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ORIGINAL RESEARCH

Lung Ultrasound to Assess Pulmonary Congestion in Patients with Acute Exacerbation of COPD

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Purpose: Heart failure (HF) often coexists with chronic obstructive pulmonary disease (COPD) and is associated with worse outcomes. We aimed to assess the feasibility of detecting vertical artifacts (B-lines) on lung ultrasound (LUS) to identify concurrent HF in patients hospitalized with acute exacerbation of COPD (AECOPD). Second, we wanted to assess the association between B-lines and the risk of rehospitalization for AECOPD or death.

Patients and Methods: In a prospective cohort study, 123 patients with AECOPD underwent 8-zone bedside LUS within 24h after admission. A positive LUS was defined by ≥3 B-lines in ≥2 zones bilaterally. The ability to detect concurrent HF (adjudicated by a cardiologist committee) and association with events were evaluated by logistic- and Cox regression models.

Results: Forty-eight of 123 patients with AECOPD (age 75±9 years, 57[46%] men) had concurrent HF. Sixteen (13%) patients had positive LUS, and the prevalence of positive LUS was similar between patients with and without concurrent HF (8[17%] vs 8[11%], respectively, p=0.34). The number of B-lines was higher in concurrent HF: median 10(IQR 6–16) vs 7(IQR 5–12), p=0.03. The sensitivity and specificity for a positive LUS to detect concurrent HF were 17% and 89%, respectively. Positive LUS was not associated with rehospitalization and mortality: Adjusted HR: 0.93(0.49–1.75), p=0.81.

Conclusion: LUS did not detect concurrent HF or predict risk in patients with AECOPD.

Keywords: chronic obstructive pulmonary disease, heart failure, lung ultrasound, acute exacerbations, pulmonary congestion, B-lines

Introduction

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are increasing global epidemics, estimated to affect approximately 392 and 64 million people worldwide, respectively.[1–5] These diseases share risk factors and symptoms, and both propose major public health challenges due to substantial morbidity and mortality.[6] It is estimated that ~25% of COPD patients have coexisting HF, and the combination is associated with worse outcomes.[7] While current treatment options for improving COPD outcomes are limited, potent life-saving medications for HF exists. Detecting and treating HF in COPD is therefore essential.

Lung ultrasound (LUS) is a quick, easy, and validated technique used to diagnose and assess pulmonary congestion in patients with suspected acute HF in the emergency department (ED).[8,9] Current guidelines recommend its use in the initial diagnostic work-up of acute HF.[2] LUS relies on detecting pleural effusions and vertical artifacts, B-lines. B-lines have a high sensitivity for extravascular lung water, a major property of congestive HF.[10] B-lines on LUS may also indicate pathophysiological processes associated with increased lung density, ie lung parenchyma inflammation. Increased lung density is not one of the hallmarks of COPD. Thus, LUS has the potential to discriminate diseases affecting lung parenchyma, such as HF with pulmonary congestion, from non-parenchymal lung diseases like COPD.[8,9,11] However, the current empirical evidence for LUS is derived from studies of patients with suspected acute

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HF or undifferentiated patients with acute dyspnea, and the ability of LUS to discriminate concurrent acute HF in patients with acute exacerbation of COPD (AECOPD) is unclear.[12–14]

The aim of this study was to 1) assess the feasibility of bedside LUS to detect concurrent acute HF and 2) to examine the associations between B-lines and clinical parameters during hospitalizations and rehospitalizations and mortality.

Materials and Methods

Study Design and Population

We conducted a prospective cohort study at Akershus University Hospital in two periods: 1) Between May and June 2017, and 2) between February 2020 and September 2021. Patients ≥18 years, admitted with a tentative diagnosis of AECOPD, were assessed for eligibility at the morning rounds on days when the trained LUS technicians were present. AECOPD was diagnosed at the admitting physician's discretion and defined as a sudden worsening of airway function and respiratory symptoms in patients with COPD, as defined by the established criteria by the global initiative for obstructive lung disease (GOLD).[15] Patients with a COPD diagnosis from outside the hospital, for example from their primary care physician, who did not have available spirometry data in the hospital medical record were also included. We excluded patients with pneumothorax, thorax deformities, recent thoracic surgery, a history of comorbid asthma, pulmonary fibrosis, pleural disease, and current COVID-19, as these conditions may interfere with the interpretation of B-lines.[11] Other exclusion criteria were mental disorientation, organic delirium, dementia, or other factors that hinder obtaining informed consent. Baseline clinical characteristics, prior comorbidities, regular medications, and laboratory data were extracted from the hospital's electronic health records (EHR).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the regional medical ethics committee (REK approval no. 2017/663) and by the local Data Protection Officer (project approval 17/135). The attending physician was notified and prompted to consider relevant investigations in cases where LUS uncovered pathological conditions that were not acknowledged.

