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

Pivetta E[1,2], Goffi A[3,4,5], Nazerian P[6], Castagno D[7], Tozzetti C[8], Tizzani P[2,9], Tizzani M[2], Porrino G[2], Ferreri E[2], Busso V[2], Morello F[2], Paglieri C[2], Masoero M[10], Cassine E[11], Bovaro F[10], Grifoni S[6], Maule MM[1], Lupia E[2,12]; Study Group on Lung Ultrasound from the Molinette and Careggi Hospitals

1Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Italy.
2Division of Emergency Medicine and High Dependency Unit, AOU Città della Salute e della Scienza di Torino, Turin, Italy.
3Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada.
4Department of Medicine, Division of Respirology (Critical Care), University Health Network, Toronto, Canada.
5Department of Medicine, University of Toronto, Toronto, Canada.
6Department of Emergency Medicine, Careggi University Hospital, Florence, Italy.
7Division of Cardiology, Department of Medical Sciences, University of Turin, Turin, Italy.
8Division of Internal Medicine, Department of Emergency Medicine, Careggi University Hospital, Florence, Italy.
9Residency Program in Internal Medicine, University of Turin, Turin, Italy.
10Residency Program in Emergency Medicine, University of Turin, Turin, Italy.
11School of Medicine, University of Turin, Turin, Italy.
12Department of Medical Sciences, University of Turin, Turin, Italy.

Abstract

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 then 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.

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.

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 standards[26] and performed and interpreted at least 40 LUS examinations[5]) 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 aetiologic 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, 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 failure[28] (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 (±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 data[31] 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 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, and clinical and laboratory findings detected during the initial clinical assessment.
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)

	Study arm		All patients (n = 518)	Final diagnosis	
	LUS (*n* = 258)	CXR/NT□proBNP (*n* = 260)		ADHF (*n* = 224)	Non□ADHF (*n* = 294)
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.
- [a] Acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, tirofiban, and dipyridamole.
- [b] In 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.
- [c] Current or remote use.
- [d] Any type or grade of disorder/disease.
- [e] Any type of cardiac rhythm disorders.
- [f] Presence or absence of obesity as reported in the ED chart.
- [g] CKD defined as chronic renal failure with creatinine level > 2 mg/dL (> 177 mol/L).
- g Warfarin, 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)

	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_aO_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)

	Study arm		All patients (*n* = 518)	Final diagnosis	
	LUS (*n* = 258)	CXR/NT‐proBNP (*n* = 260)		ADHF (*n* = 224)	Non‐ADHF (*n* = 294)
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_aO_2/FiO_2, ratio of partial pressure of arterial oxygen and fraction of inspired oxygen.
- [a] Tympanic temperature > 38.3°C (or > 101°F).
- [b] Calculated using P_aO_2 (mmHg) measured at the time of the first arterial blood gas analysis, and FiO_2 provided, as reported in the case report form.
- [c] Any type of non‐invasive mechanical ventilation.

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; $P < 0.01$).

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.

Bedside 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
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 studies12, 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 Januzzi[13]), 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 standards[26]). 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. dialysis[50] 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.

Acknowledgements
We would like to thank all the colleagues of participating emergency departments for their work and collaboration.
Conflict of interest: none to declare.

Appendix

Study Group on Lung Ultrasound from the Molinette and Careggi Hospitals

Città della Salute e della Scienza di Torino – Molinette University Hospital

Baron Paolo, Bono Alessia, Buonafede Giuseppina, Collini Andrea, Conterno Andrea, Davini Ottavio, Del Rizzo Paola, Evangelista Andrea, Fascio Pecetto Paolo, Ferrera Patrizia, Forno Daniela, Giachino Francesca, Gregoretti Maria Grazia, Grillo Sara, Lerda Alda, Lison Davide, Merico Franca, Merletti Franco,

Moiraghi Corrado, Novelli Giulia, Pigozzi Luca, Pivetti Sonia, Quaglia Paolo, Sacchi Claudia, Saglio Elisa, Segre Elisabetta, Soardo Flavia, Steri Fabio, Sozzi Michela, Suman Francesca, Tamone Cristina, Veglio Maria Grazia.

Careggi University Hospital

Allinovi Marco, Betti Laura, Bigiarini Sofia, Bondi Ernesta, Casanova Barbara, Castelli Matteo, Chiarlone Melisenda, Dilaghi Beatrice, Fallani Grazia, Federico Roberto, Giannazzo Giuseppe, Gigli Chiara, Gualtieri Simona, Haxhiraj Eriola, Mariannini Juri, Moroni Federico, Nencioni Andrea, Ottaviani Maddalena, Pavellini Andrea, Pepe Giuseppe, Ponchietti Stefano, Risso Michele, Salti Francesca, Ticali Piero Francesco, Trause Federica, Simone Vanni, Viviani Gabriele.

