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A randomised, controlled trial

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Impact of serial cardiopulmonary point-of-care ultrasound exams in patients with acute dyspnoea: a randomised, controlled trial

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ABSTRACT

Background Serial point-of-care ultrasound (PoCUS) can potentially improve acute patient care through treatment adjusted to the dynamic ultrasound findings. The objective was to investigate if treatment guided by monitoring patients with acute dyspnoea with serial cardiopulmonary PoCUS and usual care could reduce the severity of dyspnoea compared with usual care alone.

Methods This was a randomised, controlled, blinded-outcome trial conducted in three EDs in Denmark between 9 October 2019 and 26 May 2021. Patients aged ≥18 years admitted with a primary complaint of dyspnoea were allocated 1:1 with block randomisation to usual care, which included a single cardiopulmonary PoCUS within 1 hour of arrival (control group) or usual care (including a PoCUS within 1 hour of arrival) plus two additional PoCUS performed at 2 hours interval from the initial PoCUS (serial ultrasound group). The primary outcome was a reduction of dyspnoea measured on a verbal dyspnoea scale (VDS) from 0 to 10 recorded at inclusion and after 2, 4 and 5 hours.

Results There were 206 patients recruited, 102 in the serial ultrasound group and 104 in the control group, all of whom had complete follow-up. The mean difference in VDS between patients in the serial ultrasound and the control group was −1.09 (95% CI −1.51 to −0.66) and −1.66 (95% CI −2.09 to −1.23) after 4 and 5 hours, respectively. The effect was more pronounced in patients with a presumptive diagnosis of acute heart failure (AHF). A larger proportion of patients received diuretics in the serial ultrasound group.

Conclusion Therapy guided by serial cardiopulmonary PoCUS may, together with usual care, facilitate greater improvement in the severity of dyspnoea, especially in patients with AHF compared with usual care with a single PoCUS in the ED. Serial PoCUS should therefore be considered for routine use to aid the physician in stabilising the patient faster.

Trial registration number NCT04091334.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiopulmonary point-of-care ultrasound (PoCUS) can be used to diagnose patients with acute dyspnoea.
⇒ It is not known if treatment guided by serial cardiopulmonary PoCUS can result in a faster improvement in patient-reported dyspnoea.

WHAT THIS STUDY ADDS

⇒ In this randomised study, patients with dyspnoea managed with serial PoCUS, together with usual care, had a greater reduction in self-reported severity of dyspnoea within 5 hours from arrival at an ED compared with those receiving a single ultrasound.
⇒ The difference was more pronounced in those patients with acute heart failure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Monitoring patients with dyspnoea presenting to the ED with serial PoCUS should be considered to facilitate faster relief of symptoms.

INTRODUCTION

Background

Patients with acute dyspnoea constitute a large proportion of adult patients admitted to an ED.[1] Dyspnoea can be caused by different conditions, for example, acute heart failure (AHF), chronic obstructive lung disease exacerbation and pneumonia.[2] The subjective feeling of dyspnoea causes a range of unpleasant sensations, for example, anxiety, air hunger and chest discomfort, and is an essential patient-reported outcome.[3] Furthermore, patients admitted with dyspnoea have high mortality compared with patients with other complaints.[4]

Point-of-care ultrasound (PoCUS) has been used to diagnose the underlying aetiologies of dyspnoea in ED patients for several years. The utilisation of PoCUS of the heart, lungs and the legs' deep veins has improved the diagnostic accuracy in patients with dyspnoea from about 60% to 90% when done within 4 hours from arrival.[5] However, subsequent monitoring is often done with just a combination of the trajectories of symptoms, vital signs and medical tests. The benefit of adding serial PoCUS to reassessment has the potential to improve the diagnostic accuracy and monitoring of the severity of certain conditions because of the dynamic nature of some ultrasound parameters. In particular, B-lines, which can be seen in the loss of peripheral lung aeration, for example, in cardiogenic and non-cardiogenic pulmonary oedema, and pneumonia,

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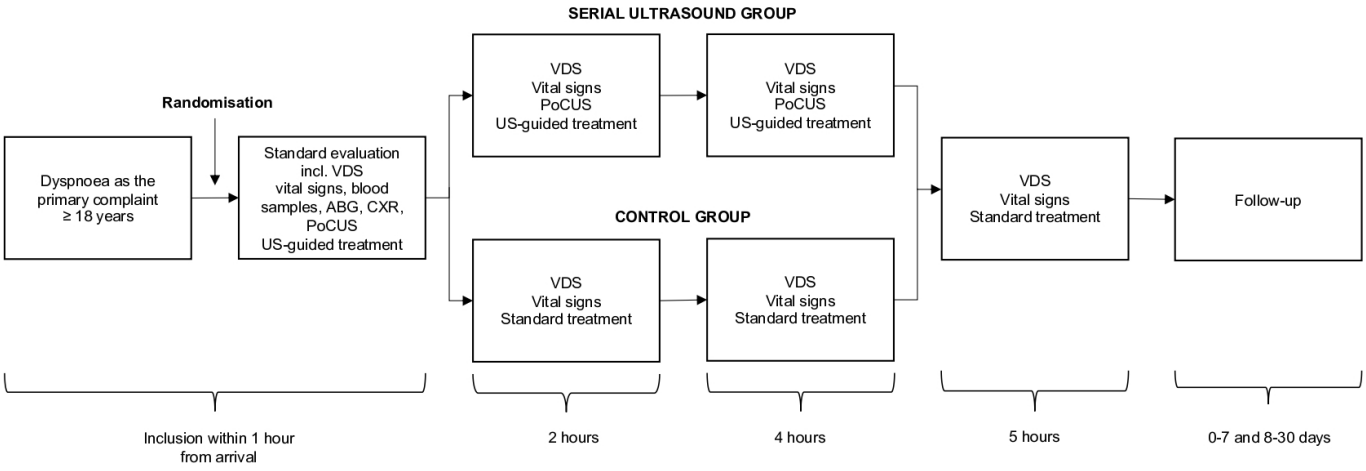


Figure 1 Study design and flow. PoCUS, point-of-care ultrasound; US, ultrasound; VDS, verbal dyspnoea scale.

can resolve with treatment, especially in patients with heart failure.[6 7] However, in our systematic review leading to this trial, no studies reported an effect of treatment guided by serial PoCUS on the severity of dyspnoea.[6]

The objective of this randomised, controlled trial was to investigate if therapy guided by monitoring adult ED patients with a primary complaint of dyspnoea using serial cardiopulmonary PoCUS in addition to usual care could reduce the severity of dyspnoea compared with treatment guided by usual care alone including a single POCUS exam.

METHODS

Study design and setting

We conducted a randomised, controlled and blinded-outcome trial in three EDs in Denmark between 9 October 2019 and 26 May 2021 (figure 1). The EDs provide 24-hour care and receive all acute medical and surgical patients referred from a general practitioner or as direct emergency admissions. In Denmark, healthcare is tax-funded and thereby provides equal access.