Lung Ultrasound Protocol and B-Line Analysis

The examinations were performed on the first day after admission to the medical ward, and thereafter on two consecutive weekdays of the hospital stay. The examination protocol adhered to international guidelines for LUS to assess pulmonary congestion.[8,11,16] All LUS examinations were done with two types of low-cost handheld ultrasound devices. We examined patients in the first inclusion period (n=60) with a dual-probe V-scan Extend™ (General Electric, Vingmed, Horten, Norway) using the linear array transducer (bandwidth 3.3–8.0 MHz). Patients in the second inclusion period (n=65) were examined with a Phillips Lumify™ (Phillips) equipped with an S4–1 broadband sector array transducer (bandwidth 1–4 MHz) using the cardiac setting. The difference in devices was due to availability in the two inclusion periods. The scanning depth was set to 5 to 16 cm and cine-loops of 3–6 seconds were recorded in each lung zone. We used a simplified 8-zone protocol: four thoracic zones on each side; two anterior zones and two lateral zones. The probe was placed in the sagittal orientation, perpendicular to the thorax. We transferred the cine-loops to a computer for offline storage, deidentification and analysis. The cine-loops were read by a single examiner (ØJ).

We defined LUS B-lines as discrete hyperechoic vertical artifacts arising from the pleural line and stretching from the pleural line to the edge of the screen. To quantify B-lines, we counted and summed the highest number of B-lines from a freeze-frame after reviewing the entire clip from each of the 8 lung zones, in line with previous studies.[10,17,18] Patients with ≥3 missing lung zones on either side were excluded from further analysis, per protocol (n=1). Patients reported perceived distress of the examination on the 5-point Likert psychometric scale. Two investigators (ØJ and FU) performed all examinations and measurements. Intra- and interobserver variability were determined by Bland–Altman analyses in 10 randomly selected patients. Temporal and clinical blinding was assured during all measurements.

In accordance with previous studies, the presence of three or more B-lines in two or more thoracic zones bilaterally was used to define a "positive LUS", eg alveolar interstitial syndrome (AIS) suggestive of pulmonary congestion.[11]

Clinical Outcomes

A clinical endpoint committee (CEC) composed of three cardiologists (RB, TØ, and PLM), blinded to all LUS findings, independently reviewed each case to adjudicate whether or not the patient had HF. The CEC had full access to the patient records, including charts, laboratory parameters, imaging (chest X-rays [CXR] and computed tomography), electrocardiograms, and echocardiograms. The CEC based the HF diagnosis on the criteria proposed by the European Society of Cardiology; typical signs and symptoms of HF and objective evidence of structural or functional myocardial abnormality.[19] The CEC also classified whether or not the HF was decompensated and contributing to the hospitalization for AECOPD from reviewing imaging data, biomarker concentrations and considerations by the treating physicians in the medical record. Based on this, patients were classified into three categories: 1) HF present and a concurrent cause for exacerbation, 2) HF present, but not a concurrent cause of exacerbation or 3) HF not present.

The primary clinical outcome was a composite of rehospitalization for AECOPD and all-cause mortality within 12 months after enrollment. Outcome data were obtained from EHR review. Hospitalization for AECOPD was defined as a final diagnosis of AECOPD and objective findings, typical history, and treatment for AECOPD according to GOLD criteria.[15]

Other Clinical Data

All patients underwent routine clinical diagnostic work-up for acute dyspnea on hospital admission in the ED before admission to the pulmonary department. The work-up included clinical examination, including height and weight, standard laboratory values (creatinine, C-reactive protein [CRP]), blood gas analysis, and CXR. In addition, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and high-sensitivity cardiac Troponin T (cTnT) (both Roche Diagnostics, Basel Switzerland) were sampled at the clinician's discretion. The last known spirometry result, including forced expiratory volume during the 1st second (FEV_1) was obtained from the medical records. In addition, we registered the presence of pulmonary congestion, or an infiltrate as described by the radiologist in the clinical routine. Point of care LUS was not implemented as a standard work-up of acute dyspnea in the ED.

