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Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: A systematic review

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Abstract

Aims: Pulmonary congestion is an important finding in patients with heart failure (HF) that can be quantified by lung ultrasound (LUS). We conducted a systematic review to describe dynamic changes of LUS findings of pulmonary congestion (B-lines) in HF and to examine the prognostic utility of B-lines in HF.

Methods and Results: We searched online databases for studies of patients with chronic or acute HF using LUS to assess dynamic changes or the prognostic value of pulmonary congestion. We included studies of adults, published in English, including ≥25 patients. Of 1327 identified studies, 13 (n=25 to 290) met the inclusion criteria: 6 reported on dynamic changes in LUS findings (438 patients) and 7 on the prognostic value of B-lines in HF (953 patients). In acute HF, B-line number changed within as few as 3 hours of HF treatment. Among patients with acute HF, ≥15 B-lines on 28-zone LUS at discharge identified patients at a more than 5-fold risk for HF readmission or death. Similarly, in ambulatory patients with chronic HF ≥3 B-lines on 5- or 8-zone LUS marked those at a nearly 4-fold risk of 6-month HF hospitalization or death.

Conclusions: LUS findings change rapidly in response to HF therapy and may represent a useful, non-invasive method to track dynamic changes in pulmonary congestion. Furthermore, residual congestion at the time of discharge in acute HF or in ambulatory patients with chronic HF may identify those at high risk for adverse events.

Keywords: heart failure, congestion, lung ultrasound, prognosis, systematic review

Introduction

Pulmonary congestion is a common finding in patients with heart failure (HF) and may itself contribute to worsening pulmonary vascular disease and biventricular HF.[1] Although the pathophysiologic mechanisms are incompletely understood, the presence of pulmonary congestion in patients with HF may identify those at higher risk of HF hospitalizations and death, both in acute and chronic HF.[1, 2] In addition, pulmonary edema can cause dyspnea which often limits patients' activities, urges them to seek medical care and may lead to hospitalization. Pulmonary congestion is, therefore, an important therapeutic target in patients with HF. Traditionally, pulmonary congestion has been assessed by physical examination and chest radiography but more recently lung ultrasonography (LUS) has been identified as a sensitive and semi-quantitative tool in the assessment of pulmonary congestion in HF.[3-5] B-lines are hyperechoic artifacts on LUS which appear as vertical lines that arise from the pleural surface and can be quantified in several zones of the chest.[6] In the serial examination of patients with either chronic HF in the outpatient setting or with AHF requiring hospitalization, patient-reported symptom improvement and auscultation, in addition to other measures of treatment effect (e.g. urine output, weight loss) are currently used to guide therapy. In the absence of specific, quantitative measures both over- and under-treatment may occur. While over-treatment may result in orthostatic symptoms, including syncope or worsening renal function, under-treatment with associated residual congestion may lead to early readmissions.[7, 8] In order to better delineate treatment targets for pulmonary congestion, the definition of both measurable treatment effects and prognostically relevant cut-off values are essential.[9]

The goal of this systematic review was to describe the dynamic changes of LUS findings in patients with HF and to examine the prognostic utility of B-lines as well as potential cut-off values in patients with acute and chronic HF. Our hypotheses were that B-line number changes in response to therapy in patients with HF and that HF patients with a higher number of B-lines on LUS are at greater risk for adverse outcomes.

Methods

We collected data from clinical studies of adult patients with HF to examine the dynamic changes and prognostic utility of B-lines on LUS.

Literature search strategy

We searched the electronic databases PubMed, EMBASE and Web of Science using relevant terms detailed in the *Supplements*.

Eligibility criteria for inclusion in this systematic review were: Full text article available in English language, studies in humans, adults, sample size n≥25, study includes patients with HF, LUS used to assess dynamic changes and/or prognostic value of pulmonary congestion. We excluded studies that were available in abstract form only, review articles, those focused on non-HF populations, or those limited to diagnosing HF. We used the MOOSE checklist to describe the data collection and to identify potential biases of included studies (**Table S1**).[10]

Data synthesis and statistical analyses

We included all clinical studies regardless of the setting, chronicity of HF and ejection fraction. Eligible studies were divided into 4 groups: 1) Dynamic changes in B-line number in response to HF therapy, 2) Dynamic changes in B-line number in response to other interventions in patients with HF, 3) Prognostic value of B-lines in acute dyspnea and AHF, 4) Prognostic value of B-lines in chronic HF. Reported variables were selected based on their relevance with respect to the study population, ultrasound methodology, intervention, study outcomes and potential confounders.