The study was prospectively registered at ClinicalTrials.gov (NCT04091334) and adhered to the Consolidated Standards of Reporting Trials guideline.[8 9] The published protocol is provided in online supplemental appendix S1[10] and protocol alterations in online supplemental appendix S2.

Selection of participants

Patients were recruited over 24 hours all days when an investigator was present in the ED during clinical duty. During the trial period of 595 days, patients were screened on 426 of the days (72%) and included over 159 days. Patients were eligible for inclusion if they: (1) arrived at the ED with a primary complaint of dyspnoea (confirmed by asking the patient on arrival); (2) were 18 years or older; (3) could provide informed consent and (4) the first evaluation of the patient including the first PoCUS exam could be done within 1 hour from arrival. No requirements regarding vital signs.

Exclusion criteria included: (1) trauma patients; (2) patients invasively ventilated within the first hour after arrival and (3) if an investigator was not present in the ED.

Randomisation and blinding

Patients in both groups were enrolled within 1 hour from arrival at the ED and received the same initial standard evaluation, including a PoCUS (figure 1). Patients were allocated on 1:1 ratio into the intervention or control group. Patients were randomised with Research Electronic Data Capture. Block randomisation was employed to ensure balance and reduce bias when assigning participants to different treatment groups.[11] The allocation sequence was concealed from the investigators. Randomisation was conducted after informed consent but before the patient's first examination. The investigators (MDA, SWG, HØP and GT) performed the screening, enrolment, all the examinations and treatment adjustments regardless of the study group. The investigators were all certified by the same PoCUS standards[12] and had similar working experience with PoCUS (about 5 years).

Intervention

In both groups, the initial assessment consisted of routine physical examination, medical history, measurement of vital signs, blood samples, ABG, CXR and PoCUS (figure 1). In the subsequent assessments of the patients 2, 4 and 5 hours from inclusion, usual care consisted of a clinical evaluation of the patients, including vital signs and VDS.

In the serial ultrasound group, usual care was supplemented by a lung ultrasound (LUS) and a focused cardiac ultrasound (FoCUS). LUS and FoCUS were performed according to international standards,[13 14] and a protocol developed for this trial (online supplemental appendix S3).[10] LUS was performed with an 8-zone scanning protocol with the patient in a semi-supine position. The investigators looked for B-lines, pleural effusions, consolidations and the absence of lung sliding. In the FoCUS, the investigators assessed the right ventricle for dilatation, the function of the left ventricle, presence of pericardial effusion and calculating the inferior vena cava-collapsibility index (IVC-CI). The ultrasound was performed with a Venue (General Electric, Boston, Massachusetts, USA) or Sonosite X-Porte (FUJIFILM Sonosite, Bothell, Washington, USA) with a curvilinear probe (2–5 MHz and 1.4–5.7 MHz on the Sonosite and Venue, respectively) and a phased array probe (1–5 MHz and 1.1–4.7 MHz on the Sonosite and Venue, respectively). The investigators were instructed to adjust the treatment according to clinical parameters as per routine care as well as the serial ultrasound findings, for example, to give more diuretics if the clinical presentation and/or number of B-lines were the same or increased during the subsequent scans and a diagnosis of AHF was suspected (online supplemental appendix S1).

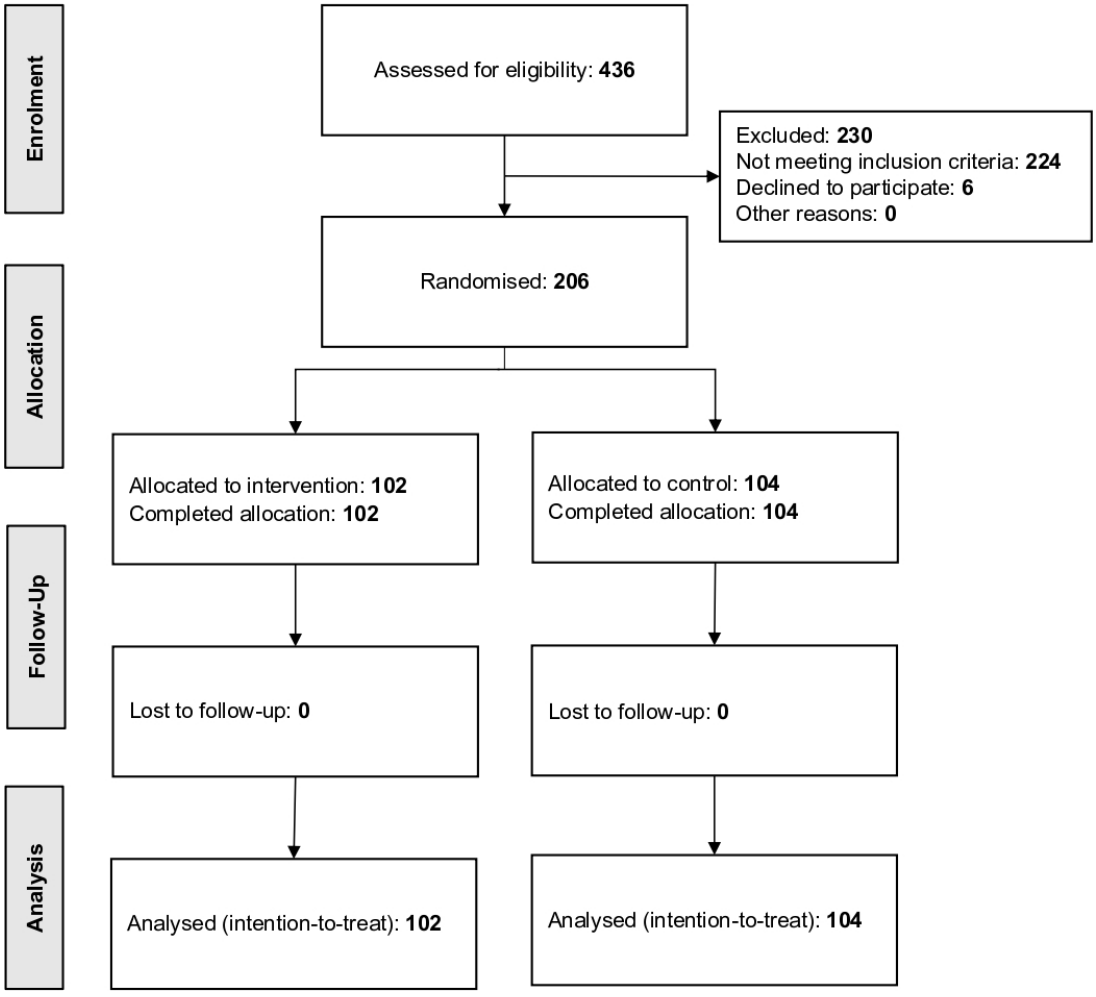


Figure 2 Consolidated Standards of Reporting Trials flow diagram.

Assessment

The patients' degree of dyspnoea was measured on enrolment, and then at 2, 4 and 5 hours after arrival. Dyspnoea was measured on a verbal dyspnoea scale (VDS) from 0 to 10, with 0 indicating no dyspnoea and 10 the worst dyspnoea imaginable. VDS is previously validated in the ED setting.[15 16] Assessments of dyspnoea were made by healthcare professionals serving as outcome assessors who were blinded to the allocation and any interventions and approached the patient independently of the investigator.