Statistical Analysis

We used commonly described approaches for summary statistics according to data distribution. Between-group comparisons of baseline characteristics were analyzed with two-sample *t*-test, Wilcoxon rank sum test, or Chi-square, as appropriate. Skewed variables (NT-proBNP, CRP, and cTnT) were log-transformed before regression analysis. The diagnostic properties of a positive LUS to correctly classify concurrent acute HF in AECOPD were assessed using receiver operator characteristics (ROC) analysis including sensitivity and specificity calculations. Patients with a diagnosis of chronic HF which was not considered as a contributing factor to the hospitalization (ie not decompensated acute HF) were analyzed together with patients without HF because patients with compensated HF are less likely to have pulmonary congestion. We also explored a less strict threshold for a positive LUS; ≥3 B-lines in *one* zone bilaterally (as opposed to two zones). We performed a predefined sensitivity analysis, excluding patients with HF present but not as a concurrent cause of the exacerbation. We used univariable logistic regression to explore the associations between positive LUS examination and the following clinical variables: age, sex, body mass index (BMI), smoking, log-transformed NT-proBNP, log-transformed CRP, log-transformed creatinine, partial pressure of oxygen, diuretic treatment before LUS examination, congestion on CXR, and infiltrate on CXR. As B-lines are discrete count variables, we used unadjusted and adjusted negative binomial regression models (NBR) to assess associations between the total sum of B-lines and variables known to associate with the presence of B-lines in previous studies: age, BMI, diuretics before LUS, congestion on CXR, and infiltrate on CXR.[20–24] Results from the NBR models are reported as ratios with 95% confidence intervals (CI) and represent a % increase or decrease in B-lines. In addition, changes in B-lines from the first LUS examination to the second examination were assessed with the Wilcoxon signed rank test. Kaplan–Meier plots for the cumulative rate of AECOPD rehospitalizations or all-cause death for the positive and negative LUS examination were developed. We used Cox proportional hazard models to analyze the association between positive LUS and time to AECOPD rehospitalization or all-cause death, adjusting for the following a priori selected covariates associated with

adverse outcomes in patients with AECOPD: age, sex, and FEV_1. Intra-observer and inter-observer variabilities were tested in using Bland-Altman analysis in 10 randomly selected patients with at least four weeks between the measurements (Figure S1a and b).[25] Missing data from lung zones were imputed if there were no more than two missing zones per examination (n=7) (Table S1). LUS studies targeting concurrent HF and AECOPD are lacking. By extrapolating data from other cohorts, we estimated a need for 120 patients to detect a difference in the prevalence of a 'positive LUS' (ie 50% in AECOPD patients with concurrent acute HF and 20% in AECOPD patients without acute HF), with a power of 80% and an alpha of 0.05. Stata SE version 17.0 (StataCorp. College Station, Texas, USA) was used for all data calculations. A double-sided p-value of <0.05 was considered significant.

Results

Study Population and Patient Characteristics

In total, 123 patients (mean age 75±9 years, 57 (46%) men) with AECOPD underwent LUS (n=60 in the first and n=63 in the second inclusion period) (Figure 1). Valid data were obtained from all zones in 116 (94%), and we imputed missing zones in 7 (6%) patients. The median number of B-lines was 8 (IQR 5–13, range 0 to 33) at baseline. On day 2 (n=38), the median number of B-lines was 8 (IQR 5–12, range 0 to 21), with no significant change from baseline (p=0.07). On day 3 (n=19), the median number of B-lines was 7 (IQR 1–11, range 0 to 23).

The majority (75%) of patients had moderate or severe COPD (Table 1), and all patients received standard AECOPD treatment with bronchodilators, systemic corticosteroids, and antibiotics at the clinicians' discretion. Nine patients had unavailable spirometry data as the COPD had been diagnosed outside the hospital. The median length of hospital stay was 5 (IQR 3–5) days. Between admission and LUS examination, 17 (14%) patients had diuretic treatment initiated.

