

● Review

EFFECTS OF LUNG ULTRASONOGRAPHY-GUIDED MANAGEMENT ON CUMULATIVE FLUID BALANCE AND OTHER CLINICAL OUTCOMES: A SYSTEMATIC REVIEW

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Abstract—Lung ultrasonography is accurate in detecting pulmonary edema and overcomes most limitations of traditional diagnostic modalities. Whether use of lung ultrasonography-guided management has an effect on cumulative fluid balances and other clinical outcomes remains unclear. In this systematic review, we included 12 studies using ultrasonography guided-management with a total of 2290 patients. Four in-patient studies found a reduced cumulative fluid balance (ranging from −0.3 L to −2.4 L), whereas three out-patient studies found reduction in dialysis dry weight (ranging from −2.6 kg to −0.2 kg) compared with conventionally managed patients. None of the studies found adverse effects related to hypoperfusion. The use of lung ultrasonography-guided management was not associated with other clinical outcomes. This systematic review shows that lung ultrasonography-guided management, exclusively or in concert with other diagnostic modalities, is associated with a reduced cumulative fluid balance. Studies thus far have not shown a consistent effect on clinical outcomes. (E-mail: m.heldeweg@amsterdamumc.nl) © 2021 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Key Words: Ultrasonography, Pulmonary edema, Lung, Fluid, Management, Clinical outcomes.

INTRODUCTION

Pulmonary edema is associated with increased hospitalizations, all-cause mortality and high costs (Banerjee et al. 2007; Chazot et al. 2012; Melenovsky et al. 2015; Assimon et al. 2016). In out-patient settings, such as cardiology and nephrology, symptoms might develop after weeks of insidious overload, and physical findings only appear when pulmonary edema is significant (Stevenson and Perloff 1989; Yu et al. 2005; Torino et al. 2016). This is troublesome, as even pre-clinical pulmonary edema is associated with worse patient outcomes (Androne et al. 2004). Timely

recognition, appropriate monitoring and adequate fluid management might benefit individual patients and alleviate concurrent social burden.

Most pulmonary edema monitoring modalities lack sensitivity (Pistolesi and Giuntini 1978), specificity (Silver et al. 2004) and repeatability (Picano and Pelikka 2016) or are not sufficiently investigated (Reddan et al. 2005; Dekker and Kooman 2018). More reliable measures can be performed on the intensive care unit (ICU) but are invasive and costly (Jozwiak et al. 2015). Ultrasonography of the heart and vena cava are not very helpful to qualify or quantify pulmonary edema (Jensen et al. 2004; Kraemer et al. 2006). Lung ultrasonography can accurately identify and quantify pulmonary edema and supports prognostication in cardiology (Gargani et al. 2015; Facchini et al. 2016), nephrology (Zoccali et al. 2013; Annamalai et al. 2019; Panuccio et al., 2019), emergency department (ED) (Martindale et al. 2018; Wimalasena et al. 2018) and

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ICU patients (Winkler et al. 2018). It has been shown to out-perform traditional pulmonary edema evaluation methods regarding accuracy and comes without the limitations of traditional diagnostic modalities (Coiro et al. 2015; Enghard et al. 2015; Alexiadis et al. 2017). The next step in its validation is to substantiate whether lung ultrasonography affects fluid management and, as a result, clinical outcomes (Bossuyt et al. 2012).

The primary aim of this systematic review was to determine whether lung ultrasonography-guided management (guided by lung ultrasonography exclusively or in concert with other diagnostic modalities) affects the cumulative fluid balance. Second, we aimed to investigate whether lung ultrasonography-guided management leads to adverse effects related to hypoperfusion (*i.e.*, clinically apparent parameters: hypotension and kidney injury) and affects other clinical outcomes (*i.e.*, length of stay, length of mechanical ventilation, hospitalizations and mortality). We hypothesized that lung ultrasonography-guided management leads to a lower fluid balance without apparent hypoperfusion.

MATERIALS AND METHODS

Study design

This is a systematic review. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to ensure transparent and complete reporting of our review. The protocol was registered at PROSPERO (International Prospective Register of Systematic Reviews) (CRD42020172559).

