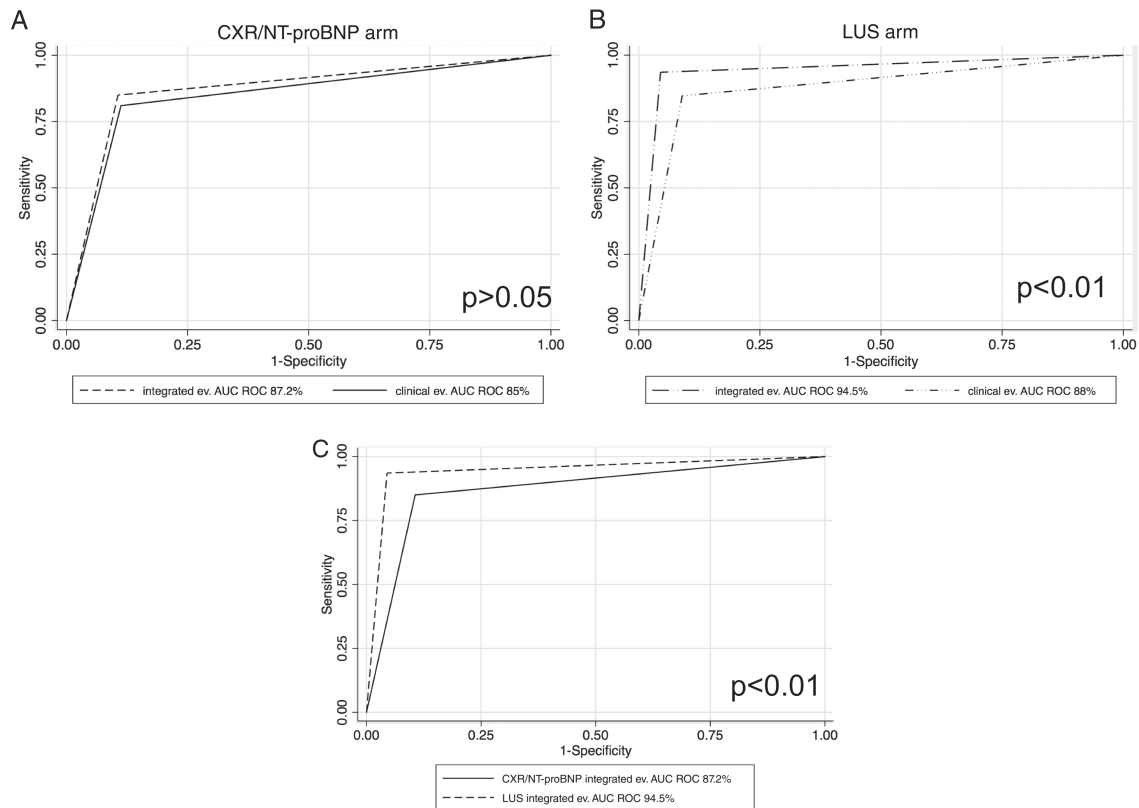
positive zones, 11% had four positive zones, and 11% had eight positive zones.

Forty-four physicians participated in the study, enrolling a median number of four patients/each (25th–75th percentiles: 2–14).

Outcomes

Figure 3 reports accuracy, ROC curves, and AUC ROC for clinical and combined evaluations in the two groups (clinical examination plus LUS or clinical examination plus CXR/NT-proBNP).

The AUC ROC of the integrated approach in the LUS arm was significantly higher than that in the CXR/NT-proBNP arm (94.5% vs. 87.2%, respectively; $P < 0.01$).



