Heart Failure Reviews (2022) 27:821–826
https://doi.org/10.1007/s10741-021-10085-x

Lung ultrasound–guided management to reduce hospitalization in chronic heart failure: a systematic review and meta-analysis

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Accepted: 10 February 2021 / Published online: 9 April 2021

Abstract

Pulmonary edema is a leading cause of hospital admissions, morbidity, and mortality in heart failure (HF) patients. A point-of-care lung ultrasound (LUS) is a useful tool to detect subclinical pulmonary edema. We performed a comprehensive literature search of multiple databases for studies that evaluated the clinical utility of LUS-guided management versus standard care for HF patients in the outpatient setting. The primary outcome of interest was HF hospitalization. The secondary outcomes were all-cause mortality, urgent visits for HF worsening, acute kidney injury (AKI), and hypokalemia rates. Pooled risk ratio (RR) and corresponding 95% confidence intervals (CIs) were calculated and combined using random-effect model meta-analysis. A total of 3 randomized controlled trials including 493 HF patients managed in the outpatient setting (251 managed with LUS plus physical examination (PE)–guided therapy vs. 242 managed with PE-guided therapy alone) were included in the final analysis. The mean follow-up period was 5 months. There was no significant difference in HF hospitalization rate between the two groups (RR 0.65; 95% CI 0.34–1.22; $P = 0.18$). Similarly, there was no significant difference in all-cause mortality (RR 1.39; 95% CI 0.68–2.82; $P = 0.37$), AKI (RR 1.27; 95% CI 0.60–2.69; $P = 0.52$), and hypokalemia (RR 0.72; 95% CI 0.21–2.44; $P = 0.59$). However, LUS-guided therapy was associated with a lower rate for urgent care visits (RR 0.32; 95% CI 0.18–0.59; $P = 0.0002$). Our study demonstrated that outpatient LUS-guided diuretic therapy of pulmonary congestion reduces urgent visits for worsening symptoms of HF. Further studies are needed to evaluate LUS utility in the outpatient treatment of HF.

Keywords Lung ultrasound · Heart failure · Pulmonary edema · Outpatient management

Introduction

Despite significant improvements in management and therapies, acute pulmonary edema remains a leading cause of mortality, hospitalization, and emergency department visits among patients with chronic heart failure (HF) [1]. History and physical examination are the cornerstones for HF evaluation. Clinical signs of HF usually fall behind the pathophysiological process of increased ventricular filling pressure. Therefore, lung auscultation has poor sensitivity and accuracy in detecting mild pulmonary congestion (PC) [2].

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Point-of-care lung ultrasound (LUS) has emerged as a simple, non-invasive tool for evaluation of PC. The mechanism of LUS is based on detecting B-lines, which are described as comet-like, vertical, hyperechoic artifacts that emerge from the pleural line [3]. The number of B-lines correlates to the risk of adverse events during and after hospitalization [4]. Furthermore, diuretic therapy alters pulmonary fluid content, resulting in a rapid resolution of B-lines [5]. Therefore, anticipatory treatment of subclinical pulmonary edema directed by point-of-care LUS may improve HF prognosis and risk of acute HF exacerbation.

The usefulness of LUS as an adjunct tool in the outpatient management of HF patients is controversial. Few underpowered randomized control trials have been performed to evaluate the clinical utility of LUS in HF patients [6–8], but its usefulness remains uncertain. Therefore, we conducted a systematic review with a meta-analysis of all published studies investigating the outcomes of HF patients managed with LUS plus

physical examination (PE)–guided therapy compared with those managed with PE-guided therapy alone.

Methods

Data sources and search strategy

We performed a comprehensive search of electronic databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to October 10 2020. We also performed a manual search for additional relevant studies using references of the included articles. The following search terms were used: ("diagnostic imaging" or "ultrasound"), ("lung" or "pulmonary"), and ("heart failure" or "ventricular dysfunction")". The search was not limited by language, study design, or country of origin. Online Supplementary Table 1 describes the full search term used in each database searched.

Inclusion and exclusion criteria

We included full texts and abstracts of randomized controlled trials, cohort studies, and case-control studies. We excluded single-arm studies, animal studies, case reports, case series, reviews, editorials, and letters to editors.

Data extraction

The following data were extracted from the studies: authors, publication year, country of origin, study design, study population, patients' characteristics, and outcome measures. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies [9]. Two investigators (MM and AB) independently performed the search and shortlisted the studies for final review. Discrepancies were resolved by a third reviewer (HA).