Search strategy

A comprehensive literature search was performed in PubMed (MEDLINE) up to March 11, 2020, and in the Cochrane Library up to April 2020 with the help of a medical librarian. The search strategies (detailed in Appendix Table A1a–c) used medical subject headings, keywords and synonyms to identify records pertaining to (i) ultrasonography and (ii) pulmonary edema or (i) ultrasonography, (iii) lung and (iv) fluid.

Study selection and inclusion

Two authors (M.L.A.H. and A.J.) conducted title and abstract screening of the studies identified by the search. Inclusion criteria were: (i) lung ultrasonography-guided management exclusively or in concert with other diagnostic modalities; (ii) primary outcome (cumulative fluid balance) or at least one of the secondary outcomes (hypoperfusion parameters, hospitalization, length of stay, length of mechanical ventilation, mortality); and (iii) informed consent from participants and approval by an institutional review board. Studies were excluded if:

(i) they were not original clinical investigations (*i.e.*, reviews, or secondary reports); (ii) they were not available as English full text; (iii) they contained duplicate data; or (iv) if they were studies aimed exclusively at pediatric or pregnant patients, or animals. Finally, reference lists of included studies were screened for additional studies. Conflicts related to inclusion or exclusion of studies were solved by discussion between three authors (M.H., A.J., P.T.). After consensus, two authors (M.H. and A.J.) extracted data of interest from the eligible studies.

Data extraction

The following data, if available, were collected from each study: (i) patient care protocol incorporating lung ultrasonography; (ii) control group management; (iii) population; (iv) management; (v) primary outcome when available (change in fluid balance or change in dry weight); (vi) clinical hypoperfusion parameters when available (hypotension and kidney injury) (vii) other clinical outcomes when available (length of stay, length of mechanical ventilation, hospitalizations, mortality); and (viii) methodological aspects (probe, lung ultrasonography scoring system, training, interrater agreement).

Data synthesis

All data were presented as provided in the original full-text studies and their supplemental data but were rounded to a relevant number of decimals. Outcome variables were presented as means and standard deviations (\pm SD), medians and interquartile range or numbers and percentage (%) when appropriate. The lung ultrasonography arm or cohort was referred to as the guided group (G), whereas the conventional management arm or cohort was referred to as the conventional group (C). Studies were presented in in-patient (generally large fluid changes over short periods) and out-patient (generally minimal changes over long periods) categories. Meta-analysis, even within sub-groups, was considered inappropriate owing to the considerable heterogeneity in pre-specified design, population, intervention, outcomes and methodology.

Quality assessment

All extracted outcomes of the included studies were evaluated for their risk of bias. Each study was assessed with an appropriate tool for the respective design. For randomized controlled trials (RCTs) the Cochrane Risk of Bias tool was used (Higgins et al. 2011). This tool classifies an RCTs' risk of bias as low, some or high concerns. Similarly, for observational studies, the Risk Of Bias In Non-randomised Studies - of Interventions tool (ROBINS-I) was applied (Sterne et al. 2016). The

ROBINS-I classifies an observational study's risk of bias as low, moderate, serious or critical. Single cohort studies were automatically classified as high risk. A Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was carried out using qualitative synthesis of evidence, as described in previous literature (Murad *et al.* 2017). A GRADE summary of findings table was constructed based on an evidence profile.

RESULTS

The search yielded a total of 3814 records (Fig. 1). Eight additional records were identified through screening of reference lists. After removal of records that did not meet inclusion criteria ($n = 3790$), 32 studies were read in full and assessed for eligibility. Finally, 12 studies with a total of 2290 patients (1022 in-patients and 1268 out-patients) were included for data extraction (Fig. 1).

The study characteristics are described in Table 1. Seven in-patient studies on the emergency department (ED) ($n = 3$), internal medicine ($n = 1$) and ICU ($n = 3$) were identified, of which three were RCTs. Five out-patient studies were identified on cardiology ($n = 2$) and nephrology ($n = 3$), of which three were RCTs. All RCTs and observational studies with more than one cohort

compared lung ultrasonography-guided management to a group of conventionally managed patients.