Concurrent acute HF during the admission for AECOPD was present in 48 (39%) patients, and 16 (13%) had HF but were not considered clinically relevant for the current admission (ie non-concurrent). Of patients adjudicated to have concurrent acute HF, 47 (45%) did not have a prior diagnosis of HF. Patients with concurrent acute HF were older with less severe COPD and had more prevalent atrial fibrillation (Table 1). They used more frequently RAAS-inhibitors, beta-blockers, and diuretics. In addition, they had more frequent congestion on CXR and higher levels of cTnT, creatinine, and NT-proBNP (median [IQR] 979 [490–2896] vs 125 [39–373] ng/L, respectively). Patients with concurrent acute HF had higher respiration frequency (p=0.02) than patients with non-concurrent HF, and their hemoglobin levels were lower

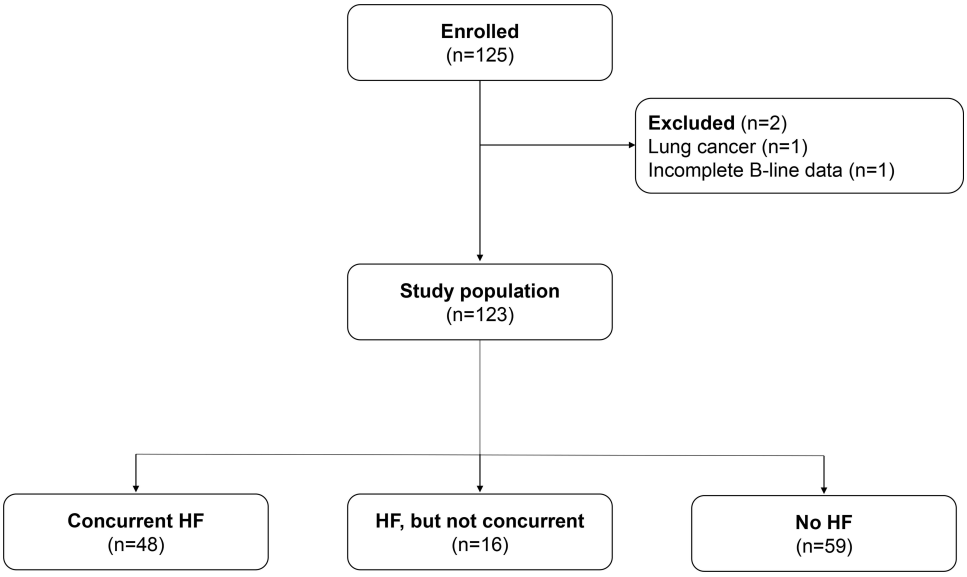

Figure 1 Flow chart of the study population.
Abbreviation: HF, heart failure.

Table 1 Baseline Characteristics of the Total Population, and Stratified by the Presence of Concurrent HF

	Total (n=123)	No Concurrent HF (n=75)	HF Concurrent (n=48)	P-value
Age (years)	75 ± 9	72 ± 9	78 ± 8	<0.001
Male	57 (46%)	31 (41%)	26 (54%)	0.16
Smoking	52 (42%)	34 (45%)	18 (38%)	0.39
Body mass index (kg/m2)	23.8 ± 6.4	23.1 ± 5.1	25.0 ± 7.9	0.11
Lung function before exacerbation				
FEV_1 > 50%	29 (25%)	15 (21%)	14 (33%)	0.061
FEV_1 30–50%	46 (40%)	26 (37%)	20 (47%)	
FEV_1 < 30%	39 (34%)	30 (42%)	9 (21%)	
Comorbidities				
Diabetes	16 (13%)	7 (9%)	9 (19%)	0.13
Hypertension	44 (36%)	28 (37%)	16 (33%)	0.65
Acute myocardial infarction	33 (27%)	17 (23%)	16 (33%)	0.19
Atrial fibrillation	20 (16%)	6 (8%)	14 (29%)	0.002
Emphysema	40 (33%)	27 (36%)	13 (27%)	0.30
Medications				
RAAS-inhibitors	50 (41%)	25 (33%)	25 (52%)	0.039
Beta Blockers	54 (44%)	25 (33%)	29 (60%)	0.003
Diuretics as regular medicine	52 (42%)	20 (27%)	32 (67%)	<0.001
Diuretics prior to LUS	61 (50%)	25 (33%)	36 (75%)	<0.001
Baseline				
Respiration frequency (/min)	27 ± 7	26 ± 6	28 ± 6	0.022
Saturation (%)	89 ± 7	89 ± 7	89 ± 6	0.89
Systolic blood pressure (mmHg)	139 ± 25	137 ± 23	141 ± 27	0.44
Pulse (beats/minute)	95 ± 18	97 ± 17	91 ± 20	0.067
Laboratory values				
CRP (ng/L)	20 (7–60)	21 (5–70)	17 (11–47)	0.99
NT-proBNP (ng/L)	455 (125–1247)	125 (39–373)	979 (490–2896)	<0.001
High sensitive Troponin T (ng/L)	30 (18–52)	24 (14–41)	45 (26–58)	<0.001
Creatinine (umol/L)	69 (58–92)	67 (55–87)	75 (59–114)	0.030
Hemoglobin (g/dL)	13.6 ± 1.9	13.9 ± 1.7	13.1 ± 2.0	0.028
Partial pressure oxygen (kPa)	8.8 ± 3.4	9.2 ± 4.1	8.2 ± 1.7	0.098
Chest X-ray				
Congestion	36 (30%)	9 (13%)	27 (56%)	<0.001

