Prognostic value and therapeutic utility of lung ultrasound (LUS) in acute and chronic heart failure: a meta-analysis

Short Title: LUS in heart failure: a meta-analysis

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Abbreviations:

CV, cardiovascular

HF, heart failure

LUS, lung ultrasound

LVEF, left ventricular ejection fraction

RR, risk ratio

Congestion drives the risk of hospitalization in heart failure (HF). Accurate and early identification and quantification of congestion could improve management, thereby leading to lower risk of poor outcomes (1). Lung ultrasound (LUS) is a quick and reliable imaging technique, based on the counts of B-lines, to assess clinical and subclinical pulmonary congestion. In this meta-analysis, we studied the prognostic value of B-lines and the treatment effect of LUS-guided therapy on cardiovascular (CV) outcomes in HF.

We conducted a systematic search of the published data in PUBMED/Medline using the keywords “lung ultrasound” AND “heart failure” AND “prognosis” for the period from 2010 to May 2021. Twelve studies assessing the prognostic value (2,293 patients) and three trials (493 patients) evaluating LUS-guided management in HF were finally included (mean LVEF range: 30 to 60%) (Figure 1(A)). Thereafter, studies on prognosis were grouped according to the clinical setting: 1) out-patient clinic, 2) at admission, and 3) at discharge for HF hospitalizations (Figure 1(B)). Clinical trials assessing LUS-guided therapy were analysed separately (Figure 1(C)).

We conducted a fixed-effect meta-analysis. Based on recommendations of available published literature, the following cut-offs for pooling the risk estimates were used: ≥15 in 28 zones (~0.5 B-line/zone); ≥ 3 in 5-8 zones (~0.4 B-line/zone); ≥ 4 in 4 zones (1 B-line/zone) LUS (1,2). Additionally, the RR for studies reporting 8 or more zone LUS was calculated to assess the effect size when maximizing the congruence of the thresholds of B-lines per zone in the discharge group. Authors were contacted for RR associated with pre-selected cut-offs if needed. In the clinical trials, B-lines ≥3 using 8 zone method was considered as significant for congestion in two studies (Figure 1(C)).

For most of the studies, the primary outcome was a composite of hospitalization for HF and all-cause mortality; two studies also reported urgent visits for worsening of HF. LUS-

guided treatment effect was evaluated by pooling the adjusted RR of primary outcome and hospitalization for HF from clinical trials. All analyses were conducted in R (v4.0.3).

A higher number of B-lines was associated with an increased risk of primary outcome irrespective of the setting (out-patient clinic: RR=1.66, 95%CI: 1.28-2.15, p=0.0001, I^2=57.5%; at admission: RR=2.32, 95%CI: 1.46-3.70, p= 0.0004, I^2=50.92%; at discharge: RR= 2.46, 95%CI: 1.56-3.86, p=0.0001, I^2=0.00%) (Figure 1(B)). In sensitivity analysis, we included all the tertiles from Platz et al., study in discharge group and the results did not change (RR=2.60, 95%CI: 1.77-3.83, p<0.001, I^2 =0.00%). When 8 or more zones were used to assess B-lines at discharge, the increase in the risk of hospitalization for HF or death was similar (RR=2.47, 95%CI: 1.55-3.93, p<0.0001, I^2=3.50%).

In clinical trials, the pooled RR for the primary outcome (urgent visits for worsening of HF, hospitalization for HF and mortality) and for hospitalization for HF was 0.50 (95%CI: 0.35-0.72, p=0.001, I^2=0.00%) and 0.62 (95%CI: 0.40-0.87, p=0.007, I^2=41.01%), respectively (Figure 1(C)). The lower risk of primary composite outcome was reported to be largely driven by a reduction in urgent visits for worsening HF in the studies that included urgent visits in primary outcome.

This analysis provides inclusive results of available literature regarding LUS, combining results from different LUS techniques (4 to 28 zones), study design (cohorts and trials) and settings (out-patient and hospitalized patients). We expand the results of the previous meta-analysis by Platz et al., and Wang et al., by the inclusion of 8 zones LUS and the assessment of the prognostic value of LUS conducted at the time of admission (2,3). Wang et al., reported higher RR compared to our results possibly because of the absence of adjustment for clinically relevant variables (age, sex, NYHA class/LVEF, renal function, NT-pro-BNP and others). The fact that the number of B-lines persisted as a significant prognostic factor even after adjustment further emphasizes the clinical utility of LUS.

In clinical trials, LUS-guided therapy was consistently associated with lower risk of CV events perhaps due to a better optimization of HF therapy in LUS-guided group. However, a recent pilot study BLUSHED-HF did not identify a benefit from LUS-guided therapy versus standard care in acute HF (4). How to best use LUS-guided therapy in HF still needs to be defined.

Our study has two main limitations. First, the number of studies in each setting is limited. Second, significant heterogeneity exists across studies, possibly due to the grouping of different B-lines thresholds from different LUS protocols (different transducer orientation, scoring/counting methods), statistical adjustment and differences in post-discharge care. This heterogeneity reinforces the need for a standardized approach to assess B-lines according to a cut-off specific to each setting.

In conclusion, findings from this meta-analysis support the use of LUS for evaluating the risk of adverse outcome in patients with HF regardless of the clinical setting, and provide evidence in favour of a beneficial effect of LUS-guided management in out-patients.