The in-patient studies had a follow-up equal to the length of stay, except one, which registered outcome at 28 and 60 d (Coen *et al.* 2014). The out-patient studies investigated fluid changes, hospitalizations and mortality over a longer period (ranging from 8 wk to 39 mo), except one study that followed maintenance dialysis patients until the next dialysis (Liang *et al.* 2019).

Three studies exclusively used lung ultrasonography-guided management. Nine studies used lung ultrasonography-guided management in concert with other modalities, of which eight studies incorporated cardiac ultrasonography and/or caval ultrasonography and three studies incorporated additional non-ultrasonographic modalities (brain natriuretic peptide and bio-impedance). One study used an elaborate ultrasonographic head-to-toe protocol composed of, among others, optic nerve sheath diameter, lung, cardiac, abdominal and venous ultrasonography (Pontet *et al.* 2019).

Primary outcome

Change in fluid balance. All four in-patient studies reporting the effects of lung ultrasonography-guided management on cumulative fluid balance (Table 2) found a more negative fluid balance in the guided group

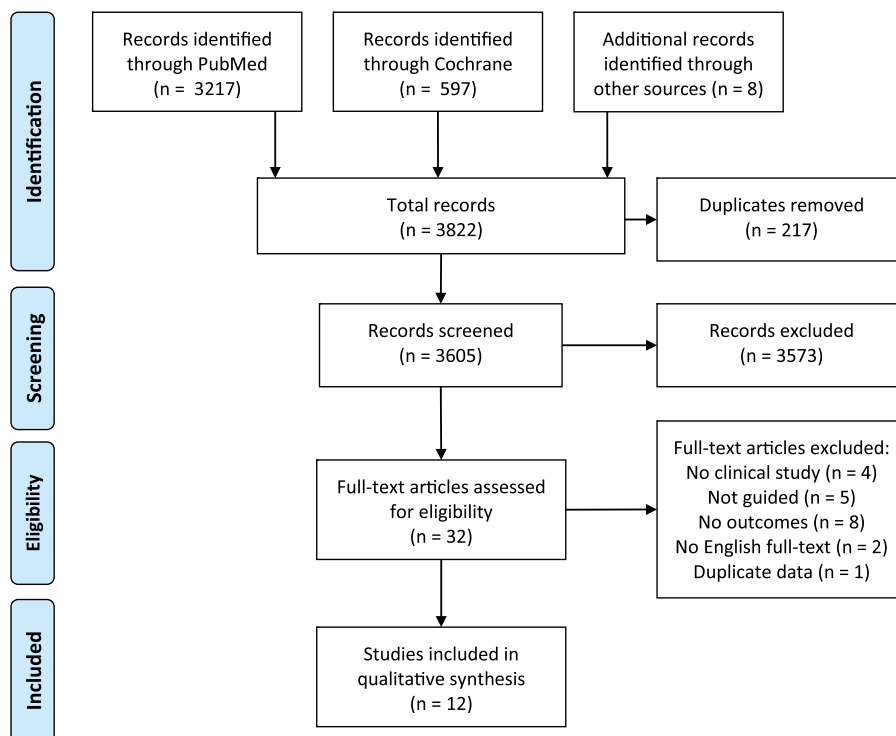


Fig. 1. PRISMA flow diagram of information through the different phases of the systematic review. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Table 1. Study characteristics

Study Design (arms/cohorts)	Department (country)	Population (total n)	Intervention	Follow-up time	Outcome reported
In-patient					
Baker et al. 2020, RCT (2)	ED (Australia)	Dyspnea (442)	LU	LoS	Secondary
Öhman et al. 2018, PCS (2)	ED (Finland)	Heart failure (120)	LU + cardiac	LoS	Primary + secondary
Coen et al. 2014, PCS (1)	ED (Italy)	Septic shock (47)	LU + IVC	28 d 60 d	Secondary
Pontet et al. 2019, RCT (2)	ICU (Uruguay)	Mechanically ventilated (80)	LU + head-to-toe	LoS	Primary + secondary
Wang et al. 2014, RCT (2)	ICU (China)	Pulmonary edema (128)	LU + Cardiac + IVC	LoS	Primary + secondary
Wang et al. 2018, PCS (2)	ICU (China)	Post-fluid infusion (85)	LU + IVC	LoS	Primary + secondary
Mozzini et al. 2018, RCT (2)	Internal (Italy)	Heart failure (120)	LU + Cardiac + IVC + BNP	LoS	Secondary
Out-patient					
Rivas-Lasarte et al. 2019, RCT (2)	Cardiology (Spain)	Heart failure (123)	LU	6 mo	Secondary
Bajraktari et al. 2018, PCS (3)	Cardiology (Italy)	Heart failure (794)	LU + Cardiac + BNP	35–39 mo	Secondary
Loutradis et al. 2020, RCT (2)	Nephrology (Greece)	Dialysis (71)	LU	8 wk	Primary + secondary
Siriopol et al. 2017, RCT (2)	Nephrology (Romania)	Dialysis (245)	LU + BIA	24 mo	Primary + secondary
Liang et al. 2019, PCS (1)	Nephrology (China)	Dialysis (35)	LU + IVC + tibial	Following dialysis	Primary