Outcomes

The primary outcome of interest was heart failure hospitalization. The secondary outcomes were all-cause mortality, urgent care visits for HF worsening, acute kidney injury (AKI), and hypokalemia rates.

Table 1 Baseline characteristics of studies included in the meta-analysis

Study	Airaiza-Garaygordobil [6]	Marini [7]	Rivas-Lasarte [8]
Study design	RCT	RCT	RCT
Country of origin	Mexico	Italy	Spain
Total participants, *n* (LUS/control)	126 (63/63)	244 (127/117)	123 (61/62)
Mean age, year (LUS/control)	62.5 (62/63) *	71.6 (73.2/69.8)	69 (69/69)
Male, % (LUS/control)	69.5 (81/58.5)	68 (69/67)	72.5 (72/73)
CKD, % (LUS/control)	24.9 (26.9/23)	29.9 (31.5/28.2)	37.5 (36/39)
Diabetes mellitus, % (LUS/control)	38.3 (38.1/38.4)	32 (28.3/35.9)	41 (38/44)
Hypertension, % (LUS/control)	55.5 (63.4/47.6)	66.8 (67.7/65.8)	72 (75/69)
COPD, % (LUS/control)	29.7 (33.3/26.1)	16.8 (15.7/17.9)	25.5 (28/23)
Ischemic HF, % (LUS/control)	59.4 (61.9/56.9)	68 (68.5/67.5)	34.5 (38/31)
LVEF, % (LUS/control)	32.5 (30/34.9)	31.4 (32.2/30.7)	39 (39/39)
NT-proBNP, ng/L (LUS/control)	4625 (4067/5183) *	1439 (1559/1319)	1728 (1559/1897)
CRT, % (LUS/control)	3.05 (3.1/3)	10.6 (12.6/8.5)	9 (5/13)
Follow-up period (m)	6	3	6
Primary endpoints	Composite of urgent HF visits, hospitalization, or death from any cause.	Hospitalization for HF worsening ADHF at the 90-day follow-up	Composite of urgent HF visits, hospitalization for worsening HF and death from any cause.
Secondary endpoints	AKI and hypokalemia	Reduction in NT-proBNP, quality-of-life test, and cardiac mortality.	Reduction in NT-proBNP, quality-of-life test, AKI, hypokalemia, hyperkalemia, hospitalization for hypotension, hyperkalemia, and AKI.

AKI acute kidney injury, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRT* cardiac resynchronization therapy, *HF* heart failure, *LUS* lung ultrasound, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *RCT* randomized controlled trial

*Median

Statistical analysis

We performed a meta-analysis of the included studies using the Review Manager 5.3 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre). The random-effects model was used to calculate the weighted pooled risk ratio (RR) and 95% confidence intervals (CI) of our desired primary and secondary outcomes. A P value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I^2 index, where I^2 values >50% implied the presence of substantial heterogeneity [10].

Bias assessment

We assessed the quality of the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [11]. Two authors (MM and SN) independently assessed each study for bias. Discrepancies were resolved by a third reviewer (HA).

Results

Study selection

Following our review of the literature, we included three RCTs that met our inclusion criteria [6–8]. Figure 1 shows the PRISMA flowchart that illustrates how the final studies were selected.

Study and patients' characteristics

A total of 493 patients were included in these three studies: (251 managed with LUS plus physical examination (PE)-guided therapy vs. 242 managed with PE-guided therapy alone). The mean age was 68.6±12.05 years, males represented 71.8% of total patients, and 66.6% of patients had HF with reduced ejection fraction. Table 1 shows the baseline characteristics of the studies included in the meta-analysis.