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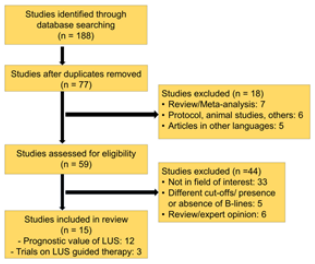
Figure Legend

Figure 1: Prognostic value of B-lines and therapeutic utility of LUS-guided therapy in patients with HF.
(A) Literature search results with exclusion criteria (B) Baseline characteristics and pooled risk estimates of the prognostic value of B-lines according to clinical setting of LUS. (C) Baseline characteristics and pooled risk estimates of the primary outcome in patients treated with LUS-guided therapy in clinical trials.

Figure 1: Systematic review and meta-analysis of Prognostic value and Therapeutic utility of LUS in Heart Failure

A



B

Author year	Total	FU^	Lung fields	B-lines >15;>3; >45*	B-lines <15; <45*	Total events	Event details		Adjusted HR/RR (CI)^
							Death	HHF	
Out-patients (B-line thresholds: ≥15 in 28 zones; ≥ 3 in 5-8 zones)									
Curbelo 2019	99	12 m	8	NA	NA	36	12	35	1.8 (0.8-4.0)
Dwyer, 2018	119 HF (total=230)	12 m	8	49	70	28 (patients with HF)	10	21	2.62 (1.15-5.96)
Pellicori 2019	342	7.8 m (4.5±11.7)	28	106	236	60	25	35	1.54 (0.68-3.48)
Platz 2016	195	6 m	8	59	126+10 incomplete data	50	15	48	4.08 (1.95-8.54)
Domingo 2020[§]	577	31±7.1	8	/	/	157	111	74	1.26 (0.89-1.77)
Overall									1.66 (95%CI: 1.28 - 2.15) p=0.0001,I^2: 57.5%
Admission (B-lines threshold: ≥ 45 in 28 zones)									
Gargani 2015	100	6 m (5.3 ±1.6)	28	NA	NA	14	4	14	4.87 (0.88-27.06)
Coiro 2016	50 (total 110)	3 m	28	19	31	33 in whole cohort	16	26	9.20 (1.82-46.61)
Gargani 2021[‡]	296 (HF) (total=1021)	14.4 m	28	NA	NA	82	40	42	1.90 (1.14-3.16)
Overall									2.32 (95%CI 1.46 - 3.70) p= 0.0004, I^2:50.92%
Discharge (B-lines thresholds: ≥15 in 28 zones; ≥ 3 in 5-8 zones; ≥ 4 in 4 zones)									
Coiro 2015; 2016	60	3 m	8 & 28	NA	NA	18	10	15	4.1 (0.95-14.63)
Gargani 2015	100	6 m	28	40	60	14	4	14	11.74 (1.3-106.16)
Rivas-lasarte 2020	100 (total 123)	6 m	8	41	59	28	3	19	2.63 (1.08-6.41)
Platz 2019	132 (total 349)	3 m	4&8	71	61	42	13	32	1.45 (0.6-3.46)
Rueda-Camino 2020	103	3m (2.4±0.9)	28	29	74	28	1	27	2.46 (1.11-5.46)
Overall									2.46, 95%CI: 1.56 - 3.86) p=0.0001, I^2:0.00%

Curbelo DOI: 10.1080/03007995.2018.1519502; Dwyer DOI: 10.1016/j.cardfail.2018.02.004; Pellicori DOI: https://doi.org/10.1002/ejhf.1383; Platz DOI: 10.1093/eurheartj/ehv745; Domingo DOI: 10.1016/j.rec.2020.07.006; Gargani DOI: 10.1186/s12947-015-0033-4; Coiro DOI: 10.1038/srep39426; Gargani DOI: 10.1002/ehf2.13206; Coiro DOI: 10.1002/ejhf.344;Rivas-lasarte DOI: 10.1002/ehf2.12842; Platz DOI: 10.1016/j.jchf.2019.07.008; Rueda-Camino DOI: 10.1016/j.medcli.2020.03.012; Rivas-Lasarte DOI: 10.1002/ejhf.1604; Araiza-Garaygordobil DOI: 10.1016/j.ahj.2020.06.003; Marini DOI: 10.1136/heartjnl-2019-316429

C

Author year	Criteria for significant congestion	FU	Total N	Number in each group	Total events	Deaths	HHF	Urgent visits	HR/RR (CI)
Clinical trials									
Rivas-Lasarte 2019	≥ 3 in 8 zones	6m	123	control (n=62)	25	2	13	13	0.518 (0.268-0.998)
				LUS (n=61)	14	3	14	3	
Araiza-Garaygordobil 2020	≥ 3 in 8 zones	6m	126	control (n=63)	30	6	8	25	0.55 (0.30-0.99)
				LUS (n=63)	20	9	4	9	
Marini 2019	LUS score based on B-line visualization in each field	3m	244	control (n=117)	25	4	25	NA	0.44 (0.23-0.84) (RR for HHF)
				LUS (n=127)	12	5	12	NA	
Overall									0.50 (95% CI: 0.35-0.72) p=0.001, I^2:0.00%

(A)Study flow chart (B) Description of studies included in the review to assess prognostic value of LUS (C) Clinical trials comparing LUS guided treatment in comparison to standard treatment in HF patients. *B-lines more than 15 in 28 zones LUS or ≥3 in 8 zones LUS in out-patients and discharge patients studies and B-lines ≥45 in admission LUS studies.(^ FU mean or median duration reported in parenthesis; a adjusted hazard ratio presented for selected cut-offs;$ values of HR provided by the authors)

NA: not available/not applicable ; FU: Follow-up; LUS: Lung Ultrasound; I^2: level of heterogeneity