BIA = bio-impedance analysis; BNP = brain natriuretic peptide; ED = emergency department; ICU = intensive care unit; IVC = inferior vena cava ultrasonography; JVP = jugular venous pressure ultrasonography; LU = lung ultrasonography; PCS = prospective cohort study; RCT = randomized controlled study; RCU = respiratory care unit.

Table 2. The effect of lung ultrasonography–guided management on cumulative fluid balance and hypoperfusion parameters

Study Design (arms)	Patients (n)	Intervention	Management	Δ fluid balance	Adverse effects
In-patient					
Öhman et al. 2018, PCS (2)	G: AHF (20) C: AHF (100)	LU + cardiac	Fluid removal till B-line resolution	G: $-5.5 \pm 5.4^*$ C: $-3.1 \pm 3.1^*$	AKI G: 15%, C: 21% Hypotension G: 0%, C: 4%
Pontet et al. 2019, RCT (2)	G: MV (40) C: MV (40)	LU + head-to-toe	Conventional	G: $-3.2 \pm 3.5^\dagger$ C: $-0.9 \pm 3.9^\dagger$	N/A
Wang et al. 2014, RCT (2)	G: PE (66) C: PE (62)	LU + cardiac + IVC	Conventional	G: $5.7 \pm 0.6^*$ C: $6.1 \pm 0.7^*$	N/A
Wang et al. 2018, PCS (2)	G: PFI (40) C: PFI (45)	LU + IVC	US-guided fluid removal protocol	G: $-1.0 \pm 0.6^\dagger$ C: $-0.7 \pm 0.5^\dagger$	Hypotension G: 0, C: 2
Out-patient					
Loutradis et al. 2020, RCT (2)	G: HD (35) C: HD (36)	LU	HD intensification when BLUS >15	G: $-0.7 \pm 1.4^*$ C: $+0.5 \pm 1.0^*$	Hypotensive episodes G: 34%, C: 56%
Siriopol et al. 2017, RCT (2)	G: HD (123) C: HD (122)	LU + BIA	HD intensification when BLUS \geq 15	G: -1.1 (71.0 95% CI 68.1–73.9) C: $+1.5$ (73.1 95% CI 70.3–76.0)	Intradialytic hypotension RR: 1.08 (95% CI 0.99–1.18)
Liang et al. 2019, PCS (1)	HD (35)	LU + cardiac + IVC + tibial	Single HD intensification when BLUS >6	–220	None developed hypovolemia

All change in fluid balance in nephrology was reported in kilogram, whereas in cardiology and critical care it was reported as liters.

AHF = acute heart failure; AKI = acute kidney injury; BLUS = B-lines ultrasonography score; C = conventional; CI = confidence interval; G = guided; HD = hemodialysis; I = intervention; IVC = inferior vena cava ultrasonography; LU = lung ultrasonography; N/A = not available; PCS = prospective cohort study; PE = pulmonary edema; PFI = post-fluid infusion; RCT = randomized controlled trial; RR = relative risk; Tibial = tibial ultrasonography; Δ difference.

* <0.05; other *p*-values are >0.05.

† ≤0.001.

(ranging from -0.3 to -2.4 L) than in the conventional group, albeit two studies did not report whether the difference was statistically significant (Siriopol *et al.* 2017; Liang *et al.* 2019).