		CXR/NT-proBNP arm (N=260)	LUS arm (N=258)
clinical evaluation	SE	81.0 (71.9-88.2)	84.7 (77.1-90.5)
	SPE	88.8 (82.8-93.2)	91.0 (84.9-95.3)
	PPV	81.8 (72.8-88.9)	89.7 (82.8-94.6)
	NPV	88.2 (82.2-92.7)	86.5 (79.8-91.7)
	LR+	7.2 (4.61-11.2)	9.46 (5.48-16.3)
	LR-	0.21 (0.14-0.32)	0.17 (0.11-0.25)
Integrated evaluation	SE	85.0 (76.5-91.4)	93.5 (87.7-97.2)
	SPE	89.4 (83.5-93.7)	95.5 (90.5-98.3)
	PPV	83.3 (74.7-90.0)	95.1 (89.6-98.2)
	NPV	90.5 (84.8-94.6)	94.1 (88.7-97.4)
	LR+	8 (5.1-12.6)	20.9 (9.54-45.7)
	LR-	0.17 (0.11-0.27)	0.07 (0.03-0.13)

Figure 3 Receiver operating characteristic (ROC) curves and diagnostic accuracy of standard of care acute decompensated heart failure diagnostic work-up (A), and a diagnostic approach based on clinical evaluation integrated with lung ultrasound (B). (C) Direct comparison between CXR/NT-proBNP- and LUS-integrated approach. The number of false negatives and false positives was 15 and 17 in the integrated CXR/NT-proBNP arm, and 8 and 6 in the integrated LUS arm, respectively; 'integrated evaluation' refers to results of clinical evaluation combined with LUS or CXR/NT-proBNP. AUC, area under the ROC curve; iCXR/NT-proBNP, integrated chest radiography/N-terminal pro-B-type natriuretic peptide; iLUS, integrated lung ultrasound; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SPE, specificity.

The accuracy of clinical evaluation alone in the identification of ADHF was not significantly different between the two groups ($P > 0.05$). There were no statistically significant differences in terms of SE and SPE between clinical evaluation and the approach combining CXR/NT-proBNP with the initial clinical assessment ($P > 0.05$). In contrast, the increase in SE and SPE between clinical evaluation alone and the approach combining LUS with the initial clinical assessment was statistically significant ($P < 0.01$ for SE, $P < 0.05$ for SPE).

We performed additional analyses in some subgroups of patients, namely patients with ADHF and co-existence of COPD (online supplementary Figure S1), patients with preserved and reduced ejection fraction (EF) (online supplementary Figure S2), and patients with acute dyspnoea likely caused by mixed aetiology (e.g. ADHF associated with an upper respiratory tract infection, or an exacerbated COPD, or any type of pneumonia) (online supplementary Figure S3).

An additional sensitivity analysis was performed by excluding patients with other possible causes of sonographic vertical artefacts/B-lines. The clinical evaluation showed a SE of 81% (95% CI 71.9–88.2%) and 84.4% (95% CI 76.8–90.4%), a SPE of 88.7% (95% CI 82.5–93.3%) and 90.3% (95% CI 83.7–94.9%), a PPV of 82.7% (95% CI 73.7–89.6%) and 89.6% (95% CI 82.5–94.5%), and a NPV of 87.5% (95% CI 81.2–92.3%) and 85.5% (95% CI 78.3–91%) in the CXR/NT-proBNP and LUS arms, respectively. In the same sub-cohort, the integrated evaluation showed a SE of 85% (95% CI 76.5–91.4%) and 93.4% (95% CI 87.5–97.1%), a SPE of 88.7% (95% CI 82.5–93.3%) and 95.2% (95% CI 89.8–98.2%), a PPV of 83.3% (95% CI 74.7–90%) and 95% (95% CI 89.4–98.1%), and a NPV of 89.9% (95% CI 83.8–94.2%) and 93.7% (95% CI 87.9–97.2%) in the CXR/NT-proBNP and LUS arms, respectively.

The net reclassification improvement provided by LUS was 8.9% and 4.5% for ADHF and non-ADHF, respectively, noticeably higher than that provided for CXR/NT-proBNP (4% and 0.6%, respectively).