References

☐ 1National Hospital Ambulatory Medical Care Survey: 2011 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2011_ed_web_tables.pdf (23 November 2018).

☐ 2Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009;11:130–139.

☐ 3Lien CT, Gillespie ND, Struthers AD, McMurdo ME. Heart failure in frail elderly patients: diagnostic difficulties, co☐morbidities, polypharmacy and treatment dilemmas. Eur J Heart Fail 2002;4:91–98.

☐ 4Ray P, Arthaud M, Birolleau S, Isnard R, Lefort Y, Boddaert J, Riou B. Comparison of brain natriuretic peptide and probrain natriuretic peptide in the diagnosis of cardiogenic pulmonary edema in patients aged 65 and older. J Am Geriatr Soc 2005;53:643–648.

☐ 5Pivetta E, Goffi A, Lupia E, Tizzani M, Porrino G, Ferreri E, Volpicelli G, Balzaretti P, Banderali A, Iacobucci A, Locatelli S, Casoli G, Stone MB, Maule MM, Baldi I, Merletti F, Cibinel GA, Baron P, Battista S, Buonafede G, Busso V, Conterno A, Del Rizzo P, Ferrera P, Pecetto PF, Moiraghi C, Morello F, Steri F, Ciccone G, Calasso C, Caserta MA, Civita M, Condo' C, D'Alessandro V, Del Colle S, Ferrero S, Griot G, Laurita E, Lazzero A, Lo Curto F, Michelazzo M, Nicosia V, Palmari N, Ricchiardi A, Rolfo A, Rostagno R, Bar F, Boero E, Frascisco M, Micossi I, Mussa A, Stefanone V, Agricola R, Cordero G, Corradi F, Runzo C, Soragna A, Sciullo D, Vercillo D, Allione A, Artana N, Corsini F, Dutto L, Lauria G, Morgillo T, Tartaglino B, Bergandi D, Cassetta I, Masera C, Garrone M, Ghiselli G, Ausiello L, Barutta L, Bernardi E, Bono A, Forno D, Lamorte A, Lison D, Lorenzati B, Maggio E, Masi I, Maggiorotto M, Novelli G, Panero F, Perotto M, Ravazzoli M, Saglio E, Soardo F, Tizzani A, Tizzani P, Tullio M, Ulla M, Romagnoli E, SIMEU Group for Lung Ultrasound in the Emergency Department in Piedmont. Lung ultrasound☐implemented diagnosis of acute decompensated heart failure in the ED: a SIMEU Multicenter Study. Chest 2015;148:202–210.

☐ 6Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González☐Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.

☐ 7Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA 2005;294:1944–1956.

☐ 8Peacock WF, Braunwald E, Abraham W, Albert N, Burnett J, Christenson R, Collins S, Diercks D, Fonarow G, Hollander J, Kellerman A, Gheorghiade M, Kirk D, Levy P, Maisel A, Massie BM, O'Connor C, Pang P, Shah M, Sopko G, Stevenson L, Storrow A, Teerlink J. National Heart, Lung, and Blood Institute working group on emergency department management of acute heart failure: research challenges and opportunities. J Am Coll Cardiol 2010;56:343–351.

☐ 9Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996–1004.