Three out-patient nephrology studies, where fluid extraction was performed through intensification of periodic maintenance dialysis (*i.e.*, reduction of dry weight), reported a decrease in dry weight in the guided group (ranging from -1.1 to -0.2 kg) compared with an increase in the conventional group (ranging from $+0$ to $+1.5$ kg).

Secondary outcomes

Hypoperfusion parameters. Two of the in-patient studies reported hypoperfusion parameters, but none found a difference (Table 2). Additionally, two studies reported a lower lactate in the guided group ($p < 0.05$) (Wang *et al.* 2014; Wang *et al.* 2018).

All of the out-patient studies reported hypoperfusion parameters, but none found a difference (Table 2). One study did report less pre-dialytic dyspnea (relative risk: 0.81, 95% confidence interval [CI] 0.68–0.96), but more intra-dialytic cramps (relative risk: 1.26, 95% CI 1.16–1.37) in the guided group (Siriopol *et al.* 2017).

Other clinical outcomes. Eight in-patient studies recorded clinical outcomes (Table 3). Out of six studies reporting on length of stay, two found a lower length of

stay in the guided group (Mozzini *et al.* 2018; Öhman *et al.* 2018). Two studies reported duration of mechanical ventilation, of which one found fewer days of mechanical ventilation in the guided group (Pontet *et al.* 2019). Five studies found no difference on mortality.

Of the out-patient studies, four reported hospitalizations and mortality during follow-up (Appendix Table A2). One had a composite outcome of hospitalizations and mortality and found that the guided group had the least number of events compared with symptom-based or un-organized follow-up (Bajraktari *et al.* 2018). The other three studies did not find a difference in, hospitalizations or mortality. One study found no difference in 2-y cardiovascular event rates (Siriopol *et al.* 2017).

Lung ultrasonography methodology. The methodology used for lung ultrasonography was different in various aspects (Appendix Table A3): number of zones examined (ranging from 6–32), its appraisal (sum of B-lines, the Bedside Lung Ultrasound in Emergency (BLUE) protocol or other scoring systems), the ultrasonographic equipment used and the examiner's level of training. Two studies calculated an inter-observer reliability of 0.73 and 0.96, respectively.

Quality assessment of studies. The risk of bias assessment of the included studies is summarized in

Table 3. The effect of lung ultrasonography-guided management on other clinical outcomes reported by in-patient studies

Study Design (arms)	Patients (n)	Intervention	Management	Outcome		
				LOS (d)	MV (d)	Mortality
ED						
Baker <i>et al.</i> 2020, RCT (2)	G: ARF (218) C: ARF (224)	LU	Conventional	G: 3.1 [1.0–6.1] C: 2.9 [1.1–5.0]	N/A	G: 1.4% C: 4.5%
Öhman <i>et al.</i> 2018, PCS (2)	G: AHF (20) C: AHF (100)	LU + Cardiac + IVC	Fluid removal till B-line resolution	G: $3.7 \pm 2.0^*$ C: $6.9 \pm 4.2^*$	N/A	N/A
Coen <i>et al.</i> 2014, PCS (1)	Septic shock (47)	LU + IVC	Conventional	N/A	N/A	28 d: 34% 60 d: 38.3%
ICU						
Pontet <i>et al.</i> 2019, RCT (2)	G: MV (40) C: MV (40)	LU + head-to-toe	Conventional	G: 9 ± 8 C: 13 ± 10	G: $5.1 \pm 5.7^\dagger$ C: $8.8 \pm 9.4^\dagger$	G: 17.5% C: 15%
Wang <i>et al.</i> 2014, RCT (2)	G: PE (66) C: PE (62)	LU + Cardiac + IVC	Conventional	G: 4.5 ± 2.1 C: 5.2 ± 2.3	N/A	G: 6.1% C: 8.1%
Wang <i>et al.</i> 2018, PCS (2)	G: PFI (40) C: PFI (45)	LU + IVC	US-guided fluid removal protocol	G: 3.1 ± 1.9 C: 4.2 ± 4.6	G: 17.5 [28.5] C: 21.0 [47.3]	G: 0 C: 2.2%
Internal medicine						
Mozzini <i>et al.</i> 2018, RCT (2)	G: AHF (60) C: AHF (60)	LU + IVC + BNP	Conventional	G: 7 [3–10]* C: 8 [4–17]*	N/A	N/A

The continuous variables were expressed as mean \pm standard deviation if normally distributed or median [interquartile range] if not normally distributed.