The final hospital diagnosis was made by two independent physicians (CF and IRS) who audited the patients' records but were blinded to the allocation and the results of the additional ultrasound examinations done in the serial ultrasound group. Furthermore, these physicians were not involved in the enrolment process at any point. Disagreements were resolved by a third reviewer (SP). The audit was performed according to predefined diagnostic criteria (online supplemental appendix S4).

The intra-rater and inter-rater reliability of the PoCUS findings, including B-lines and IVC-CI, were estimated in a subsample of 25 randomly selected scans by an independent reviewer (HØP).[17 18] Furthermore, the overall quality of the clips was graded from 1 to 5, where 5 was best.[19]

Outcomes

The primary outcome was decreased dyspnoea on VDS evaluated at four different time points (figure 1). The secondary outcomes were: (1) length of hospital stay (LOS); (2) the proportion of readmissions within 0–7 and 8–30 days from discharge date; (3) in-hospital mortality; (4) 0–7 days and 8–30 days mortality from admission date; (5) proportion of patients with a final ED diagnosis in agreement with the audit diagnosis; (6) IVC-CI correlated to vital signs and VDS; (7) B-line count correlated to vital signs and VDS; (8) the dynamic changes in IVC-CI between the PoCUS; (9) the dynamic changes in B-line count between the PoCUS; (10) medications and fluids administered in the groups; (11) proportions of differential diagnoses during the ED stay; (12) intra-rater and inter-rater reliability of the PoCUS findings and (13) image quality of the PoCUS.

Analysis

The sample size was based on a minimally clinically important difference of 1 point on VDS.[20 21] The patients in the serial ultrasound group were expected to have a 2-point change in VDS compared with a 1-point change in the control group at the final evaluation of the patient in the ED. With a power of 80%, type 1 error of 5% and 10% dropouts, the sample size was calculated to be 206 patients.

The primary outcome was analysed using a mixed-effect model with a change from baseline VDS as the dependent variable. Factors assumed to have the same effect across many patients were baseline score in VDS, trial group, time points and interaction of trial group with time points. The individual patient was treated as the random effect. A subgroup analysis

Table 1 Baseline characteristics of patients in the serial ultrasound and the control group

	Serial ultrasound group (n=102)		Control group (n=104)	
Sites				
Slagelse Hospital	102		101	
Horsens Hospital	0		2	
Zealand University Hospital	0		1	
Patient characteristics				
Sex				
Female	42	(41.2)	52	(50.0)
Male	60	(58.8)	52	(50.0)
Age, years	76	(66–83)	76	(66–81)
BMI, mean, kg/m^2	26.6	(5.7)	27.5	(7.0)
Smoking status				
Never	25	(24.5)	20	(19.2)
Current	14	(13.7)	15	(14.4)
Previous	63	(61.8)	69	(66.3)
Medical history				
COPD	36	(35.3)	34	(32.7)
Asthma	18	(17.6)	7	(6.7)
Other lung disease	4	(3.9)	0	(0.0)
Chronic heart failure	28	(27.5)	19	(18.3)
Arterial hypertension	55	(53.9)	49	(47.1)
Coronary arterial disease	27	(26.5)	27	(26.0)
Thromboembolic disease	5	(4.9)	8	(7.7)
Stroke	13	(12.7)	17	(16.3)
Chronic kidney disease	5	(4.9)	9	(8.7)
Diabetes mellitus	21	(20.6)	16	(15.4)
Psychiatric disorder	13	(12.7)	14	(13.5)
Current or previous cancer	15	(14.7)	24	(23.1)
Dyslipidaemia	29	(28.4)	31	(29.8)
Atrial fibrillation/flutter	35	(34.3)	25	(24.0)
None	5	(4.9)	5	(4.8)
Others	70	(68.6)	75	(72.1)
Symptoms and physical examination				
Chest pain	27	(26.5)	25	(24.0)
Cough	56	(54.9)	53	(51.0)
Sputum	34	(33.3)	36	(34.6)
Palpitations	19	(18.6)	13	(12.5)
RR, brpm	21	(18–23)	20	(18–23)
Oxygen saturation, %	95	(92–98)	96	(93–98)
Oxygen supply, L/min	1	(1–1)	1	(1–1)
Oxygen delivery method				
Nasal cannula	30	(29.4)	21	(20.2)
Mask	4	(3.9)	13	(12.5)
Other	2	(2.0)	1	(1.0)
Systolic blood pressure, mm Hg	138	(124–152)	136	(120–152)
Diastolic blood pressure, mm Hg	75	(64–90)	74	(65–85)
Heart rate, bpm	88	(76–105)	85	(74–103)
Temperature, °C	36.5	(36.5–37.3)	36.5	(36.5–37.2)
Oedema				
None	65	(63.7)	69	(66.3)
One leg	2	(2.0)	0	(0.0)
Both legs	35	(34.3)	35	(33.7)
Focused lung ultrasound				
B-lines present	87	(85.3)	77	(74.0)
Sum of B-lines in eight zones	5	(2–9)	2	(0–9)
Consolidation	38	(37.3)	29	(27.9)
Absence of lung sliding	1	(1.0)	2	(1.9)
Pleural effusion	46	(45.1)	29	(27.9)
Focused cardiac ultrasound				
Ejection fraction				
Normal	50	(49.0)	58	(55.8)
Mild dysfunction	21	(20.6)	19	(18.3)
Moderate dysfunction	15	(14.7)	15	(14.4)
Severe dysfunction	14	(13.7)	7	(6.7)
Hyperdynamic	2	(2.0)	5	(4.8)
Pericardial effusion	1	(1.0)	2	(1.9)
Right ventricle dilatation	5	(4.9)	5	(4.8)
TAPSE, mm	20	(16–24)	20	(16–24)
IVC max diameter, mm	20	(20–20)	20	(10–20)
IVC min diameter, mm	10	(10–20)	10	(10–20)
IVC-CI, %	36	(25–56)	39	(23–61)
Most common final ED diagnoses				
Acute heart failure	41	(40.2%)	40	(38.5%)
Pneumonia	34	(33.3%)	28	(26.9%)
Exacerbation of COPD	22	(21.6%)	26	(25.0%)

Data are n (%) or median (IQR), unless otherwise noted.
ARB, angiotensin receptor blocker; BMI, body mass index; brpm, breaths per minute; COPD, chronic obstructive pulmonary disease; IVC, inferior vena cava; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors; TAPSE, tricuspid annular plane systolic excursion.

of the patients with AHF was conducted because dynamic B-lines are mainly seen in this patient category. The proportion of different treatments provided in the two groups was examined to explain a possible effect of the serial ultrasound intervention.