For the prognostic assessment at the time of discharge from an AHF hospitalization (group 3) only those patients alive at the time of discharge and those with complete LUS data in group 4 were included in the analyses. The HF hospitalization and all-cause mortality data for groups 3 and 4 were reported as counts and percentages of the overall study cohort and both unadjusted and adjusted hazard ratios were reported, if available. In random-effect meta-analyses we combined unadjusted hazard ratios for B-lines as categorical and continuous variables in studies limited to patients with HF, stratified by pre-discharge LUS findings (AHF) vs. LUS findings in ambulatory patients with chronic HF. Heterogeneity was assessed and interpreted using the I-squared statistic and forest plots. A P value <0.05 was considered statistically significant. All analyses were performed using STATA version 12.1 (Stata Corporation, College Station, Texas).

Results

Monitoring of dynamic changes in B-lines

Patients, settings and interventions

Results of the search and study selection are summarized in **Figure 1**. We identified 6 studies in Emergency Department (ED) or hospitalized patients with dyspnea or AHF (n=25 to n=152) (**Table 1** One investigation assessed the impact of position change from sitting to supine in ED patients with prior HF. The remainder examined the impact of treatment during a hospitalization for AHF; however, the type of HF treatment was only specified in 2 studies, and HF treatment was not standardized in any of them. Patients with known conditions that may contribute to B-line number independent of pulmonary edema due to HF, such as pulmonary fibrosis or end-stage renal disease requiring dialysis, were excluded from some but not all publications (**Table S2**).[6]

Ultrasound equipment, imaging protocol and analysis

Ultrasound equipment and imagine protocols are summarized in **Table 1**. Investigators examined between 4 and 28 chest zones. **Figure 2** illustrates two types of imaging protocols and LUS image examples with and without B-lines.[6, 11, 12] Several different quantification methods were employed: Broadly, these can be categorized into two groups, a count based method, summing B-lines across several pre-specified chest zones and a score based method, in which a chest zones is considered "positive" if a certain number of B-lines is seen. Three studies performed concomitant echocardiography at the time of LUS assessment and one also examined the presence of pleural effusions. B-line quantification was performed blinded to some or all clinical findings in four studies and blinding was not specified in the remaining ones (**Table S2**).

Time interval and change in B-line number

Time intervals ranged from minutes to several days during the hospitalization and were not specified in one study. All publications reported a change in B-line number or score following their intervention. Two AHF studies, which used the same 28-zone quantification method, reported a mean change of 22 B-lines (53.4 (±17.2) to 31.7 (±13.5); P<0.01) after 24 hours of treatment and 28 B-lines (48 (±48) to 20 (±23); P<0.0001) between admission and discharge. Two other AHF studies examined B-lines in 11 zones and found a significant reduction in "positive" LUS zones (based on a score) in 3 hours of HF therapy, and between admission and discharge. Only one of the reviewed publications reported temporal blinding of the ultrasound readers (**Table S2**).[13]

Prognostic value of lung ultrasound in HF

Patients and settings

We identified 7 publications which reported on the prognostic utility of LUS: Two in hospitalized patients with acute dyspnea (n=66 and n=290), 3 in patients hospitalized for AHF (n=60 to n=149) and 2 in ambulatory, chronic HF populations (n=104 and n=195) (**Table 2**). The majority of studies included both patients with HF with reduced ejection fraction (HFrEF) and HF with preserved EF (HFpEF) but none presented results stratified by EF. Four studies excluded patients with conditions that may have contributed to an increased number of B-lines independent of pulmonary edema due to HF (**Table S3**).