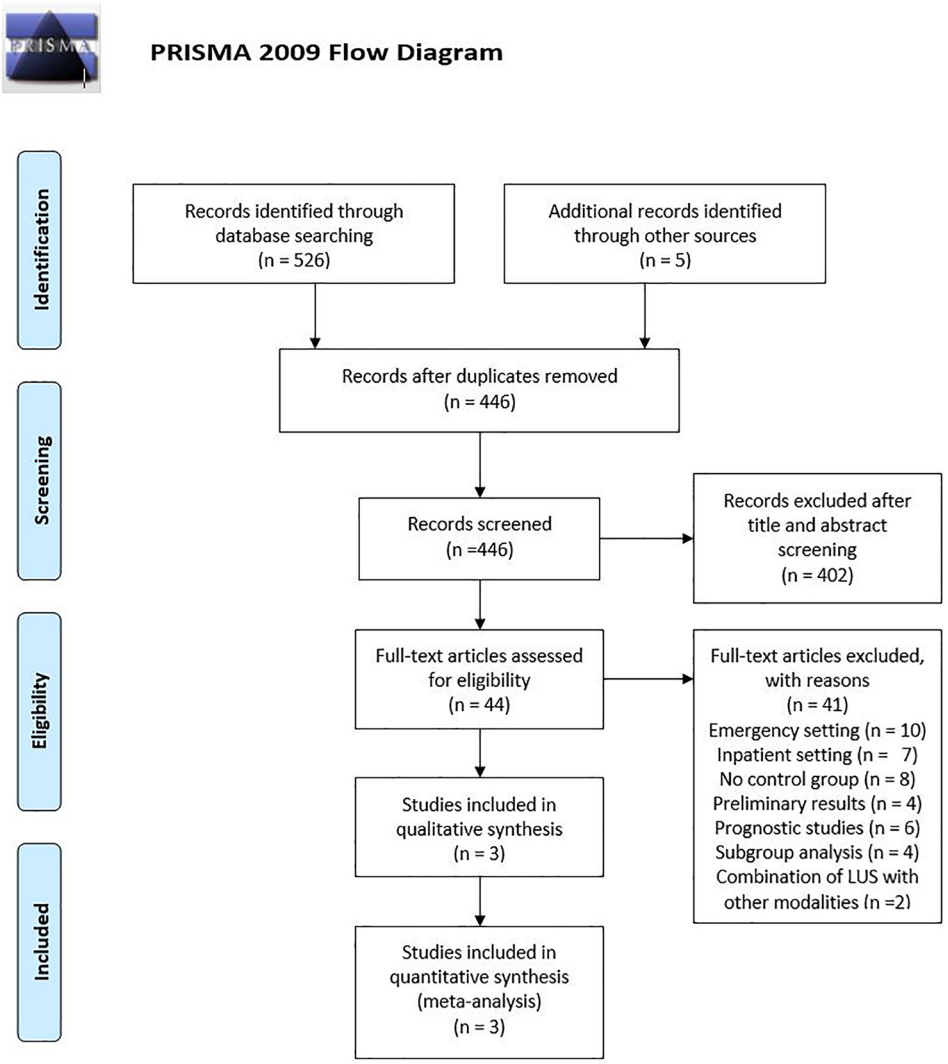

Fig. 1 PRISMA flow diagram for the selection of studies

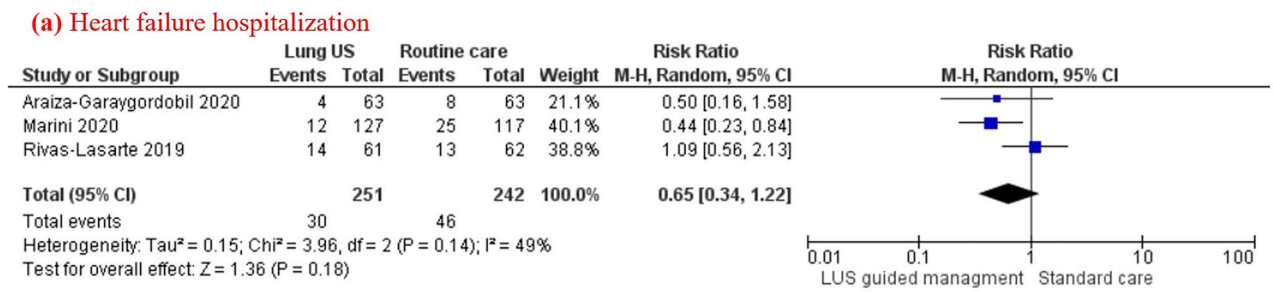

Fig. 2 Forest plot of the primary outcomes comparing LUS and control groups shows no difference in risk of heart failure hospitalization