Using the prevalence of ADHF measured in our study (43%) as the threshold probability for a NB analysis, the use of the current standard ADHF diagnostic work-up (clinical evaluation plus CXR/NT-proBNP) would reduce the diagnostic errors of the clinical assessment alone by 2.42 cases/100 patients. In contrast, the approach combining LUS with clinical evaluation would reduce the diagnostic errors by 7.98 cases/100 patients. Figure 4 shows the reclassification tables and decision curves for each group. Table S1 reports a sensitivity analysis for NBs using different prevalence of ADHF.

In total, 359 patients underwent LUS during their ED stay; 159 patients showed pleural effusion; the effusion was unilateral in 73 (with right pleural effusion in 41 cases) and bilateral in 86 patients (Table 1). Both unilateral and bilateral sonographic presence of pleural effusion had only moderate accuracy for the diagnosis of ADHF, with a SE of 36.4% (95% CI 27.4–46.3%) and 51.1% (95% CI 42.5–59.6%), and SPE of 79.5% (95% CI 72.6–85.4%) and 89.8% (95% CI 83.7–94.2%), respectively.

The median time needed to formulate the diagnostic hypothesis, measured from the time when the first diagnostic hypothesis was recorded to when the integrated diagnosis taking onto

account the results of the following tests (CXR/NT-proBNP or LUS, respectively) was formulated, was 104.5 min (25th–75th percentiles: 80–131.5 min) in the CXR/NT-proBNP group, and 5 min (25th–75th percentiles: 4–9 min) in the LUS group ($P < 0.01$).

A diagnostic algorithm in which LUS is integrated with the other diagnostic tests is presented in the online supplementary Figure S4.

Discussion

In this trial we found that, in adult patients presenting to the ED with acute dyspnoea, a diagnostic approach combining LUS with clinical evaluation outperforms the current standard diagnostic work-up (based on clinical evaluation plus CXR and NT-proBNP measurement) in the diagnosis of ADHF. In particular, in our study, adding LUS to the initial clinical assessment (i.e. past medical history, history of present illness, physical examination, ABG and ECG) significantly increased both SE and SPE, whereas inclusion of CXR and NT-proBNP did not improve diagnostic accuracy for ADHF. With the exception of a single-operator study,³⁷ no other randomized studies had previously tested this research hypothesis.

To evaluate not only the accuracy, but also the clinical usefulness of LUS integration for ADHF diagnosis, we estimated NRI and NB, using reclassification tables and decision curve analysis, respectively. Diagnostic accuracy, by estimating the association between a diagnostic test and the true disease status, only represents a performance measure, but it does not inform on the clinical usefulness of a diagnostic test in the 'real world'. 'Useful' tests must have high diagnostic accuracy, but 'accurate' tests do not necessarily provide a real clinical benefit.³⁵ The addition of LUS was able to correctly reclassify 8.9% of patients with ADHF, and 4.5% of patients with non-ADHF causes of dyspnoea. Moreover, in our population, with a prevalence of ADHF similar to the one observed in high-income countries (40–45%), this LUS approach reduced diagnostic errors resulting from the initial clinical assessment in approximately 8 cases out of 100 patients. Addition of CXR and NT-proBNP measurement only reduced the diagnostic error in approximately 2.5 cases out of 100 patients evaluated.

Beside LUS had shown a high diagnostic accuracy in patients presenting to the ED with acute respiratory conditions in several observational studies.^{5,20–22,38,39} In particular, detection of B-lines by LUS, expression of increased lung density and often secondary to increased water content,^{27,40} has been shown to be useful in diagnosing ADHF in patients presenting with acute dyspnoea.²⁵ However, most of the studies addressing this issue have significant limitations, being either single centre studies, with a relatively small population,^{20–22,38} or performed by a single, highly skilled investigator.^{37,41} No previous studies, including our previous prospective observational multicentre study,⁵ compared directly this approach with the standard work-up currently recommended for ADHF diagnosis.⁶

In addition, the identification of pleural effusion by LUS showed only moderate accuracy for the diagnosis of ADHF in patients with acute dyspnoea in our study, as already found in previous studies.^{7,13}