Ultrasound equipment, imaging protocol and analysis

Ultrasound equipment and imaging protocols are summarized in **Table 2**. In contrast to the acute dyspnea and AHF studies, investigators used pocket ultrasound devices to acquire LUS images in 2 chronic HF publications. Imaging protocols were similar to those described for the assessment of dynamic changes in B-line number, ranging from 5 to 28 zones and quantification methods included count and score measures. One chronic HF study also included the assessment of posterior lung zones.[14] B-line quantification was performed blinded to clinical findings in 4 investigations but whether the image analysis was performed in real-time or off-line was only specified in 2 (**Table S3**). All acute dyspnea and AHF studies reported performance of concomitant echocardiography and 2 also reported assessment of pleural effusions. Neither of the chronic HF publications reported concomitant assessment of echocardiography but one included pleural effusions.

Outcomes and meta-analysis

One acute dyspnea publication reported ICU mortality rates, all other acute dyspnea, acute and chronic HF studies reported composite outcomes including HF hospitalizations or worsening HF and either all-cause or CV death. Follow-up time ranged from 3 months to a median of 18 months. Events were verified by a variety of methods (**Tables 2** and **S3**). The mean/median age in the acute dyspnea, acute and chronic HF studies ranged from 50 to 81 years and median EF from 37 to 48%. HF hospitalization rates ranged between 6.9 and 25% and all-cause mortality rates from 4 to 16.7% over the follow-up period. Unadjusted and adjusted hazard ratios by B-line method and cut-off values are reported in **Table 3**.

Meta-analyses were performed for those acute and chronic HF studies reporting composite outcomes of HF hospitalizations (or worsening HF) and death. The pooled hazard ratio for 3 to 5 month HF readmission or death in 308 patients being discharged from the hospital after an AHF episode was 5.56 (95% CI 2.24, 13.80; P<0.001) suggesting that ≥15 B-lines on 28-zone LUS identifies patients at risk for subsequent adverse events (**Figure 2**). This pooled hazard ratio should be interpreted in the context of the heterogeneity analysis comparing the occurrence of these events across the 3 studies (I-squared 40.3%, P=0.187). For 289 patients with chronic HF the pooled hazard ratio for 6-month HF hospitalization or death was 3.41 (95% CI 2.02, 5.75; P<0.001) indicating that ≥3 B-lines in 5-8 chest zones identifies patients at risk for these adverse events (**Figure 2**).

Incremental prognostic value of lung ultrasound findings

The incremental value of LUS beyond traditional risk markers was assessed by two studies: In one AHF study of 60 patients the addition of ≥30 B-lines (28 zones) at the time of discharge provided incremental prognostic information with respect to 3-month HF readmission or all-cause death beyond NYHA class and baseline log BNP (IDI 15%, P=0.02; continuous NRI 65%, P=0.03).[15] In a subset of 51 patients, the addition of log BNP did not provide incremental prognostic information beyond NYHA, while ≥30 B-lines at the time of discharge may (IDI 17%, –1% to 43%, P=0.09; continuous NRI=66%, –30% to 84%, P=0.07). Similarly, in one chronic HF study of 185 ambulatory patients (NYHA II-IV) ≥3 B-lines (8 zones) the incremental prognostic value of LUS when compared with auscultation as assessed by the IDI was 6.4% (95% CI 1.0, 14.4) and 0.194 by the AUC delta (95% CI 0.147, 0.315; P=0.001) for 6-month HF hospitalizations or all-cause death.[16] The incremental prognostic value of LUS when compared with a congestion score by the IDI was 6.6% (95% CI: 1.9, 15.1) and 0.136 by the AUC delta (95% CI 0.082, 0.228; P=0.002) for the primary outcome.

Discussion

This systematic review of clinical studies in adult patients with HF evaluated by LUS had two principal findings: first, in patients hospitalized for AHF, B-line number on LUS changes within as few as 3 hours of HF treatment. The number of B-lines may also change within minutes following position change from sitting to supine. Second, among patients who were hospitalized for AHF, ≥15 B-lines on discharge 28-zone LUS identify patients at a more than 5-fold risk for HF readmission or death. Similarly, in ambulatory patients with chronic HF, ≥3 B-lines on 5- or 8-zone LUS marked those at a nearly 4-fold risk of 6-month HF hospitalization or death. These data should be considered hypothesis generating given the heterogeneity of the reviewed AHF studies and overall small sample size.

Can lung ultrasound be used to monitor pulmonary congestion?