☐ 10Collins SP, Lindsell CJ, Storrow AB, Abraham WT. ADHERE Scientific Advisory Committee, Investigators and Study GroupPrevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med 2006;47:13–18.
☐ 11Gillespie ND, McNeill G, Pringle T, Ogston S, Struthers AD, Pringle SD. Cross sectional study of contribution of clinical assessment and simple cardiac investigations to diagnosis of left ventricular systolic dysfunction in patients admitted with acute dyspnoea. BMJ 1997;314:936–940.
☐ 12Januzzi JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd☐Jones DM, Brown DF, Foran☐Melanson S, Sluss PM, Lee☐Lewandrowski E, Lewandrowski KB. The N☐terminal Pro☐BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948–954.
☐ 13Martindale JL, Wakai A, Collins SP, Levy PD, Diercks D, Hiestand BC, Fermann GJ, deSouza I, Sinert R. Diagnosing acute heart failure in the emergency department: a systematic review and meta☐analysis. Acad Emerg Med 2016;23:223–242.
☐ 14Bayés☐Genís A, Santaló☐Bel M, Zapico☐Muñiz E, López L, Cotes C, Bellido J, Leta R, Casan P, Ordóñez☐Llanos J. N☐terminal probrain natriuretic peptide (NT☐proBNP) in the emergency diagnosis and in☐hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail 2004;6:301–308.
☐ 15McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B☐type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation 2002;106:416–422.
☐ 16Berdagué P, Caffin PY, Barazer I, Vergnes C, Sedighian S, Letrillard S, Pilossof R, Goutorbe F, Piot C, Reny JL. Use of N☐terminal prohormone brain natriuretic peptide assay for etiologic diagnosis of acute dyspnea in elderly patients. Am Heart J 2006;151:690–698.
☐ 17Collins SP, Peacock WF, Lindsell CJ, Clopton P, Diercks DB, Hiestand B, Hogan C, Kontos MC, Mueller C, Nowak R, Chen WJ, Huang CH, Abraham WT, Amsterdam E, Breidthardt T, Daniels L, Hasan A, Hudson M, McCord J, Naz T, Wagoner LE, Maisel A. S3 detection as a diagnostic and prognostic aid in emergency department patients with acute dyspnea. Ann Emerg Med 2009;53:748–757.
☐ 18Lokuge A, Lam L, Cameron P, Krum H, de Villiers S, Bystrzycki A, Naughton MT, Eccleston D, Flannery G, Federman J, Schneider HG. B☐type natriuretic peptide testing and the accuracy of heart failure diagnosis in the emergency department. Circ Heart Fail 2010;3:104–110.
☐ 19Robaei D, Koe L, Bais R, Gould I, Stewart T, Tofler GH. Effect of NT☐proBNP testing on diagnostic certainty in patients admitted to the emergency department with possible heart failure. Ann Clin Biochem 2011;48:212–217.
☐ 20Cibinel GA, Casoli G, Elia F, Padoan M, Pivetta E, Lupia E, Goffi A. Diagnostic accuracy and reproducibility of pleural and lung ultrasound in discriminating cardiogenic causes of acute dyspnea in the emergency department. Intern Emerg Med 2012;7:65–70.
☐ 21Liteplo AS, Marill KA, Villen T, Miller RM, Murray AF, Croft PE, Capp R, Noble VE. Emergency thoracic ultrasound in the differentiation of the etiology of shortness of breath (ETUDES): sonographic B☐lines and N☐terminal pro☐brain☐type natriuretic peptide in diagnosing congestive heart failure. Acad Emerg Med 2009;16:201–210.
☐ 22Volpicelli G, Mussa A, Garofalo G, Cardinale L, Casoli G, Perotto F, Fava C, Frascisco M. Bedside lung ultrasound in the assessment of alveolar☐interstitial syndrome. Am J Emerg Med 2006;24:689–696.
☐ 23Al Deeb M, Barbic S, Featherstone R, Dankoff J, Barbic D. Point☐of☐care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta☐analysis. Acad Emerg Med 2014;21:843–852.
☐ 24Gargani L, Frassi F, Soldati G, Tesorio P, Gheorghiade M, Picano E. Ultrasound lung comets for the differential diagnosis of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. Eur J Heart Fail 2008;10:70–77.
☐ 25Collins S, Storrow AB, Albert NM, Butler J, Ezekowitz J, Felker GM, Fermann GJ, Fonarow GC, Givertz MM, Hiestand B, Hollander JE, Lanfear DE, Levy PD, Pang PS, Peacock WF, Sawyer