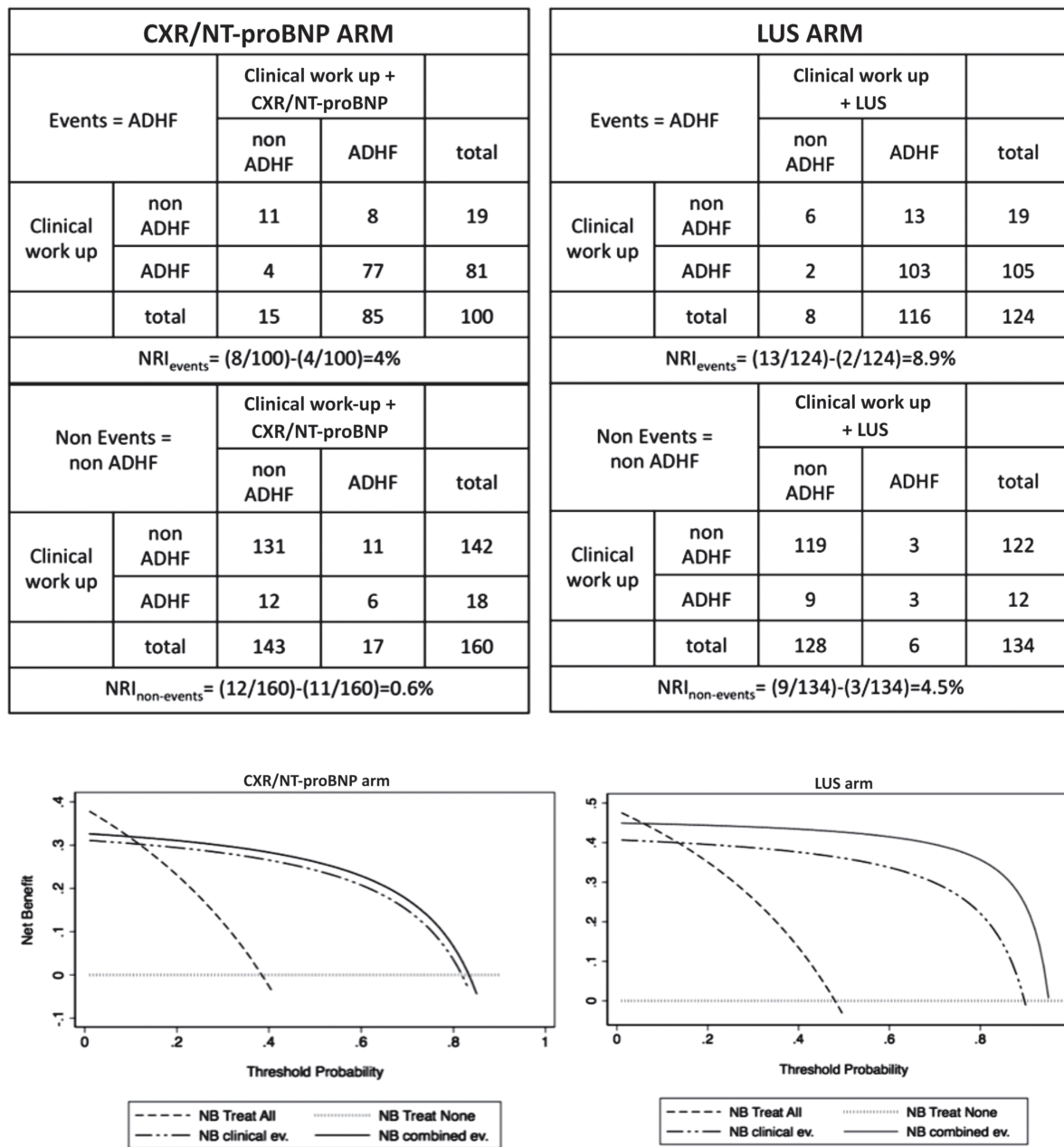


Figure 4 (Upper panel) Reclassification tables and net reclassification index (NRI) for acute decompensated heart failure (ADHF) and non-ADHF for each group. (Lower panel) Decision curves for clinical assessment and standard ADHF diagnostic work-up (left), and for combining clinical assessment and lung ultrasound (LUS) (right). CRX/NT-proBNP, chest radiography/N-terminal pro-B-type natriuretic peptide; NB, net benefit.