The quantitative assessment of adequate peripheral and pulmonary decongestion in HF continues to represent a challenge for both clinicians and clinical trialists.[7, 17] Thus, novel, quantitative measures are essential in order to evaluate the effect of current and new therapies, to determine when therapy may need to be adjusted and when patients can be safely discharged from the hospital. Although based on a small number of studies, our findings from this systematic review suggest that LUS may enable tracking of changes in pulmonary congestion with treatment. The varied number of imaging protocols and quantification methods, as well as a lack of standardized therapy, make the comparison of these trials difficult and as such our results must be interpreted with caution. Moreover, the lack of blinding of ultrasound readers, e.g. to clinical findings, may introduce bias. Based on the limited available data, scanning as few as 11 lung zones could provide sufficient information over the course of 3 hours to a mean of 4.2 days to identify a change in the number of positive zones in patients hospitalized for AHF. These findings will need to be confirmed in larger, well designed studies. At least based on the findings of one AHF study, patient positioning should be kept constant for serial assessments in order to avoid measurement of dynamic changes due to position change alone. This finding is in line with those from a study in which lung impedance appeared to be sensitive to changes in body position.[18] In a small trial of 25 AHF patients with HFrEF the mean B-line number was slightly higher at baseline (mean 53.4 ±17.2) than in a mixed HFrEF and HFpEF cohort of 100 AHF patients (mean 48 ± 48) employing the same 28-zone scan protocol. Despite different time intervals both studies reported significant changes in B-line number with HF therapy. Whether B-lines are similarly prevalent and change at a similar rate in patients with HFrEF vs. HFpEF warrants further investigation.

Does lung ultrasound provide prognostic information in HF?

All-cause mortality rates in recent AHF trials including both patients with HFrEF and HFpEF range from 12% for 90 days to 11-21% for 180 days of follow-up.[11] All-cause mortality rates were lower (4 and 7.4%) in two of the AHF trials we reviewed despite similar follow-up periods and age range as in recent AHF trials. However, these acute HF trials enrolled patients with lower mean EF than the ones included in our review which may explain the associated higher mortality rates in these trials. Reported rates for HF readmissions varied substantially between the reviewed studies, and, with the exception of one,[15] were lower than those in recent AHF trials (6% for 30 days), AHF registries or national databases (24-31% for 30-90 days).[19-21] The lower event rates, especially for HF readmissions, in the publication by Gargani et al., may explain the heterogeneous results of the meta-analysis for the reviewed AHF trials. The 6-month event rates of the 2 LUS studies in patients with chronic HF were relatively high compared with recent chronic HF trials in patients with HFrEF or HFpEF.[22] Nevertheless, our data suggest that a high number of B-lines identifies patients at greater risk of subsequent HF hospitalizations and mortality in studies of both acute and chronic HF. Findings of studies reporting the evaluation of fewer chest zones (5 to 8) seem to provide similar prognostic information as those with a higher number of zones evaluated (e.g. 28 zones). The potential utility of protocols evaluating fewer chest zones is an important area of research and requires further investigation. By reducing the number of zones scanned, and therefore reducing the exam time, the test will potentially become more widely used. Standardized image acquisition and analysis, blinded to clinical findings will be important to allow comparison of study results across trials and develop meaningful cut-off values.

Current gaps in knowledge

Based on this systematic review there are a number of gaps in the current literature. It is unclear what an important or sufficient change in the B-line number in response to standardized treatment for AHF is and whether adequately treated AHF patients at the time of discharge should achieve a similarly low B-line number as ambulatory patients with chronic HF. Standardized reporting of LUS measures (e.g. number of zones), both continuous and categorical would be an important feature of future HF trials reporting LUS findings in order to facilitate comparison of findings across trials. There is also a lack of data describing the prevalence of LUS findings in different HF phenotypes such as HFrEF vs. HFpEF both in acute and in chronic HF, as well as the response to therapy by HF group and prognostically important cut-off values. In addition, the incremental value of LUS in the monitoring and prognosis of patients with HF beyond other markers of congestion and risk in this population warrants further investigation.