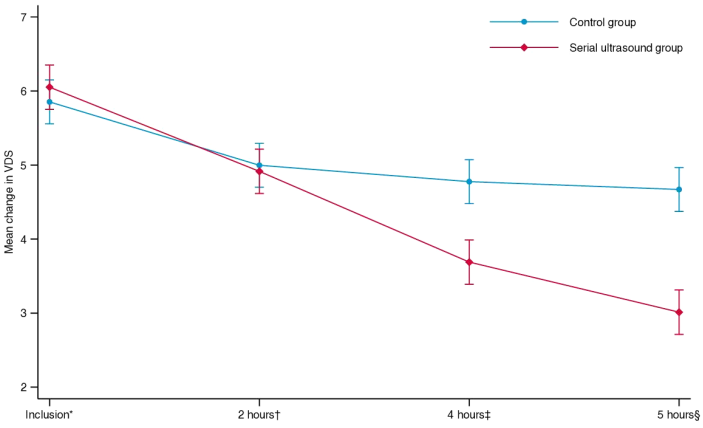
For the secondary outcomes, the continuous variable (LOS) was compared with the Mood's median test and the categorical variables with the χ^2 test and supplemented with a two-sided significance level of 5% and a risk difference with 95% CI. A heatmap was used to visualise the correlations between B-lines, IVC-CI, VDS and vital signs. Box plots were employed to illustrate the variations in B-lines and IVC-CI. The proportion of ED diagnoses in agreement with the final hospital diagnoses was expressed as numbers and percentages. Inter-rater reliability between the presumptive diagnoses made by the investigator and the blinded audit was calculated with Cohen's kappa. Cohen's kappa was also used to calculate the intra-rater and inter-rater reliability of the ultrasound clips. Image quality was calculated as median.

Missing data were present in 6 out of 410 measurements of the IVC-CI and were only excluded in the analysis of the changes in IVC-CI during the ED stay.

All statistical analyses were performed with Stata V.17.0 (StataCorp, Texas, USA).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.



Differences between groups and within groups at different time points

Between groups	VDS difference (95% CI)
Serial ultrasound versus control group at inclusion	0·20 (-0·23 to 0·63)
Serial ultrasound versus control group +2 hours	-0·08 (-0·51 to 0·35)
Serial ultrasound versus control group +4 hours	-1·09 (-1·51 to -0·66)
Serial ultrasound versus control group +5 hours	-1·66 (-2·09 to -1·23)
Within the control group	
Control group at +2 hours versus control group <1 hour	-0·86 (-1·16 to -0·55)
Control group at +4 hours versus control group at +2 hours	-0·22 (-0·53 to 0·09)
Control group at +5 hours versus control group +4 hours	-0·11 (-0·41 to 0·20)
Within the serial ultrasound group	
Serial ultrasound group at +2 hours versus serial ultrasound group <1 hours	-1·14 (-1·45 to -0·83)
Serial ultrasound group at +4 hours versus serial ultrasound group at +2 hours	-1·23 (-1·54 to -0·91)
Serial ultrasound group at +5 hours versus serial ultrasound group at +4 hours	-0·68 (-0·99 to -0·37)

Figure 3 Change in the primary outcome (VDS) between the two groups at the different time points. Data are mean (95% CI). *Inclusion: same standard diagnostics in both groups, including LUS and FoCUS. †2 hours: standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS. ‡4 hours: standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS. §5 hours: same standard care in both groups. No ultrasound examinations. FoCUS, focused cardiac ultrasound; LUS, lung ultrasound; VDS, verbal dyspnoea scale.

RESULTS

Characteristics of study subjects

Eligibility was assessed in 436 acute patients (figure 2). Of those, 206 (47%) patients were included and randomly assigned to the serial ultrasound group with 102 patients and the control group with 104 patients. The most common cause for patients not being included following assessment for study eligibility was absence of dyspnoea as the primary complaint during the screening of the patients. Most patients were enrolled and managed by two investigators in one ED (table 1).

The patients had a median age of 76 years, many were previous smokers and had chronic obstructive pulmonary disease or arterial hypertension as the most common comorbidities (table 1, online supplemental table S1). More patients in the serial ultrasound group had chronic heart failure. Besides dyspnoea, cough was the most common complaint. The patients had overall vital signs within normal levels.

One-third of patients had bilateral oedema of the legs. On the PoCUS, one-third had consolidations or pleural effusions. Nearly 80% had B-lines at arrival, and half had reduced ejection fraction. The proportion of pathological ultrasound findings was higher in the serial ultrasound group.

Main results

Patients in both groups experienced a decline in the severity of VDS (figure 3). At 4 and 5 hours from inclusion (measuring the effect of the first and the second extra PoCUS, respectively), the mean difference in VDS between the patients in the serial ultrasound and the control group was −1.09 (95% CI −1.51 to −0.66) and −1.66 (95% CI −2.09 to −1.23). In the planned subgroup analysis of the primary outcome in patients with a presumptive diagnosis of AHF, the difference in VDS at 4 and 5 hours were −1.52 (95% CI −2.52 to −0.78) and −1.97 (95% CI −2.70 to −1.23) (figure 4, online supplemental figure S1). A larger proportion of patients received diuretics, inhaled beta2-adrenergic agonists and oxygen in the serial ultrasound group (online supplemental table S2). However, the difference was only significant for diuretics, where patients in the serial group received a dose 6–8 times greater at 2 and 4 hours from inclusion compared with the control group.

No statistically significant differences were observed between the two groups regarding LOS, readmissions within 0–7 and 8–30 days, in-hospital mortality and 0–7 and 8–30 days mortality (table 2). The proportion of the final ED diagnoses in agreement with the audit diagnoses was higher in the serial ultrasound group (64% vs 59%), but the difference was not statistically significant. The final ED diagnoses of AHF were similar in the two groups (table 1) and with the audit diagnosis (online supplemental table S3). The overall agreement between the raters of the final audit diagnoses was 96% (kappa=0.69).

In the serial ultrasound group, the number of B-lines was nearly identical between the initial LUS and the second LUS but decreased at the final LUS exam (online supplemental figure S2A). In a subgroup of patients with a presumptive diagnosis of AHF, a similar pattern was found but with a higher median number of B-lines (online supplemental figure S2B). IVC-CI did not change between the scans (online supplemental figure S3) and there was no correlation between B-lines or IVC-CI and vital signs or VDS (online supplemental figures S4 and S5). The intra-rater and inter-rater reliability of the assessed ultrasound clips had an agreement of 96% (kappa=0.91) and 94% (kappa=0.87), respectively. Overall median image quality was 4.

DISCUSSION

This randomised trial assessed whether treatment guided by serial cardiopulmonary PoCUS in acute adult patients admitted with a primary complaint of dyspnoea could shorten the time to improvement in symptoms. We found that patients who underwent repeated PoCUS examinations had greater improvement in patient-reported dyspnoea than patients who had only a single PoCUS on arrival during their ED visit, with a larger statistically significant difference in those with AHF. The effect of serial PoCUS is likely due to the significantly greater use of diuretics in the serial ultrasound group.

The effect of treatment guided by serial ultrasounds was a reduction in VDS by 1.23 after 4 hours from inclusion and a further reduction by 0.68 after 5 hours. A carry-over effect might explain the smaller improvement between hours 4 and 5 besides the patient being more stabilised in the later phase. The overall effect was primarily driven by the effect of PoCUS in patients with AHF, which might be due to the underlying cause of the B-lines found in these patients, contrary to B-lines found in other conditions, for example, pneumonia. The effect can partly be explained by the increasing amount of diuretics administered in the serial ultrasound group.