(*Continued*)

Table 1 (Continued).

	Total (n=123)	No Concurrent HF (n=75)	HF Concurrent (n=48)	P-value
Infiltrate	29 (24%)	14 (19%)	15 (31%)	0.14
Index hospitalization				
Length of stay (days)	5 (3–7)	4 (3–6)	5 (3–10)	0.15

Note: Mean ± standard deviation, n (%) or median (25–75th percentile).
Abbreviations: CRP, C-reactive protein; FEV_1, forced expiratory volume in the 1st second (n=114); HF, heart failure; hs-cTnT, high sensitive cardiac Troponin T (n=106); LUS, lung ultrasound, NT-proBNP, N-terminal pro-B-type natriuretic peptide (n=92); RAAS, renin-angiotensin system antagonist.

(p=0.03). The proportion of patients with emphysema was similar. Baseline characteristics for patients with acute concurrent HF, chronic HF and no HF are presented separately (Table S4).

Predictors for B-Lines on Lung Ultrasound

Patients with positive LUS had comparable age, sex distribution, BMI, FEV_1, comorbidity burden, and vital parameters to those with a negative LUS (Table S2). Patients with a positive versus negative LUS had more often infiltrates present on CXR: 8 (53%) versus 21 (20%), p=0.005. The median level of NT-proBNP was 855 (130–2949) and 444 (120–1029) ng/L in patients with and without positive LUS, respectively (p=0.29). The total number of B-lines across 8 zones was associated with older age, lower BMI, lower arterial partial pressure, diuretics use, higher CRP, and the presence of infiltrates on CXR (Figure 2 and Table S3).

Performance of LUS for Detecting Concurrent Acute Heart Failure

The median number of B-lines was 10 (IQR 6–16) for patients with concurrent acute HF and 7 (IQR 5–12) for patients without concurrent acute HF (p=0.03). Concurrent acute HF was positively associated with the number of B-lines across