DB, Teerlink JR, Lenihan DJ, SAEM/HFSA Acute Heart Failure Working Group. Early management of patients with acute heart failure: state of the art and future directions. A consensus document from the Society for Academic Emergency Medicine/Heart Failure Society of America Acute Heart Failure Working Group. J Card Fail 2015;21:27–43.
☐ 26Italian Society of Emergency Medicine standards. https://www.simeu.it/w/download/get/0/LineeGuida%20Eco%20SIMEU%201210.pdf/download/articoli/famiglie/250 (5 December 2018).
☐ 27Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breitkreutz R, Seibel A, Neri L, Storti E, Petrovic T. International Liaison Committee on Lung Ultrasound (ILC☐LUS) for International Consensus Conference on Lung Ultrasound (ICC☐LUS)International evidence☐based recommendations for point☐of☐care lung ultrasound. Intensive Care Med 2012;38:577–591.
☐ 28McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez☐Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803–869.
☐ 29Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Stat 1947;18:50–60.
☐ 30DeLong ER, DeLong DM, Clarke☐Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–845.
☐ 31McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947;12:153–157.
☐ 32Pearson K. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. Lond Edinb Dubl Phil Mag J Sci 1900;50:157–175.
☐ 33Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172 discussion 207–212.
☐ 34Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565–574.
☐ 35Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York: Springer; 2009.
☐ 36Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960;20:37–46.
☐ 37Laursen CB, Sloth E, Lassen AT, dePont Christensen R, Lambrechtsen J, Madsen PH, Henriksen DP, Davidsen JR, Rasmussen F. Point☐of☐care ultrasonography in patients admitted with respiratory symptoms: a single☐blind, randomised controlled trial. Lancet Respir Med 2014;2:638–646.
☐ 38Martindale JL, Noble VE, Liteplo A. Diagnosing pulmonary edema: lung ultrasound versus chest radiography. Eur J Emerg Med 2013;20:356–360.
☐ 39Goffi A, Pivetta E, Lupia E, Porrino G, Civita M, Laurita E, Griot G, Casoli G, Cibinel G. Has lung ultrasound an impact on the management of patients with acute dyspnea in the emergency department? Crit Care Lond Engl 2013;17:R180.
☐ 40Soldati G, Demi M, Inchingolo R, Smargiassi A, Demi L. On the physical basis of pulmonary sonographic interstitial syndrome. J Ultrasound Med 2016;35:2075–2086.
☐ 41Zanobetti M, Poggioni C, Pini R. Can chest ultrasonography replace standard chest radiography for evaluation of acute dyspnea in the ED? Chest 2011;139:1140–1147.
☐ 42Moors G. Exploring the effect of a middle response category on response style in attitude measurement. Qual Quant 2008;42:779–794.
☐ 43Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A,

Kazanegra R, Herrmann HC, McCullough PA, Breathing Not Properly Multinational Study Investigators. Rapid measurement of B□type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–167.
□ 44 Ohman J, Harjola V□P, Karjalainen P, Lassus J. Rapid cardiothoracic ultrasound protocol for diagnosis of acute heart failure in the emergency department. Eur J Emerg Med 2017 Oct 3. https://doi-org.bibliopass.unito.it/10.1097/MEJ 0000000000000499 [Epub ahead of print].
□ 45Gargani L, Pang PS, Frassi F, Miglioranza MH, Dini FL, Landi P, Picano E. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. Cardiovasc Ultrasound 2015;13:40.
□ 46See KC, Ong V, Wong SH, Leanda R, Santos J, Taculod J, Phua J, Teoh CM. Lung ultrasound training: curriculum implementation and learning trajectory among respiratory therapists. Intensive Care Med 2016;42:63–71.
□ 47Corrao G, Ghirardi A, Ibrahim B, Merlino L, Maggioni AP. Burden of new hospitalization for heart failure: a population□based investigation from Italy. Eur J Heart Fail 2014;16:729–736.
□ 48Metra M, Mentz RJ, Hernandez AF, Heizer GM, Armstrong PW, Clausell N, Corbalan R, Costanzo MR, Dickstein K, Dunlap ME, Ezekowitz JA, Howlett JG, Komajda M, Krum H, Lombardi C, Fonarow GC, McMurray JJV, Nieminen MS, Swedberg K, Voors AA, Starling RC, Teerlink JR, O'Connor CM. Geographic differences in patients in a global acute heart failure clinical trial (from the ASCEND□HF trial). Am J Cardiol 2016;117:1771–1778.
□ 49Chen J, Dharmarajan K, Wang Y, Krumholz HM. National trends in heart failure hospital stay rates, 2001 to 2009. J Am Coll Cardiol 2013;61:1078–1088.
□ 50Noble VE, Murray AF, Capp R, Sylvia□Reardon MH, Steele DJ, Liteplo A. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. Chest 2009;135:1433–1439.
□ 51Reissig A, Kroegel C. Transthoracic sonography of diffuse parenchymal lung disease: the role of comet tail artifacts. J Ultrasound Med 2003;22:173–180.
□ 52Barskova T, Gargani L, Guiducci S, Randone SB, Bruni C, Carnesecchi G, Conforti ML, Porta F, Pignone A, Caramella D, Picano E, Cerinic MM. Lung ultrasound for the screening of interstitial lung disease in very early systemic sclerosis. Ann Rheum Dis 2013;72:390–395.
□ 53Manolescu D, Davidescu L, Traila D, Oancea C, Tudorache V. The reliability of lung ultrasound in assessment of idiopathic pulmonary fibrosis. Clin Interv Aging 2018;13:437–449.