AHF = acute heart failure; ARF = acute respiratory failure; C = conventional; ED = emergency department; G = guided; ICU = intensive care unit; IVC = inferior vena cava ultrasonography; LOS = length of stay; LU = lung ultrasonography; MV = length of mechanical ventilation; N/A = not available; PCS = prospective cohort study; PFI = post-fluid infusion; PE = pulmonary edema; RCT = randomized controlled trial.

* $p \leq 0.001$

† $p < 0.05$.

Table 4. GRADE Summary of findings of studies on lung ultrasonography-guided management

Outcome	Effect	Number of participants	Certainty in the evidence
Fluid balance	All of seven studies showed more fluid removal in the intervention group (Wang 2014; Siriopol 2017; Ohman 2018; Wang 2018; Liang 2019; Pontet 2019; Loutradis 2020).	774 participants are included in 3 observational studies and 4 RCTs	Very low ●○○○
Length of stay	Five studies showed a lower length of hospitalization in the intervention groups (Wang 2014; Mozzini 2017; Ohman 2018; Wang 2018; Pontet 2019). One showed an insignificant longer hospital length (Baker 2020).	975 participants are included in 2 observational studies and 4 RCTs	Very low ●○○○
Length of mechanical ventilation	Two studies showed lower lengths of mechanical ventilation in the guided groups (Wang 2018; Pontet 2019).	85 participants are included in an observational study, and 80 are included in an RCT.	Low ●●○○
Hospitalizations	One study showed a significantly lower rate of hospitalizations in the intervention group (Bajraktari 2018). Three studies did not show a significant difference (Siriopol 2017; Rivas 2019; Loutradis 2020).	1183 patients in out-patient setting are included in one observational study and 3 RCTs	Low ●●○○
Mortality	Six studies did not show a difference in mortality between the intervention and control groups (Wang 2014; Siriopol 2017; Wang 2018; Rivas 2019; Pontet 2019; Baker 2020). One study showed a difference in favor of the intervention group (Bajraktari 2018). One was a single-arm study of which no inferences could be made (Coen 2014).	1885 participants are included in 3 observational and 5 RCTs	Very low ●○○○

RCT = randomized controlled trial.

Appendix Table A4 (a, b). One RCT was considered to have of low risk of bias across its outcomes, five had some concerns and one had a high risk of bias. Both single-cohort observational studies were judged to have a high risk of bias because of their innate lack of blinding and control group. The three multi-cohort observational studies were considered to have either a serious or critical risk of bias. None of the observational studies mentioned any adjustments for confounding.

The GRADE summary of findings is presented in Table 4. The full evidence profile is provided in Appendix Table A5 (a–e). When synthesizing the outcomes across all studies, the evidence is considered to be of low or very low quality because of their risk of bias and indirectness. The latter is influenced by studies' considerable heterogeneity in study population, method of measurements, duration of follow-up and difference in outcomes.

DISCUSSION

The main findings of this systematic review on lung ultrasonography-guided management are as follows. First, lung ultrasonography-guided management reduced in-patient and out-patient cumulative fluid balance compared with conventional management. Second, lung ultrasonography-guided management did not lead to

adverse effects related to hypoperfusion. Third, lung ultrasonography-guided management had the following effects on clinical outcomes: (i) Some studies found a reduced length of stay and fewer days on mechanical ventilation, but most found no difference; and (ii) the majority of studies did not find a difference in hospitalizations and mortality.

The fact that lung ultrasonography-guided management is able to reduce fluid balance should not be underestimated. It is well known that a positive fluid balance is associated with increased morbidity and mortality (Schuller et al. 1991; Nisanevich 2005; Wiedemann et al. 2006). Normalizing interstitial fluid and circulating volume is therefore a critical therapeutic target that requires appropriate diagnostic and monitoring tools (Boyle et al. 2007). The findings of this systematic review strongly suggest that lung ultrasonography fosters further decongestion than conventional management without risking adverse effects of over-zealous fluid extraction, which is substantial considering its ease of implementation, use, low cost and safety.