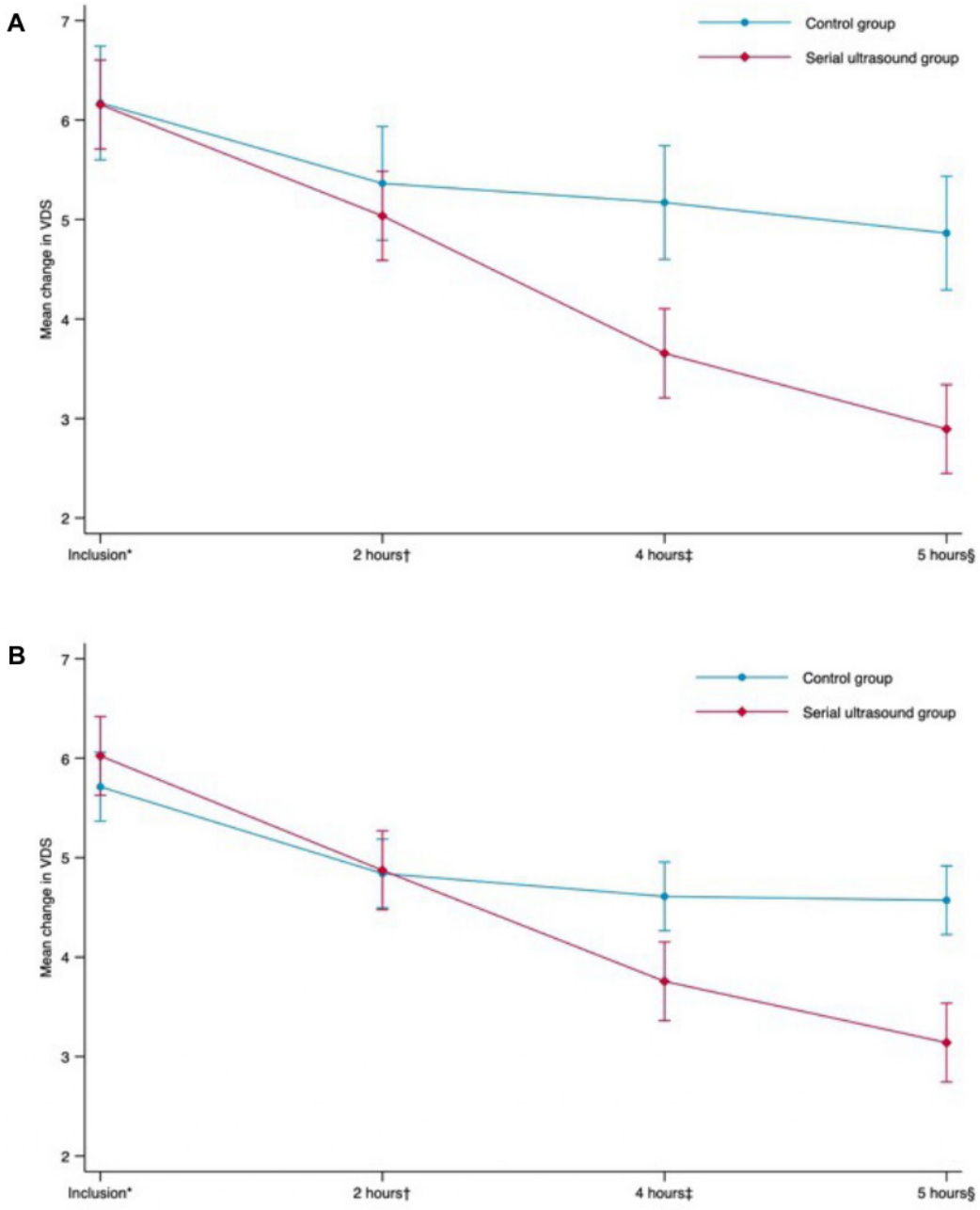


Figure 4 Change in the primary outcome (VDS) in patients with (A) and without a presumptive diagnosis of AHF (B). *Inclusion: same standard diagnostics in both groups, including LUS and FoCUS. †2 hours: standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS. ‡4 hours: standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS. §5 hours: same standard care in both groups. No ultrasound examinations. AHF, acute heart failure; FoCUS, focused cardiac ultrasound; LUS, lung ultrasound; VDS, verbal dyspnoea scale.

We found no difference in LOS, readmissions or short-term mortality between groups receiving a single or serial POCUS exam. Previous studies conducted in a similar setting using only a single PoCUS exam have yielded the same results.[5 22] To further elucidate the potential impact of PoCUS performed within the first hours in the ED on patient prognosis, larger-scale studies are needed. However, it is noteworthy that if the final PoCUS exam is conducted prior to discharge in patients with AHF, it influences mortality and readmission rates.[23 24]

The diagnostic accuracy of PoCUS was not significantly higher in the serial PoCUS group, presumably because an initial PoCUS was done in both groups. Still, the number of differential diagnoses was lower in the serial PoCUS group indicating that PoCUS might help the clinician to refine and narrow the diagnostic possibilities. However, we observed a lower overall agreement rate of 64% in our study compared with higher agreement rates of 79%–88% reported in comparable studies.[5 22] This discrepancy could be attributed to differences in the audit process. In our study, we used the final ED diagnosis made by the treating investigator, whereas the other studies relied on the final diagnosis recorded in the medical journal.

Two smaller studies limited to patients with AHF have found a correlation between B-lines and RR or VDS.[25 26] Although this intuitively makes sense, we found no correlation between

Table 2 Secondary outcomes in serial ultrasound and the control group

	Serial ultrasound group (n=102)		Control group (n=104)		Risk difference (95% CI)	P value
Length of hospital stay, days	4	(1–7)	3	(0–6)	3.9 (–9.8 to 17.5)	0.58
Readmissions						
0–7 days	15	(14.7)	10	(9.6)	5.1 (–3.8 to 14.0)	0.26
8–30 days	15	(14.7)	7	(6.7)	8.0 (–0.4 to 16.4)	0.06
In-hospital mortality	4	(3.9)	4	(3.8)	0.1 (–5.2 to 5.4)	0.98
Mortality						
0–7 days	2	(2.0)	3	(2.9)	–0.9 (–5.1 to 3.3)	0.67
8–30 days	2	(2.0)	2	(1.9)	0.0 (–3.7 to 3.8)	0.98
No. of correct final ED diagnoses	64	(62.7)	59	(56.7)	6.0 (–7.4 to 19.4)	0.38

Data are n (%) or median (IQR).

the number of B-lines or IVC-CI and vital signs or VDS, so the patients' vital signs and clinical status do not necessarily mirror the dynamic parameters on the PoCUS or in VDS. This means that the clinician cannot solely rely on the vital signs to determine whom to re-scan.