Limitations

Our systematic review is limited by the small number of studies and small sample size reporting on dynamic changes and prognostic value of LUS findings in HF. The small sample size also allowed for only limited assessment of the incremental value of LUS beyond traditional clinical and biochemical risk markers such as congestion score, NYHA class or natriuretic peptides. In addition, the lack of standardization of the number of evaluated chest zones and B-line quantification methods make it difficult to compare findings across studies and perform meta-analyses. Nevertheless, we believe that this systematic review provides hypothesis generating data that can inform future HF trials.

Conclusions

Among patients hospitalized for AHF, B-line number on LUS decreases with HF treatment. A large number of B-lines in both patients with acute and chronic HF identify those at high risk for HF hospitalization or death. These data suggest that LUS may represent a useful, non-invasive method to track dynamic changes in pulmonary congestion in response to treatment and that residual congestion at the time of discharge or in ambulatory patients with chronic HF may identify those at high risk for decompensation.

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Conflicts of Interest

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Table 1. Overview of lung ultrasound technique in acute and chronic HF: Dynamic changes in B-lines

Author (year)	Cohort	n	Ultrasound system & transducer	Number of zones	Method	B-line quantification	Pleural effusions/ echo	Intervention	Time interval	Change in B-lines
Monitoring: Dynamic changes in B-lines with HF therapy										
Volpicelli (2008)[23]	Dyspnea, ED then hospitalized, "established diagnosis of AHF"	70	High-end, convex	11	Score	If >2 B-lines/zone = positive zone Score = number of positive zones	No	HF treatment	4.2 (±1.7) days	Pre: Median 8 positive zones (range: 3-9) Post: 0 positive zones (range: 0-7) (P<0.05) Change: Median 8 positive zones
Vitturi (2011)[24]	Dyspnea, hospitalized medicine patients; 45% treated for HF	152	High-end, convex	*NR*	Count	>8 B-lines	No	45% treated for HF	48 hours	Decrease in B-lines at 48 h greater (P< 0.005) among patients treated for HF
Gargani (2015)[25]	Hospitalized for AHF (HFrEF & HFpEF)	100	High-end, phased	28	Score & Count	Score: Mild: 6-15 B-lines Moderate: 16-30 Severe: >30 B-lines; Count: Sum of B-lines in all zones	Echo & pleural effusions	HF treatment	Admission and discharge (time period *NR*)	Pre: Mean 48 (±48) B-lines Post: 20 (±23) (P <0.0001); Change: Mean 28 B-lines
Facchini (2016)[26]	ED, then hospitalized (HFrEF)	25	High-end, phased	28	Count	Sum of B-lines in 28 zones vs. right hemithorax only; if sum <5 B-lines, then = 0 B-lines	Echo	Intravenous furosemide (125-250 mg total), +/- other diuretics	24 hours	Pre: Mean 53.4 (±17.2) B-lines Post: 31.7 (±13.5) (P<0.01); Change: Mean 21.7 B-lines

Cortellaro (2016)[27]	Clinical and imaging findings of pulmonary congestion; ED, then hospitalized for AHF (HFrEF & HFpEF)	41	High-end, convex	11	Score	0 points: <3 B-lines in a zone, 1 point: ≥3 B-lines in ≥1 zone, 2 points: Multiple/ confluent B-lines	Echo (not at time of LUS)	Intravenous furosemide, nitroglycerin, morphine and/or non-invasive ventilation	3 and 24 hours	Pre: Mean score 1.59 (± 0.40) Post 3h: 0.73 (± 0.44) Post 24h: 0.38 (± 0.44)
Monitoring: Dynamic changes in B-lines in HF with other interventions										
Frasure (2014)[13]	ED, prior HF (HFrEF & HFpEF)	50	High-end, phased	Both 4 & 8	Score	0–2 B-lines: 0 points 3–7 B-lines: 1 point >7 B-lines: 2 points	No	Position change from sitting to supine	2 minutes after position change	Sitting: Median score 5 (IQR 1–8) Supine: 6 (IQR 2–10); Change: Median 1 score

Legend:

ED: Emergency Department, AHF: Acute heart failure, NR: Not reported, HFrEF: Heart failure with reduced ejection fraction, HFpEF: HF with preserved EF, NYHA: New York Heart Association, IQR: Interquartile range

Table 2. Prognostic value of lung ultrasound in HF (I)