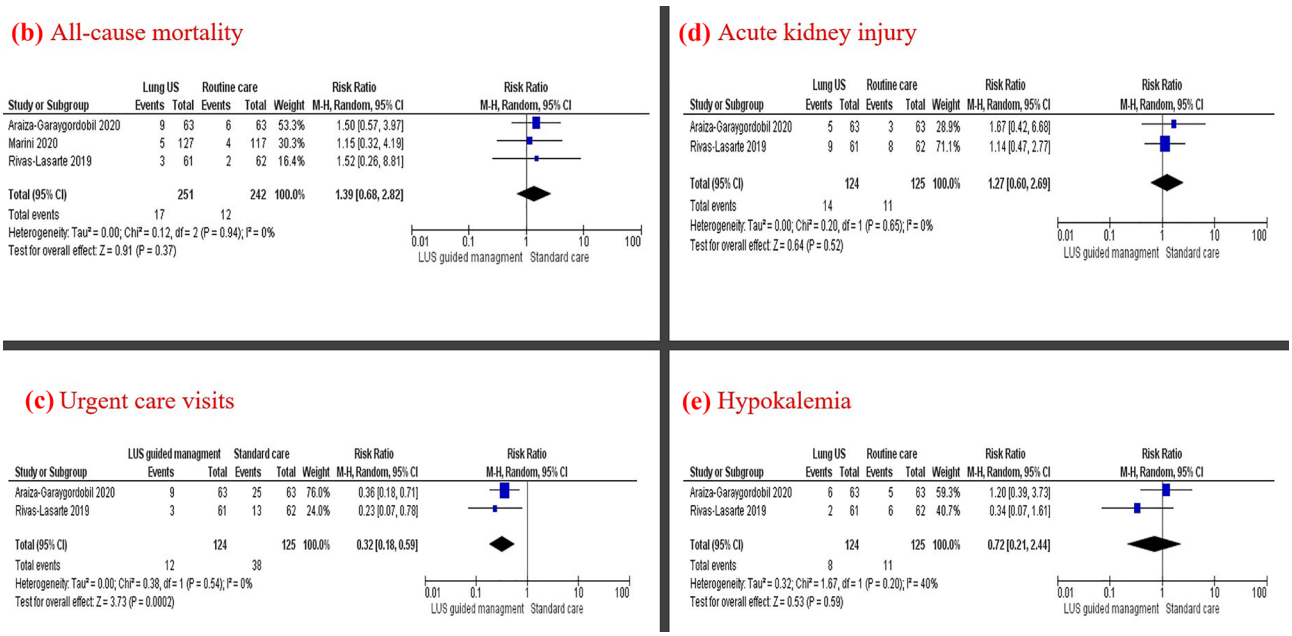

Fig. 3 Forest plot of the secondary outcomes comparing LUS and control groups shows statistically significant difference in risk of urgent care visits favoring LUS-guided management with no safety concerns. A) All-cause mortality, B) Urgent care visits, C) Acute kidney injury, and D) Hypokalemia

Cochrane risk-of-bias assessment demonstrated a low risk of bias for the included RCTs (Online Supplementary Table 2).

Primary outcomes

There was no significant difference in the rates of heart failure hospitalization between the two groups (RR 0.65; 95% CI 0.34–1.22; $P = 0.18$), no significant heterogeneity was found ($I^2 = 49\%$, $P = 0.14$) (Fig. 2).

Secondary outcomes

There was no significant difference with regards to all-cause mortality (RR 1.39; 95% CI 0.68–2.82; $P = 0.37$), AKI (RR 1.27; 95% CI 0.60–2.69; $P = 0.52$), and hypokalemia (RR 0.72; 95% CI 0.21–2.44; $P = 0.59$). However, LUS-guided therapy was associated with a significantly lower rate for urgent care visits (RR 0.32; 95% CI 0.18–059; $P = 0.0002$) (Fig. 3). No significant heterogeneity was found in the measurement of all-cause mortality ($I^2 = 0\%$, $P = 0.94$), neither in risks of urgent visits, AKI and hypokalemia ($I^2 = 0\%$, P = 0.54), ($I^2 = 0\%$, $P = 0.65$), and ($I^2 = 40\%$, $P = 0.2$) respectively. (Online Supplementary Table 3)

Discussion

In this meta-analysis of published RCTs investigating the clinical utility of LUS in chronic HF patients as an adjunct tool in the outpatient setting, we found that LUS-guided strategy significantly reduced the rate of urgent care visits for worsening HF. However, there was no

significant improvement in heart failure hospitalization and all-cause mortality. Furthermore, there were no safety concerns regarding the risks of hypokalemia and AKI.