In our study, the clinical examination alone showed a quite good diagnostic accuracy (86%), still not far from that reported (85%) by other authors.¹⁵ In their study, McCullough and colleagues asked the participant emergency physicians of seven EDs to evaluate the probability of heart failure classifying dyspnoeic patients in three classes of risk (low, intermediate, and high). An intermediate probability was reported in 27.8% of patients, but the amount of patients clinically classified with more certainty, i.e. low or

high probability, was 72.2%. This can be due to the well-known phenomenon of the 'intermediate choice'. When given the option to choose an 'uncertain' and maybe more 'comfortable' diagnosis vs. more definite diagnoses, the former is more often selected.⁴² This is the reason why, in our protocol, we purposely decided to dichotomize the assigned diagnoses.

In comparison with previous studies^{12,43} showing an improved accuracy of the natriuretic peptides compared to the clinical

examination in diagnosing heart failure, it could be surprising that in our study adding NT-proBNP and CXR did not ameliorate the AUC ROC of the clinical evaluation. However, both cited studies were intrinsically different from ours, since they tested the accuracy of a new diagnostic test, whereas our aim was to compare two integrated approaches vs. clinical examination alone. In our study, the integrated approach with NT-proBNP and CXR still improved the accuracy of the clinical examination, although statistical significance was not achieved. This can be likely related to the difference in terms of sample size (1586 patients were enrolled in the Maisel's study,⁴³ and 1256 in that of Januzzi¹³), and to the use of two diagnostic tests together, NT-proBNP and CXR. CXR is known, indeed, to have a high rate of false negatives (about one out of five patients) among patients with suspected ADHF in the ED,¹⁰ and it may have contributed to reduce the overall accuracy of the integrated standard of care arm.

In our study, there is a relatively high percentage of patients with elevated level of NT-proBNP in the non-ADHF group, and of patients with high inflammatory parameters in the ADHF group. In our opinion, these results suggest the presence of multiple co-morbidities, rather than of dyspnoea of 'mixed' origin. We would like also to stress the concept that the results of biomarkers were interpreted by the treating physician (and later by the 'adjudicators') together with the information coming from history, physical examination, ECG, ABG, and other diagnostic tests, allowing a more accurate and complete definition of the aetiology of dyspnoea in each patient.

We performed additional analyses for assessing the diagnostic accuracy in some subgroups of patients.

First, we tested our hypothesis in patients dichotomized on the basis of their EF (reduced or preserved; online supplementary Figure S2). In both arms and in both groups, the integrated approach showed a better AUC ROC than clinical evaluation alone, although only the LUS-integrated diagnostic approach reached the statistical significance, both, compared to the clinical evaluation alone and to the CXR/NT-proBNP-integrated approach, among ADHF patients with preserved EF. However, since these analyses were run on small samples (113 patients with reduced EF and 138 with preserved EF), these results need to be confirmed in other cohorts before being translated in daily clinical practice.

Second, we tested the research hypothesis in patients with concomitant ADHF and COPD, either exacerbated or not (online supplementary Figure S1). Also in these patients, the use of LUS was more accurate than the integration with CXR/NT-proBNP, and the integration with both LUS and CXR/NT-proBNP resulted in an increase of AUC ROC compared to clinical evaluation alone, but the low number of patients in these subgroups does not allow us to reach definitive conclusions.

A similar analysis was also performed among patients with acute dyspnoea of mixed aetiology, defined after chart revision of all patients (online supplementary Figure S3). Also in this case, the combination of LUS with clinical evaluation outperformed that with CXR/NT-proBNP and the integration with both LUS and CXR/NT-proBNP suggested an increase in AUC ROC compared to the clinical evaluation alone, although not statistically

significant, again likely due to the low number of patients in these sub-categories.