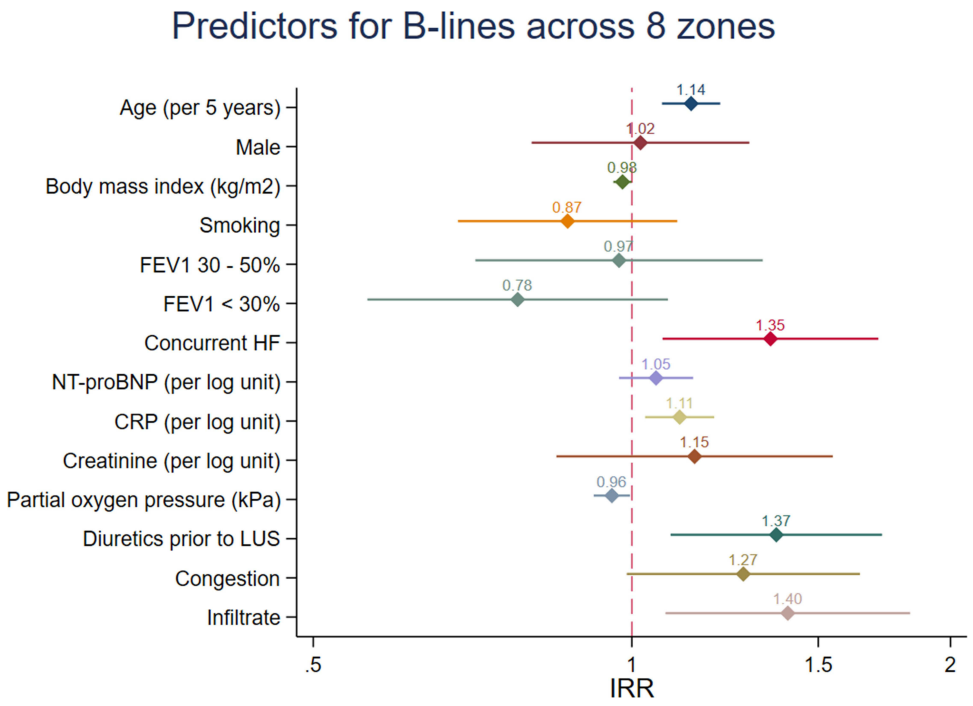

Figure 2 Clinical characteristics and findings in association with the total number of B-lines on lung ultrasound (LUS). Presented as a coefficient plot with incidence rate ratio and 95% confidence intervals.
Abbreviations: CRP, C-reactive protein; FEV_1, Forced expiratory volume during 1st second; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

8 zones (ratio 1.35 [95% CI 1.07–1.71], p=0.012), but not after adjusting for age, BMI, CRP, diuretics use, and infiltrate on CXR (p=0.18).

Sixteen patients (13%) had a positive LUS, and there was no difference between patients with and without concurrent HF: 8 (17%) vs 8 (11%), p=0.34. The ROC AUC, sensitivity, and specificity for a positive LUS for correctly classifying concurrent acute HF were 0.53 (95% CI 0.47–0.59), 17% (95% CI 7–30%), and 89% (95% CI 80–95%), respectively. These measures were consistent in a sensitivity analysis excluding 16 patients with non-concurrent HF. We also obtained similar results in sensitivity analyses excluding patients with missing lung zones. When exploring ≥3 B-lines in one positive zone bilaterally as the definition of a positive LUS, this was present in 23 (48%) patients with concurrent HF and 20 (27%) patients without concurrent HF (ROC AUC 0.61). Adjusting for the inclusion period or probe did not change the AUC for either cut-off. The presence of a positive LUS did not differ between acute concurrent HF patients with and without previous myocardial infarction (19% vs 13%, respectively, p=0.58).

Association Between Findings from LUS and Clinical Outcomes

During the 12 months follow-up period after enrollment, there were 92 events (75 rehospitalizations for AECOPD and 17 deaths, Table 2 and Figure 3). Two (13%) patients in the positive LUS group and 15 (14%) in the negative LUS group died (p=0.87). Nine (56%) patients with positive LUS versus 66 (62%) with negative LUS were hospitalized for AECOPD (p=0.68). There was no significant association between positive LUS and time-to-event in the Cox proportional hazard regression analysis (HR 0.98 [95% CI 0.52–1.84], p=0.94), with consistent results after adjustments. Among the six patients who died in the hospital, five died from the infectious cause of AECOPD, and one died from end-stage COPD.

Discussion

The main finding of our study is that bedside LUS is easily applicable in patients hospitalized with AECOPD but performs poorly as a diagnostic tool for detecting concurrent HF. Furthermore, B-lines on LUS during hospitalization had no prognostic value for rehospitalizations and all-cause mortality.