ED physicians could incorporate serial PoCUS when handling patients with dyspnoea, especially patients suspected of fluid accumulations in the lungs. These patients could be identified upfront with PoCUS as part of a standard clinical evaluation. However, as the minimally clinically important difference for VDS is 1, which was achieved at the 2-hour evaluation, our trial suggests that only one extra PoCUS could be sufficient. Because only B-lines and not IVC change in the first couple of hours in the ED, the second PoCUS might be limited to a LUS. Although serial PoCUS is more time-consuming, the patients are, on the other hand, stabilised faster, thereby potentially resulting in early disposition.

Limitations

First, most patients were recruited only in one ED and by two investigators when they were present, which could influence external validity. However, baseline characteristics were similar to other comparable studies.[2 27 28] Second, despite baseline characteristic imbalances with a higher proportion of patients with a history of heart failure in the serial ultrasound group, this should not influence the primary outcome because treatment decisions were based on the presumptive diagnoses, and the final ED diagnosis of AHF was similar in both groups. Third, we did not implement a precise algorithm for changes in the ultrasound parameters (B-line count and IVC-CI) that should trigger a specific treatment as it would have been too complex and does not reflect the reality and the setting where the emergency physician works. Fourth, the investigator and patients were not blinded to the intervention; hence an 'ultrasound assessment placebo effect' might have influenced the primary outcome in the serial PoCUS group because of the intervention itself and the more time spent on the patient. Still, randomisation was carried out before the first evaluation of the patients to avoid selection bias, and all patients had a PoCUS done despite allocation. The patients in the control group were also exposed to clinical judgement and subsequent treatment by the same investigator at matching time points as in the serial ultrasound group. Most importantly, the outcome assessors were blinded. Fifth, patients unable to consent were excluded which could introduce selection bias. But, with the chosen primary outcome, it was a prerequisite that the patients were mentally cable of assessing their dyspnoea on VDS, and another study from Denmark has shown that the most acute patients constituted only approximately 6% of all patients with dyspnoea.[29]

CONCLUSION

Our study establishes that serial cardiopulmonary PoCUS serves as an effective treatment guide for patients with dyspnoea, offering valuable support alongside standard care to alleviate the discomfort linked to dyspnoea. Notably, the observed impact is predominantly found in patients with AHF. These findings endorse the use of serial cardiopulmonary PoCUS as a beneficial tool in managing dyspnoea, with particular attention to patients with AHF.

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Contributors Idea and study design: MDA, CBL, PHG and ATL. Database creation: MDA and AKH. Generation of allocation sequence: AKH. Recruitment and data collection: MDA, SWG, HØP and GT. Audit of diagnoses: CF, IRS and SP. Intravariability and intervariability analysis of ultrasound clips: MDA and HØP. Writing of draft: MDA. Statistical analysis: MDA with guidance from SM. Data access and verification: MDA, ATL, PHG and CBL. Interpretation of data, review, editing, approval of the final manuscript and the decision for submission: all authors. MDA is the guarantor of the study.

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Competing interests MDA received funding from the Department of Emergency Medicine, Slagelse Hospital, Naestved, Slagelse and Ringsted Hospitals' Research Fund, Research Fund of Region Zealand and Region of Southern Denmark, and the University of Southern Denmark. ATL received royalties from Munksgaard and Gyldendal as an author of book chapters. PHG was in the advisory board of Boeringer Ingelheim and AstraZeneca. CF received a fee from AstraZeneca for a presentation on lung ultrasound at a pulmonologist expert meeting. IRS received grants from AstraZeneca, Novartis and personal fees from Teva and AstraZeneca for presentations. CBL received royalties from Munksgaard as an author of book chapters and fees from AstraZeneca for lectures at courses, educational events and symposia held by AstraZeneca. SWG, HØP and SP declare no competing interests.

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Patient consent for publication Not applicable.

Ethics approval The study was approved by the Regional Committee on Health Research Ethics for Region Zealand, Denmark (SJ-744). The trial was approved for data storage by Region Zealand, Denmark (REG-056-2019). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. De-identified participant data may be made available on request to the corresponding author if data sharing is in accordance with applicable legislation on the processing of personal data (GDPR and the Danish Data Protection Act). Data will be provided through a secured mailing address. Data can be requested after publication and until 31 December 2022, on which data will be deleted or transferred to Danish National Archives according to Danish legislation. Data can only be reused after acceptance from MDA, ATL, PHG and CBL.

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SUPPLEMENTARY MATERIAL

Table of contents

APPENDIX S1 Protocol

Monitoring patients with acute dyspnoea with serial focused ultrasound of the heart and the lungs (MODUS): a protocol for a multicentre, randomized, open-label, pragmatic, and controlled trial

The protocol has previously been published in BMJ Open. Permission for the republication of the unformatted protocol has been granted.

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ABSTRACT

Introduction
Among patients admitted to an emergency department, dyspnoea is one of the most common symptoms. Patients with dyspnoea have high mortality and morbidity. Therefore, novel methods to monitor the patients are warranted. The aim is to investigate whether therapy guided by monitoring patients with acute dyspnoea with serial ultrasound examinations of the heart and the lungs together with standard care can change the severity of dyspnoea compared to treatment guided by standard monitoring alone.

Methods and analysis
The study will be conducted as a multicentre, randomized, pragmatic, open-label, and controlled trial where patients admitted with acute dyspnoea to an emergency ward will be randomized into a standard care group and a serial ultrasound group with 103 patients in each. All patients will be examined with an ultrasound of the heart and the lungs upfront. In addition, the patients in the serial ultrasound group will be examined with an ultrasound of the heart and lungs two more times to guide further therapy during admittance. The primary outcome is a change in dyspnoea on a verbal scale. After discharge, the patients are followed for one year to assess the number of readmissions, death, and length of hospital stay.

Ethics and dissemination
The trial is conducted in accordance with the Declaration of Helsinki and approved by The Regional Committee on Health Research Ethics for Region Zealand, Denmark (identifier SJ-744). Data handling agreements with participating centres have been made (identifier REG-056-2019). The General Data Protection Regulation (GDPR) and the Danish Data Protection Act will be respected. The results of the trial will be reported in peer-reviewed scientific journals regardless of the outcomes.

Trial registration
ClinicalTrials.gov, identifier: NCT04091334.

ARTICLE SUMMARY

Strengths and limitations of this study
- First randomized trial to investigate whether therapy guided by monitoring patients with acute dyspnoea with serial focused ultrasound examinations of the heart and the lungs can change the severity of dyspnoea compared to standard care
- Designed as a multicentre study to improve the generalizability of the findings
- Not powered to investigate the differences in mortality and morbidity

- Patients are not consecutively recruited, providing a risk of selection bias

INTRODUCTION

Acute dyspnoea is a common symptom when patients are admitted to an emergency department (ED).[1] Dyspnoea is triggered by different diseases, e.g., heart failure, chronic obstructive lung disease, and pulmonary embolism.[2] Patients admitted with shortness of breath as the primary complaint have high in-hospital and out-of-hospital mortality.[3] Furthermore, dyspnoea is an important patient-related outcome causing anxiety among the patients.[4-6] The evaluation and monitoring of this patient population are consequently essential.