Finally, when we exclude the few patients who had other possible causes of B-lines (e.g. interstitial lung diseases or active dialysis), the additional analysis confirmed the increased performance of the LUS-integrated approach compared to the clinical evaluation, showing no benefit from the integration with NT-proBNP and CXR.

In our study, we probably did not enrol patients with ADHF presenting with signs and symptoms of low cardiac output but without significant lung congestion (i.e. without acute dyspnoea), who account for 5–10% of patients with ADHF.⁶ We can suppose that an integrated point-of-care sonographic approach, adding also cardiac and inferior vena cava examination to LUS, could represent a useful diagnostic tool in these patients, but this hypothesis needs to be tested in an ad hoc study. This view is supported by a recent study by Ohman and colleagues,⁴⁴ which showed that the combination of LUS with an advanced echocardiographic approach, including the evaluation of left atrial pressure (i.e. using E/e') provides excellent accuracy in the diagnosis of ADHF. However, the learning curve of this tool would be surely much longer than that for LUS and the same authors acknowledged this limitation of the study in terms of external validity. In our opinion, in this patient sub-population it is possible that natriuretic peptides preserve a high diagnostic performance.

In agreement with previously published studies,^{20,45} our study also showed that LUS significantly reduced the time needed to formulate the new diagnostic hypothesis, as compared to the standard diagnostic work-up for ADHF, suggesting potential organizational and logistical benefits. In enrolling patients, each participating physician was asked to collect the timing at the beginning of clinical evaluation and that at which the integrated diagnosis was formulated. In the CXR/NT-proBNP arm, this interval is affected by the time required to perform these diagnostic tests outside of the ED (transfer of blood tubes, analytical time, imaging — CXR was performed bedside only in 48.2% of patients). Whereas we acknowledge that the treating physician, in the meantime, evaluated other patients, and not only 'waited for the results', we decided to collect the exact time when the integrated diagnosis was formulated. In our institutions, but it is a common scenario also in other EDs, both in Italy and worldwide, even in non-tertiary centres, several ultrasound machines are almost immediately available (i.e. present in the ED and not shared with other services) and this contributed to make LUS- faster than CXR/NT-proBNP-integrated evaluation. The same emergency physician evaluating the patient also performed LUS, with no need for external resources (in the EDs participating to this study, this is the usual way of proceeding, even outside of clinical studies). Although LUS is a well-known operator-dependent diagnostic tool, it has already been shown to be highly reproducible for both image acquisition and image interpretation even when performed by relatively inexperienced sonographers.^{38,46} Also in a previous paper published by our group,⁵ we showed a very high agreement between expert and naïve operators in performing LUS in dyspnoeic patients in the ED. Based on these data, we think that in

most of the EDs, also in non-tertiary centres, several operators can now be considered 'expert' in LUS.

The generalizability of our results is supported by several factors. Firstly, the demographic characteristics of our study population, in terms of advanced age and co-morbidities, are similar to those reported in other studies and well reflect the 'real-world' ED patients.⁴⁷ The advanced age and the high rate of co-morbidity of our patients could justify a median length of stay as long as 9 days in our study, similar to that of other European but longer than in North American studies.^{48,49}

Moreover, generalizability is warranted by the large number of patients enrolled by several operators with different levels of expertise (still all considered competent in performance of LUS according to the Italian Society of Emergency Medicine standards²⁶). In addition, patient management was not regulated by a strict protocol, but rather left to clinical judgement and 'real-world' practices. Finally, to maintain a high external validity and to avoid overestimation of the diagnostic accuracy of the LUS approach, we did not exclude patients with high risk of B-lines due to other clinical conditions (e.g. dialysis⁵⁰ and interstitial lung diseases,⁵¹ 9 and 22 patients, respectively).