Our neutral findings among patients with AECOPD differ from the promising evidence for LUS in managing patients with suspected acute HF and acute dyspnea.[12] To our knowledge, there are few comparable studies with LUS in an AECOPD population. Based on prior studies and pathophysiological considerations in COPD, we hypothesized that LUS would detect concurrent HF in patients with AECOPD. There are some possible explanations for the contrasting results. First, the most common etiology for AECOPD is lower airway infection. We found consolidations on CXR to be the most robust clinical variable associated with B-lines. Thus, in AECOPD, lung parenchyma inflammation might disturb the expected association between pulmonary congestion and B-lines and decrease the diagnostic value of LUS in this

Table 2 Hospitalization for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and All-Cause Death During 12 Months Follow-Up in Patients with and without a Positive Lung Ultrasound (LUS) (≥3 B-Lines in ≥2 Zones Bilaterally)

	Negative LUS (n=107)	**Positive LUS (n=16)**
Hospitalization for AECOPD	66 (62%)	9 (56%)
All-cause death	15 (14%)	2 (13%)
Hospitalization for AECOPD or all-cause death	81 (76%)	11 (69%)
Cox-regression analysis of time to hospitalization for AECOPD or all-cause death		
Unadjusted	Ref	HR 0.98 (95% CI 0.52–1.84) p=0.94
Adjusted for age, sex and forced expiratory volume in the 1st second	Ref	HR 0.93 (95% CI 0.49–1.75) p=0.81

Abbreviations: AECOPD, Acute exacerbation of COPD; AUC, Area under the curve; CHF, chronic heart failure; COPD = chronic obstructive pulmonary disease; CRP, C-reactive protein; CI, confidence interval; FEV1, forced expiratory volume in the 1st second; LUS, lung ultrasound; HF, heart failure; HR, hazard ratio; hs-cTnT, high sensitive cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS, renin-angiotensin system antagonist.

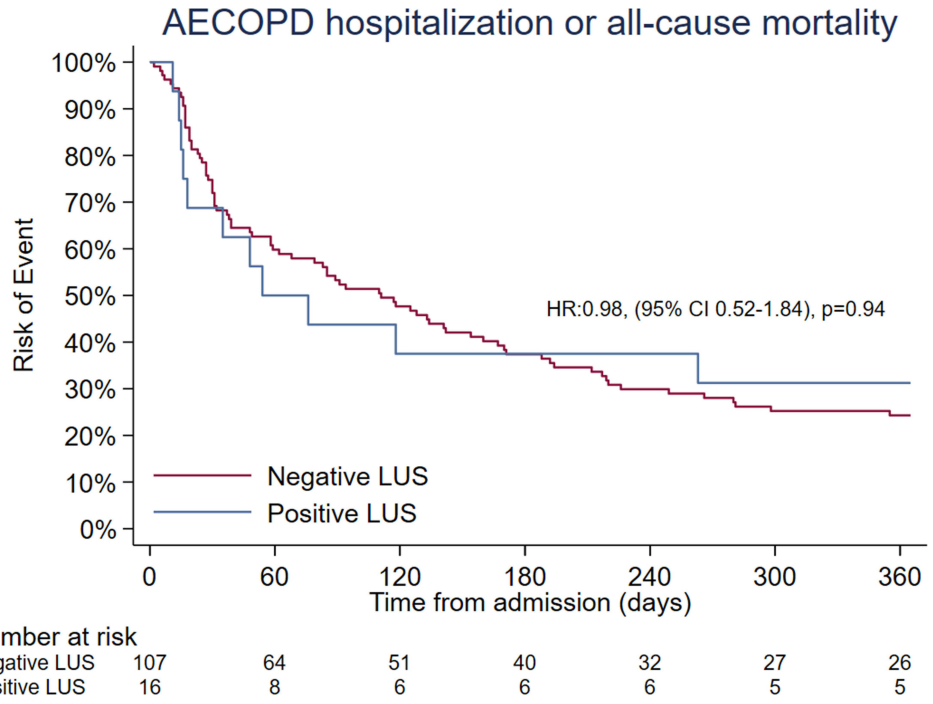

Figure 3 Survival plots for rehospitalization and all-cause mortality in patients with and without a positive lung ultrasound (LUS) during the index hospitalization for acute exacerbation of chronic obstructive pulmonary disorder (AECOPD).

population. In the subset of patients with follow-up LUS, we report that the number of B-lines does not diminish to day 2 or 3, which may support the latter explanation. A recent trial of intensive care patients reported poor ability of LUS to discriminate between pulmonary congestion and pneumonia.[26] Second, AECOPD was the tentative diagnosis at admission in all patients. The severity of HF and congestion might have been less pronounced than in patients admitted to the ED with acute HF as the primary diagnosis. Indeed, the median number of B-lines and levels of NT-proBNP were lower than in comparable studies with acute HF patients.[27] Third, we performed LUS on the first day in the medical ward. Many patients had already received diuretics or non-invasive ventilation during the first 24h, which may have resolved the pulmonary congestion and decreased the number of B-lines.[22]