Author (year)	**Cohort**	**n**	**Ultrasound system & transducer**	**Number of zones**	**Method**	**B-line quantification**	**Pleural effusions/ echo**	**Criteria standard (outcome)**	**Outcome**
Acute dyspnea									
Frassi (2007)[28]	Hospitalized patients with dyspnea or chest pain, 49% with h/o chronic HF	290	High-end, phased	28	Score	Mild: 5-14 B-lines Moderate: 15-29 Severe: ≥30 B-lines	Echo	Medical records, contact with family or physician signing death certificate	<u>Composite:</u> All-cause death, CV death, worsening HF (median follow-up 16 months)
Wang (2014)[29]	ICU patients, acute dyspnea, paO2<300 mmHg & pulm. edema on CXR	66	High-end, transducer *NR*	*NR*	*NR*	Multiple bilateral B-lines	Echo	*NR*	ICU mortality
Acute heart failure									
Gargani (2015)[25]	Hospitalized for AHF (HFrEF & HFpEF), pre-discharge	99	High-end, phased	28	Score & Count	<u>Score:</u> Mild: 6-15 B-lines Moderate: 16-30 Severe: >30 B-lines; <u>Count:</u> Sum of B-lines in all zones	Echo & pleural effusions	At least 1 of 4 sources: Medical records, patient's physician, patient	<u>Composite:</u> HF hospitalization or death (mean follow-up 159 days)
Coiro (2015)[15]	Hospitalized for AHF (HFrEF & HFpEF), pre-discharge	60	High-end, phased	Both 8 & 28	Score & Count	<u>Score:</u> ≥3 B-lines per zone = positive zone; <u>Count:</u> Sum of B-lines in all zones	Echo	Medical records & telephone contact	<u>Composite:</u> 3 month HF hospitalization or death
Cogliati (2016)[30]	Hospitalized for AHF (HFrEF & HFpEF), pre-discharge	149	High-end, curved	Both 8 & 28	Score (8 zones); Count (28 zones)	<u>Score:</u> ≥3 B-lines per zone = positive zone; <u>Count:</u> Sum of B-lines in all zones	Echo & pleural effusions	Medical records, contact with physician or caregivers; review by 2 physicians	<u>Composite:</u> 100 day HF hospitalization or all-cause death

Chronic heart failure									
Gustafsson (2015)[14]	Chronic HF (NYHA I-III), HFrEF & HFpEF	104	Pocket, phased	5	Count & Score	Score: >3 B-lines in one zone; Count: Sum of B-lines in all zones	Pleural effusion	Medical records	Composite: 6 month HF hospitalization or all-cause mortality
Platz (2016)[16]	Chronic HF (NYHA II-IV), HFrEF & HFpEF	185	Pocket, phased	8	Count	Sum of B-lines in all zones	No	Medical records, national death database, physicians & patients; adjudicated by 3 cardiologists	Composite: 6 month HF hospitalization or all-cause mortality

Legend:

High-end: Conventional ultrasound system, ICU: Intensive care unit, NR: Not reported, AHF: Acute heart failure, HFrEF: Heart failure with reduced ejection fraction, HFpEF: HF with preserved EF, NYHA: New York Heart Association, Pocket: Pocket ultrasound device

Table 3. Prognostic value of lung ultrasound in HF (II)