Monitoring acutely dyspnoeic patients is often performed by measuring vitals, scoring symptoms on different scales, and analysing medical tests, e.g., blood samples, chest X-ray, and arterial blood gases, but these approaches lack precision.[7-10] Point-of-care ultrasound can be used in both the initial diagnostic evaluation and in the monitoring of acutely dyspnoeic patients. Ultrasound examination of the inferior vena cava (IVC), either alone or as part of focused cardiac ultrasound (FoCUS) is used to evaluate if the patients are fluid tolerable judged by the diameter and the respiratory collapsibility of the IVC.[11] Ultrasound of the IVC is also used as a diagnostic tool for identification of congestive heart failure in patients presenting with dyspnoea.[12] Focused lung ultrasound (FLUS) can be used to diagnose interstitial syndrome (lung diseases affecting the lung interstitium, e.g., lung oedema), lung consolidation, pneumothorax, or pleural effusion.[13-15] In some studies, FLUS[16-20,] and ultrasound of the IVC[21-23] has been used to monitor and guide therapy in patients with acute dyspnoea, but the studies were clinically heterogenic. The studies have only included patients with or suspected of heart failure and not unselected patients with dyspnoea. A few studies have been conducted with the combination of FLUS and ultrasound of the IVC but were inconclusive.[24,25]

The aim is to investigate whether therapy-guided monitoring of patients with acute dyspnoea with serial focused ultrasound examinations of the heart and the lungs can reduce the severity of dyspnoea compared to standard care.

METHODS

This study protocol is prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[26] The SPIRIT checklist is provided in supplementary material 1.

Study design

The trial is designed as a multicentre, randomized, controlled, pragmatic, and open-label study with parallel group design with an allocation ratio of 1:1. The overall structure of the study is provided in figure 1.

Study settings

The study will take place in five different EDs in Denmark. The EDs represent a wide variety of different setups regarding logistics, patient load, time from initial assessment to admission to another ward, and crowding challenges. It is anticipated that each center is contributing an equal amount to the study population to make the results generalizable, but the amount is not a fixed size due to the potential risk of the trial being delayed because of different working circumstances for the investigators.

Investigators

The investigators have been recruited from project managers' (MDA) own network and at different conferences in emergency medicine. It is a prerequisite that the participating physicians are certified in focused acute ultrasound through the education provided by The University of Southern Denmark or at Aarhus University.[27,28] The courses are comprised of theoretical and practical education and supervision of ultrasound examinations in one's own department and with a final written and practical exam. The participating physicians have used ultrasound in their daily work for at least three years. The project manager (MDA) is responsible for educating the investigators in the data collection process and the specific ultrasound protocol used in this study. This is achieved by written information and onsite presentation, and demonstration of the database and the ultrasound protocol.

Eligibility criteria

Participants are recruited non-consecutively during all 24 hours of the day, all weekdays, to get a representative sample. The participants cannot be consecutively enrolled because it is not possible to have a

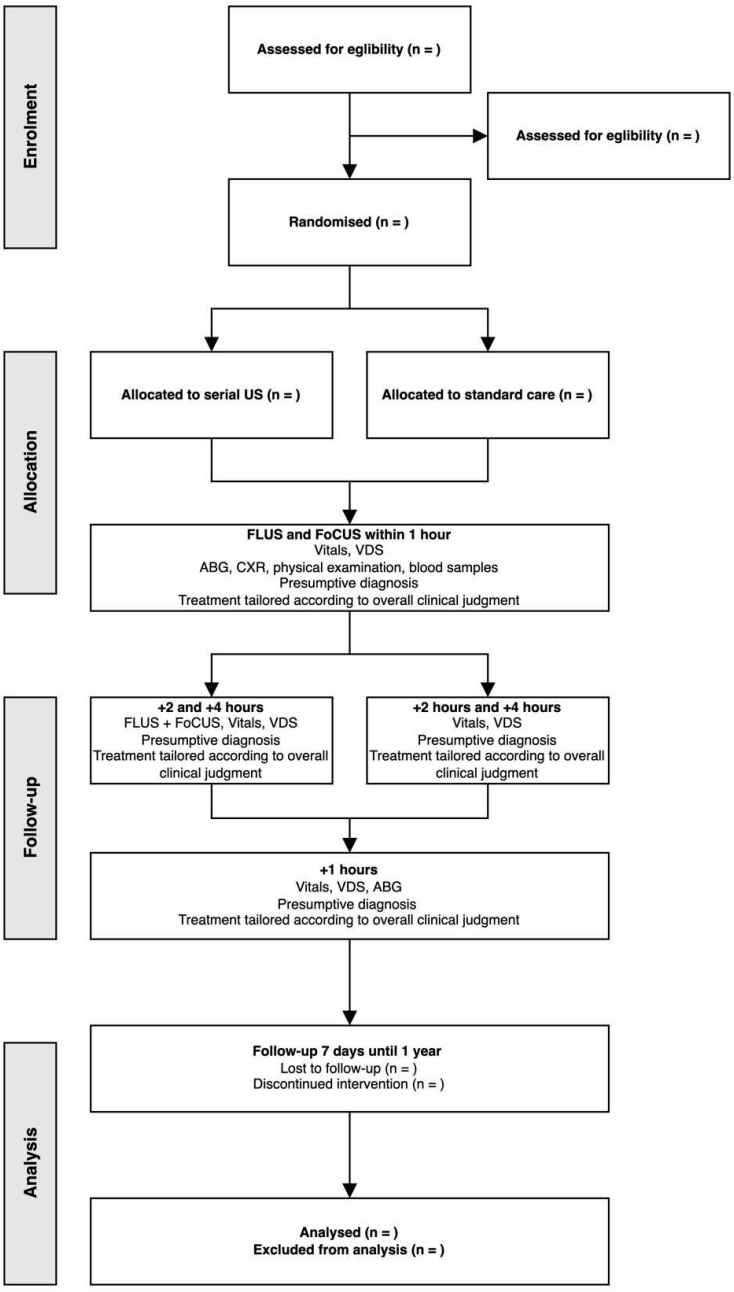

Figure 1. The flow diagram for the randomized trial.
ABG, arterial blood gas; *CXR*, chest X-ray; *ED*, emergency department; *FLUS*, focused lung ultrasound; *FoCUS*, focused cardiac ultrasound; *US*, ultrasound; *VDS*, verbal Dyspnoea Scale.

doctor on call all the time in all centres. The investigators will do the screening, enrolment, and diagnostic evaluation of the patients regardless of which study arm the patient is allocated to, thereby avoiding a different level of expertise in the treatment of the patients. The investigators will screen for potential candidate patient until an eligible patient is present. If the patient is fulfilling the eligibility criteria, which can only be achieved by asking the patient upon arrival about their primary complaint, the investigator will

provide the patient with oral and written information in order to receive informed content. The reasons for exclusion from the study will be recorded. To further avoid selection bias, the randomization is done after the screening and consent but before the first examination of the patient and allocation to the two groups. Thereby, systematic differences between the groups should be avoided.