The optimal approach to LUS imaging and B-line quantification is debated, and the threshold we used for a positive LUS may be too strict.[14,28] A recent methodological study with patients in the ED found that a 6-zone and 8-zone method, using ≥3 B-lines in one zone bilaterally as a cut-off, improved the diagnostic accuracy in patients with an unclear diagnosis of AHF compared to several other thresholds (two positive zones bilateral threshold, ≥15 B-lines, and ≥30 B-lines).[28] A correlation between the bilateral presence of ≥3 B-lines in ≥1 zones and higher natriuretic peptide levels have been reported in a population with AECOPD.[29] We found a similar trend in our study using ≥1 zones, but this was not statistically significant. Patients with concurrent HF had 35% more B-lines than patients with either non-concurrent HF or no HF. Prior studies suggest that using B-lines as a continuous parameter performs better with diagnosis and prognosis than using dichotomized cut-offs.[10] For example, a recent randomized trial in acute HF comparing LUS-guided therapy to standard care in acute HF failed to reach a pre-defined B-line threshold, despite a significant overall reduction in B-lines.[30] Other studies in acute HF have found worse short- and long-term outcomes associated with higher B-lines.[10] These results and the current study suggest that pulmonary congestion may be better depicted as a spectrum of B-lines rather than thresholds in patients with established COPD.

We and others have previously shown that cardiac comorbidity is associated with a poor outcome in patients with moderate or severe COPD.[31] Subsequently, cardiac biomarkers such as natriuretic peptides and troponins seem to have independent prognostic value beyond COPD-related variables.[32,33] B-lines on LUS have been associated with worse outcomes in patients with AHF. However, we did not find any association between B-lines and the risk of readmission or

death in patients with AECOPD. Considering that LUS associated more strongly with pulmonary infiltrates than concurrent HF in our study, this may not be surprising.

Strengths and Limitations

Strengths of the study include that all patients underwent the same 8-zone protocol in semi-recumbent positions, and the B-line readers were blinded clinically and temporally. The study is novel and addresses the paucity of studies with LUS in the AECOPD population.

There are several limitations. Our study lacks study-specific echocardiographic imaging, which would allow for specific HF-phenotyping and detecting isolated right HF. We tried to overcome this limitation with HF adjudication by a CEC who had access to routine echocardiographic examinations and clinical examination reports from the medical records. Although the use of CEC in clinical trials is debated, it provides a standardized, consistent and less biased evaluation of suspected end points compared to the use of EHR-derived diagnoses.[34] The timing of the LUS may influence the results. Treatment with diuretics and non-invasive ventilation may lead to quicker resolution of pulmonary edema than antibiotics do with the infection/infiltrates,[22] skewing the results towards more false positives and a lower specificity for LUS. We used two different probes for LUS, which may introduce bias. However, there were no significant differences in the B-line count and the relation to the outcome when comparing the two study periods. A linear probe has limited depth (max 5.2 cm), which may misinterpret pleural artifacts without clinical significance (Z-lines) as B-lines. However, this limitation is more relevant in obese patients, and our patients were normal- or underweight. Although we did not measure skin-to-probe distance, we found only weak correlations between BMI and B-lines. The criteria for AECOPD and treatment remained relatively the same in the two inclusion periods. It is, however, unclear whether the COVID-19 pandemic introduced bias other than excluding a larger-than-usual portion of the COPD population, as patients with COVID-19 were excluded per protocol amendment.

Lastly, we used a time-to-first event analysis which may lead to a loss of information compared to recurrent event analysis and underestimate the risk associated with the presence of B-lines.

Conclusions

Amongst patients hospitalized for AECOPD, B-lines are frequently observed on LUS with a handheld pocket ultrasound device. Concurrent acute HF was present in about one-third of patients and these patients had a higher number of B-lines. However, a positive LUS with a threshold of a bilateral finding of ≥3 B-lines in two zones could not reliably detect concurrent HF. Infiltrates on CXR were the most important predictor of B-lines. Although assessment of B-lines by LUS is recommended by HF guidelines, our results suggest that it may be less useful for detecting HF in patients with AECOPD.

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Disclosure

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