Author (year)	n	Mean age (years)	Mean EF (%)	Median NT-proBNP (pg/ml)	HF re-admissions n (%)*	All-cause deaths n (%)	Total events n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Covariates	B-line cut off
Acute dyspnea											
Frassi (2007)[28]	290	68 (±13)	45 (±14)	-	20 (6.9)	39 (13.5)	59 (20.3)	2.35 (1.36-4.00)	1.9 (1.1-3.4)	Diabetes, NYHA	Continuous (28 zones)
Wang (2014)[29]	66	50 (±10)	-	Mean 4125 (±3843)	N/A	4 (6.1)	4 (6.1)	-	-	-	N/A
Acute heart failure											
Gargani (2015)[25]	99	70 (±11)	37 (±14)	Mean 5291 (±5877)	14 (14.1)	4 (4.0)	18 (18.2)	1.03 (1.01–1.04)	NS	NYHA, hemoglobin <10 m/dl, NT-proBNP >1635 ng/l at discharge, >50 B-lines at admission	Continuous (28 zones)
								24.12 (3.15–184.55)	11.74 (1.30–106.16)		>15 B-lines (28 zones)
Coiro (2015)[15]	60	72 (±10)	Median 38 (IQR 27–52)	BNP 575 (229–1147)	15 (25.0)	10 (16.7)	18 (30.0)	1.03 (1.02–1.05)	NS	NYHA ≥III, IVC diameter	Continuous (28 zones)
								5.8 (2.1–16.3)	NS		≥15 B-lines (28 zones)
								9.94 (3.51–28.20)	5.66 (1.74–8.39)		≥30 B-lines (28 zones)
								12.7 (4.8-33.69)	4.2 (0.8-21.1)		≥2 positive zones (of 8 zones)
								7.51 (2.88–19.57)	3.30 (1.00–10.91)		≥1 positive zone (of 8 zones)
Cogliati (2016)[30]	149	Median 81 (IQR 76–85)	48 (±17)	2407 (1032–5273)†	23 (15.4)	11 (7.4)	34 (22.8)	1.005 (1.002 -1.008)	NS	NT-proBNP category†	Continuous (28 zones)
								3.10 (1.20- 8.02)	NS		>15 B-lines (28 zones)
								2.85 (1.36- 5.96)	NS		>30 B-lines (28 zones)
								3.62 (1.76- 7.43)	NS		≥2 positive zones (of 8 zones)

Chronic heart failure											
Gustafsson (2015)[14]	104	72 (±13)	-	1820 (870-3800)	18 (17.3)	14 (13.5)	24 (23.1)	3.0 (1.4-6.7)	3.5 (1.5-7.9)	Age >72 yrs, EF<40%	>3 B-lines (5 zones)
									2.9 (1.3-6.6)	Age >72 yrs, EF<40%, log NT-proBNP	
Platz (2016)[16]	185	66 (±15)	37 (±16)	2519 (1070-5080)‡	44 (23.8)	13 (7.0)	50 (27.0)	3.78 (1.88-7.63)	4.08 (1.95-8.54)	Age, sex, NYHA class III or IV, congestion score	≥3 B-lines (8 zones)

Legend:

* Or worsening heart failure

† NT-proBNP in a subset of n=99 patients

‡ NT-proBNP in a subset of n=97 patients within 7 days of clinic visit

EF: Ejection fraction, (NT-pro)BNP: (NT-pro) Brain natriuretic peptide, HR: hazard ratio, NYHA: New York Heart Association, IVC: Inferior vena cava, N/A: Not applicable, NS: Not significant