Some limitations should be considered in interpreting our results. The most important, although common in similar studies,^{12,43} is the lack of a standard criterion to determine the final diagnosis of ADHF. To this end, we used the independent review of the medical records by two expert physicians, with a third physician reviewing discordant cases, an approach already chosen by other investigators.^{5,20,38,39}

Second, we asked both investigators and reviewers, especially in patients with possible multiple concomitant causes of dyspnoea (e.g. pneumonia and ADHF), to indicate the aetiology they considered to be the most relevant in order to minimize the risk of 'intermediate level' classification.⁴² Although this could have led to some diagnostic errors, these should have occurred in both groups and directions, likely not affecting our findings.

Third, LUS, alone, is definitively characterized by the inability to discriminate different forms of diffuse interstitial syndrome (e.g. interstitial lung disease, ADHF, acute respiratory distress syndrome, interstitial pneumonitis). On the contrary, the integration of LUS with clinical data would increase its diagnostic accuracy in all these conditions.^{24,52,53} In the effort to stress the 'real-world' nature of our study, we decided not to exclude patients with reported or suspected interstitial lung disease.

Fourth, the proportion of adjudicated ADHF diagnoses is higher in the LUS group than in the CXR/NT-proBNP group. This can be at least partially explained by a potentially less ambiguous diagnostic definition provided by LUS. Furthermore, although the adjudicators were blinded to the LUS results, they may have likely impacted on treatment and further diagnostic work-up, potentially leading to a higher agreement between emergency physicians and adjudicators in the LUS group.

Fifth, we could not enrol all consecutive patients presenting to the ED with acute dyspnoea, since the presence of an emergency physician with knowledge in LUS was required. Based on the ED discharge charts available for the enrolment period, we estimated that, in the worst scenario, we could have lost 20–30% of patients

with acute dyspnoea, mostly because of the ED overcrowding in the cold seasons. At the time of the study enrolment, more than 80% of staff physicians working in our ED were skilled in LUS, minimizing the loss of patients due to the absence of an expert provider.

Finally, we were not able to estimate interobserver agreement for LUS, as this would have required repeating twice LUS in acutely ill patients, potentially affecting patient care and impacting on the ED resources. However, although LUS is obviously an operator-dependent diagnostic tool, it has already been shown to have high repeatability and reproducibility for both image acquisition and image interpretation, even when performed by relatively inexperienced sonographers.^{5,38,46}

Our study demonstrates that, in adult patients presenting to the ED with acute dyspnoea, a diagnostic protocol based on the integration of LUS and clinical assessment is more accurate than the currently recommended diagnostic approach based on clinical evaluation, CXR and NT-proBNP measurement.

We do not have the ambition to modify current guidelines, but our findings are very encouraging regarding the efficacy of the integration of LUS with clinical evaluation. We think that the integration of LUS with the current diagnostic approach (online supplementary *Figure S4*) has the potential to accelerate and improve the accuracy of ADHF diagnosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Sensitivity analysis on the net benefit of integrated evaluation at different prevalence of ADHF in both trial arms.

Figure S1. AUC ROC of the clinical and the integrated evaluation for patients with ADHF and co-existence of COPD in the CXR/NT-proBNP and LUS arms (A) and direct comparison between CXR/NT-proBNP- and LUS-integrated approach (B).

Figure S2. AUC ROC of the clinical and the integrated evaluation for patients with reduced and preserved ejection fraction in the CXR/NT-proBNP and LUS arms (A) and direct comparison between CXR/NT-proBNP- and LUS-integrated approach (B).

Figure S3. AUC ROC of the clinical and the integrated evaluation for patients with dyspnoea likely caused by mixed aetiology in the CXR/NT-proBNP and LUS arms (A) and direct comparison between CXR/NT-proBNP- and LUS-integrated approach (B).

Figure S4. A proposed diagnostic algorithm for distinguishing between ADHF and non-ADHF acute dyspnoea with an approach integrating LUS with usual evaluation (i.e. clinical exam, dosage of natriuretic peptide, and chest radiography).

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Conflict of interest: none to declare.

Appendix

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