Acute decompensation of HF foresees a higher risk for hospitalization and mortality in HF patients [12]. PC is the starting point of this process, and physical examination is the mainstay way to detect; nonetheless, it has limited sensitivity and specificity [12].

LUS is a fast, low-cost, and harmless tool that can detect extravascular lung water (EVLW), and thus can reveal pulmonary edema even before the inception of clinical symptoms. An earlier study demonstrated a robust correlation between LUS and EVLW [13]. Furthermore, Platz and colleagues affirmed that PC disclosed by LUS was associated with worse outcomes in HF outpatients [4]. Another non-randomized study that utilized a cardiothoracic ultrasound, including LUS in addition to medial E/E′ ratio and vena cava index for acute HF management, showed that ultrasound-guided management was associated with better prognosis and shorter hospitalization [5].

While LUS efficacy has been extensively evaluated in critical care and emergency context to confirm diagnosis and guide diuretic treatment [14, 15], studies in the outpatient setting are scarce. A recent study among 162 patients showed that LUS has enough HF diagnostic accuracy in primary care settings [16].

Few clinical trials have investigated the LUS-guided strategy in HF patients in outpatient settings [6–8]. They, however, reported inconsistent results. Both CLUSTER-HF and LUS-HF trials [6, 8] showed that LUS-guided strategy significantly improved urgent visits for worsening HF; however, it did not significantly improve hospitalization and all-cause mortality rates. Nonetheless, Marini et al. [7] showed significant improvement in hospitalization rates for worsening HF, but there was no significant reduction in all-cause mortality rate. Our meta-analysis confirmed that the LUS-guided strategy significantly improved urgent care visits for worsening HF but showed no improvement in hospitalization and all-cause mortality rates. Failure to show clinical significance in hospitalization and all-cause mortality rates in our study may be attributed to the relatively short follow-up duration (mean of 5 months). Furthermore, the lack of significant hospital readmission reduction despite the lower risk of urgent care visits amongst the LUS group may be explained by the discrepancy in the admission criteria among different institutions [17].

N-terminal pro-brain natriuretic peptide (NT-proBNP)-guided therapy is another comparable strategy to LUS in the outpatient setting that showed improved outcomes in a recent meta-analysis [18]. LUS-HF trial showed that there were no differences in NT-proBNP values between the two groups ($P = 0.95$) [8]; however, Marini et al. [7] reported a significant reduction of NT-proBNP values in the LUS group ($P = 0.026$). These contradictory results may be attributed to lack of overall sufficient statistical power to detect such a difference.

Although we were unable to analyze the impact of the LUS-guided strategy on the quality of life, the CLUSTER-HF trial [6] showed no statistical difference of the median change in The Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary at the end of follow-up ($P = 0.95$). Similarly, Rivas-Lasarte et al. [8] reported no difference in quality of life as measured by Minnesota Living With Heart Failure quality of life (MLWHF) scale ($P = 0.95$); however, the last study showed a significant improvement of the 6-min walking test (6MWT) favoring LUS group ($P = 0.023$).

There are several limitations to our study. First, despite pooling three RCTs, the number of patients included in this meta-analysis was small which may explain the overall neutral outcomes. Second, the included trials in this meta-analysis were conducted in two regions (Mexico and Europe), which might affect the generalizability of our results to other populations. Third, we were unable to further analyze other parameters to detect a difference in functional capacity between the two groups with NYHA or 6-MWD assessment. Last, patients with right-sided heart failure do not demonstrate signs of PC; thus, LUS has no value in their management.

In conclusion, our meta-analysis demonstrated that outpatient LUS-guided diuretic therapy of pulmonary congestion showed improvement in urgent care visits for worsening HF. However, there was no significant improvement in terms of re-hospitalization and all-cause mortality rates. Further multicentric randomized clinical trials with larger sample sizes and longer follow-up periods are needed to evaluate the utility of LUS-guided strategy in the outpatient treatment of HF patients.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s10741-021-10085-x.

Author contribution MM and AB conceived of and designed the study and critically revised the manuscript. MM, EE, and SN designed the study; collected, analyzed, and interpreted the data; and drafted the manuscript. O. Sajdeya, O. Srour, and HA collected the data and reviewed the literature. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was deemed exempt by the Institutional Review Board of the University of Toledo, as it was a meta-analysis of published studies that included de-identified patient information.

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