Figure 1. Literature search results

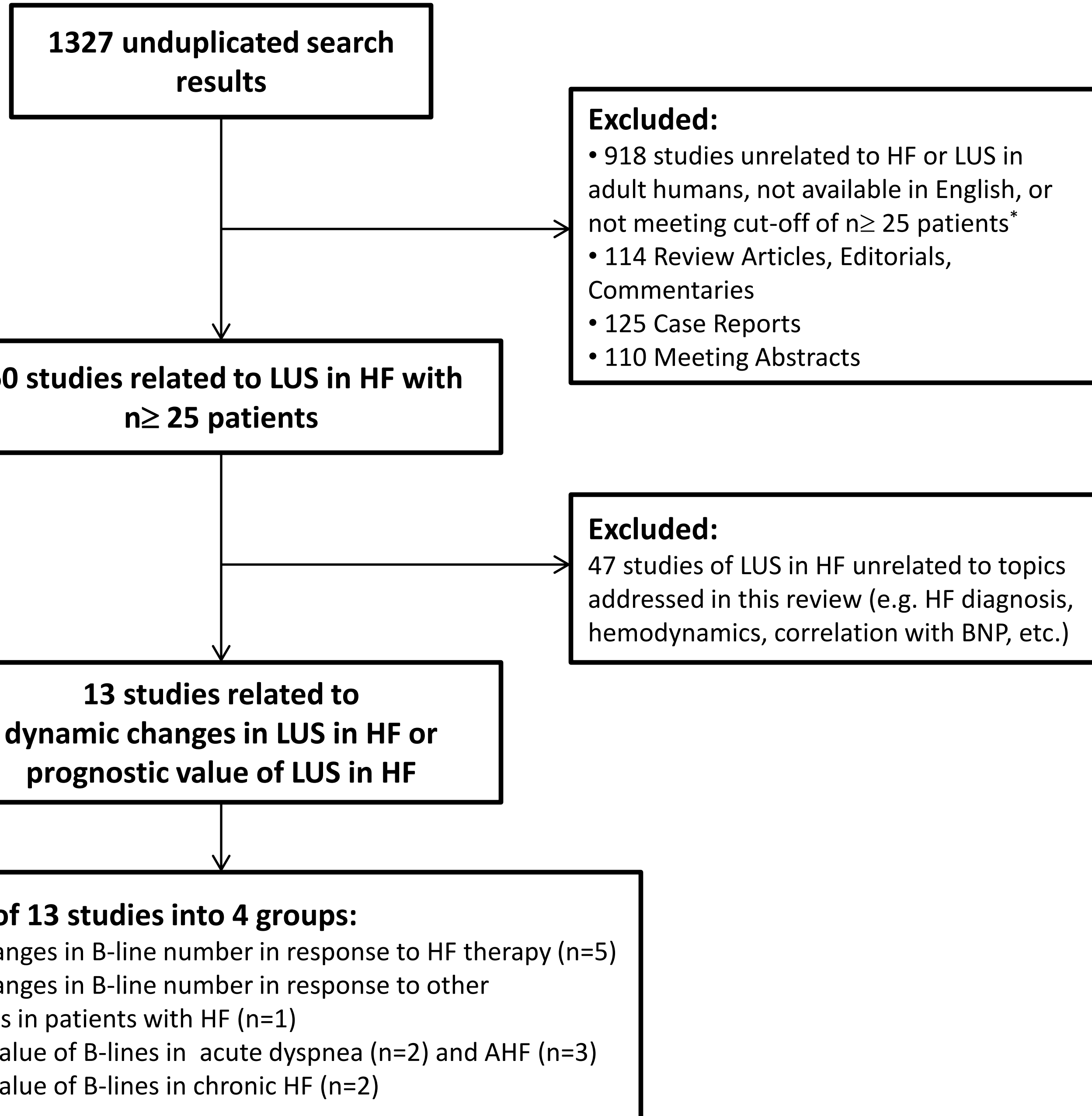
Legend:
HF: Heart failure, LUS: Lung ultrasound; AHF: Acute HF

Figure 2. Examples of lung ultrasound scanning protocols and images

Legend:
Panel A: 8-zone method; in chronic HF ≥3 B-lines identified patients at nearly 4-fold risk of 6-month HF hospitalization or death.
Panel B: 28-zone method; in patients with AHF ≥15 B-lines at the time of hospital discharge identified patients at more than 5-fold risk for HF readmissions or death.
Panel C: Lung ultrasound image without B-lines.
Panel D: Lung ultrasound image with several B-lines.

Figure 3. Unadjusted HR for HF hospitalization or death with B-lines at hospital discharge (AHF) and in chronic HF (n=597)

Legend:
Cut-off >15 B-lines (28 zones) for AHF pre-discharge from the hospital, and ≥3 B-lines (5-8 zones) for chronic HF (ambulatory patients); x-axis is on a logarithmic scale


1327 unduplicated search results
Excluded:
• 918 studies unrelated to HF or LUS in adult humans, not available in English, or not meeting cut-off of n≥ 25 patients*
• 114 Review Articles, Editorials, Commentaries
• 125 Case Reports
• 110 Meeting Abstracts
60 studies related to LUS in HF with n≥ 25 patients
Excluded:
47 studies of LUS in HF unrelated to topics addressed in this review (e.g. HF diagnosis, hemodynamics, correlation with BNP, etc.)
13 studies related to dynamic changes in LUS in HF or prognostic value of LUS in HF
Sub-division of 13 studies into 4 groups:
1) Dynamic changes in B-line number in response to HF therapy (n=5)
2) Dynamic changes in B-line number in response to other interventions in patients with HF (n=1)
3) Prognostic value of B-lines in acute dyspnea (n=2) and AHF (n=3)
4) Prognostic value of B-lines in chronic HF (n=2)