Although some studies did find a difference in clinical outcomes, the majority did not. The lack of consistent effects on clinical outcomes is not surprising. First and most importantly, large well-designed studies are required to establish the true effect of lung

ultrasonography-guided management on these outcomes. Second, previous research has shown that diagnostic tools do not necessarily equate to improved clinical outcomes (Wheeler *et al.* 2006; Zhang *et al.* 2015), likely because a myriad of unknown variables exist between use of the instrument and outcome (*e.g.*, clinician, interpretation, resultant therapy and relevance to patient context). Therefore, this systematic review primarily examines the effect of lung ultrasonography-guided management on cumulative fluid balance, which is important to substantiate the clinical utility of this diagnostic instrument (Bossuyt *et al.* 2012). Considering the pathophysiologic rationale behind normalizing interstitial fluid and circulating volume, and lung ultrasonography's ability to affect these parameters, we believe that larger, well-designed trials might be able to identify important effects on clinical outcomes. There are currently several ongoing trials on lung ultrasonography-guided management that may provide further and higher quality of evidence (Bailón *et al.* 2019; Russell *et al.* 2019; Rusu *et al.* 2019).

The quality of evidence in the current investigation was “low” or “very low” when summarized across outcomes. Moreover, most included studies were considered to have “some” to “high” concerns regarding risk of bias and were heterogeneous in nature, precluding the possibility of data pooling. The broad inclusion criteria containing multiple patient populations used in this systematic review are, in part, an explanation for this heterogeneity. Even when examining sub-groups, data pooling would be inappropriate. The studies in this review show large differences in lung ultrasonography methodology and sometimes even lack of description. This is problematic as training and experience of rater, probe, machine settings or even patient positioning could affect findings (Frasure *et al.* 2015; Haaksma *et al.* 2020). Despite being highly context-dependent, methodologic consensus is still lacking and is not sufficiently evidence based. As such, the findings in this review reflect a larger problem and are consistent with previous reports (Neuteboom *et al.* 2020). Although there are reasonable assumptions to be made about the value of lung ultrasonography-guided management, the currently available evidence is not strong enough to dictate adjustments to health care guidelines.

Of the included studies, 75% used lung ultrasonography in concert with other modalities, making it difficult to ascertain which effects can be exclusively attributed to lung ultrasonography. This might be considered inconsequential as lung ultrasonography should not be viewed as a replacement but an extension of physical examination and conventional management (Covic *et al.* 2018; Picano *et al.* 2018; Mojoli *et al.*, 2019; Arts *et al.* 2020). This is in line with a previous

study that found an integrated ultrasonographic approach, in the form of thoracic ultrasonography, outperforms its individual components (Bataille *et al.* 2014).

Strong points of this study are its robust methodology, registration and broad exploration of lung ultrasonography-guided management across out-patient and in-patient setting. Lung ultrasonography might affect clinical outcomes through fluid management, but cumulative fluid balance is not always collected or reported as an outcome. Therefore, we also included studies that did not report the primary outcome to allow for inclusive investigation of other clinical outcomes.

This is the first comprehensive systematic review on lung ultrasonography-guided management. A previous narrative review on lung ultrasonography-guided management did not identify any studies on the subject (Nair and Sauthoff, 2019). This study thereby advances scientific insight on lung ultrasonography-guided management and identifies existing knowledge gaps.

The present study also has limitations. There are no particular medical subject headings to identify studies that use a management guide. As such, an extensive search strategy paired with thorough methodologic examination was necessary. Although the search strategy was robust, it is still possible that not all studies were identified. Studies not published in English were excluded, which may have introduced some bias.

In conclusion, this systematic review shows that lung ultrasonography-guided management, exclusively or in concert with other diagnostic modalities, has the potential to improve patient care as it leads to a reduced fluid balance without adverse effects related to hypoperfusion. Studies in this systematic review have not shown a consistent effect on other clinical outcomes. Well-designed trials and evidence-driven lung ultrasonography standardization are needed.

Conflict of interest disclosure—All authors disclosed that they do not have any conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.ultrasmedbio.2021.01.024](https://doi.org/10.1016/j.ultrasmedbio.2021.01.024).

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