Inclusion criteria

- Participants should be 18 years or older
- Presented at the ED with shortness of breath as the primary complaint (confirmed by asking the patient upon arrival in the triage what their primary complaint is for a referral to the ED)
- Oral and written informed consent from the habile patient
- The first evaluation of the patient, including ultrasound, should be performed within one hour from the arrival at the ED
- Could understand Danish or English in order to provide consent

Exclusion criteria

- Patients with dyspnoea primary admitted because of a trauma
- If the patient is invasively ventilated within the first hour after arrival

Randomization

Randomization is executed using central allocation on the online web-based database REDCap (Research Electronic Data Capture) provided by OPEN (Odense Patient data Explorative Network) at Odense University Hospital, Denmark. Permuted blocks of random numbers have been created to ensure an equal number of participants in each group. Selection bias is avoided because the allocation sequence is generated by a data manager from OPEN, and thereby it is concealed from all the investigators, including the project manager (MDA). The investigators register the patient's data in the database, whereby a unique identification number is received for each patient, which allocates the patient to either the intervention or the control group.

Study flow

Patient enrolment is planned to start on 30th September 2019 and is expected to last for six months. Figure 2 provides details regarding the study flow. After arrival at the ED, patients are screened by the investigators for eligibility within one hour. The one-hour limit is chosen because it is essential that the first ultrasound scan is conducted as soon as possible to avoid that any treatment can influence the ultrasound findings. If the patients fulfil the inclusion criteria and are able to provide oral and written informed consent by themselves, the patients are randomized 1:1 to either a "serial ultrasound group" or a "control/standard care group".

Within one hour, all patients both in the "serial ultrasound group" and the "control/standard care group" will receive a standard physical examination, routine medical tests, and an ultrasound examination of the heart and the lungs. In the serial ultrasound group, the patients will undergo, in addition to standard care, two extra ultrasound examinations of the heart and the lungs. The investigators perform the ultrasound by themselves because it is the intention they act and titrate the treatment according to the ultrasound findings. The investigators are instructed to register the precise treatment provided. Ultrasound parameters should be interpreted together with all the other clinical information. Regarding the dynamic ultrasound parameters (B-lines, IVC, and right ventricle dysfunction), the investigators are instructed as follows:

- If the patients have a new-onset/increased/status quo number of B-lines, the patients should be treated with diuretics adjusted to the clinical scenario (e.g., blood pressure) and to stop or decrease the amount of fluid provided
- If the IVC is flat and compressible to give fluid
- If the IVC is big and not compressible to stop fluid
- If the patients develop right ventricle dysfunction to order D-dimer or and CT scan directly

In the course of admittance, the patients will have their dyspnoea registered on a verbal dyspnoea scale (VDS) from 0-10. This scale has been validated in an acute setting and is both feasible and easy to use.[29,30] The VDS is registered by a nurse blinded to the allocation and not informed about the trial or the intervention.

Table 1 Schedule of enrolment, interventions, and assessments according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement

	Study period									
	Enrolment	**Allocation**	**Admission**				**Follow-up**			
Timepoints	**0**	**0**	***< 1 hour***	***+ 2 hours***	***+ 4 hours***	***+ 5 hours***	***7 days***	***30 days***	***90 days***	***12 months***
Enrolment										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
Interventions										
FLUS			●	—	●					
FoCUS			●	—	●					
US of the IVC			●	—	●					
Assessments										
Baseline variables*			X							
VDS (0-10)			X	X	X	X				
Vitals†			X	X	X	X				
Lung auscultation			X							
Oedema‡			X							
Blood tests§			X							
ABG‖			X			X				
CXR			X							
Other imaging¶			X							
Treatment#			X	X	X	X				
Diagnosis			X	X	X	X	X			
ICU transfer							X			
Length of stay							X			
Readmission(s)							X	X	X	X
Death							X	X	X	X

*Age, sex, smoker status, alcohol, medical history, and medications.
†Blood pressure, heart rate, respiratory rate, peripheral saturation, and temperature.
‡One or both legs.
§Haemoglobin, leucocytes, platelets, sodium, potassium, creatinine, C-reactive protein, D-dimer, and troponins.
‖pH, PCO2, O2, bicarbonate, base excess and lactate.
¶CT, MR, angiography, and others.
#Antibiotics, fluid, inhaled medication, diuretics, antihypertensive, and others.
ABG, arterial blood gas; CXR, chest X-ray; FLUS, focused lung ultrasound; FoCUS, focused cardiac ultrasound; ICU, intensive care unit; IVC, inferior vena cava; US, ultrasound; VDS, verbal Dyspnoea Scale.

Patients in both groups will, at the same point in time (two, four, and five hours after initial assessment), be clinically evaluated bedside by the investigator, and changes in diagnostics and treatment will be registered.

After discharge from the hospital, the patients are followed for one year. Post-discharged data regarding death, readmissions, and length of hospital stay will be accessed through the patient's electronic patient journal, or the data will be based on the Danish National Patient Registry[31], or The Danish Civil Registration System[32] Diagnoses will be evaluated with an audit of the patient's journal according to the diagnostic criteria provided in supplementary material 2. The audit is performed by two independent physicians blinded to the

allocation and the extra ultrasound examinations done in the intervention group (these will not be journalized). Disagreement will be resolved by a third reviewer making a consensus agreement.

Intervention – the ultrasound protocol
The ultrasound protocol consists of the following elements:

FoCUS
The ultrasound of the heart is based on the International evidence-based Recommendations for Focused Cardiac Ultrasound.[33] The heart will be scanned in four views: Subcostal, parasternal long axis, parasternal short axis, and apical 4-chamber. In the FoCUS, the following pathologies will be assessed: Pericardial effusion, left ventricle dysfunction, and right ventricle dysfunction. The diagnostic criteria are specified in supplementary material 3.

Ultrasound of the IVC
IVC will be scanned in the subcostal long-axis window with the patient in the semisupine position. The IVC is measured approximately 3-4 cm from the junction of the IVC into the right atrium (1-2 cm caudal to the hepatic vein). The diameter of the IVC will be measured during in- and expiration, and the IVC-collapsibility index (IVC-CI) will be calculated from the formula: IVC-CI = (IVCmax − IVCmin)/IVCmax × 100.

FLUS
The lungs will be scanned in eight zones. The anterior and lateral part of the thorax is divided into a superior and inferior quadrant. Each quadrant represents a zone in which the probe shall be placed longitudinally between to ribs and create a picture of the costae and pleura. The patient will be positioned in the semisupine position, and in each zone, the patient is scanned for at least one respiratory cycle. A convex will preferably be used.[34] The target depth will depend on the constitution of the patient and where on the thorax the patient is scanned, but desirable a depth of 18 cm will be used to evaluate the presence of B-lines. The maximum number of B-lines (dynamic ultrasound artefacts representing interstitial syndrome) in each zone will be counted manually. Furthermore, other pathologies, e.g., pleural effusion, pneumothorax, and consolidations, will be assessed. The principles of the FLUS examination are based on the International Recommendations for Lung Ultrasound[13], and the precise diagnostic criteria are provided in supplementary material 3.

Outcomes

Primary outcome
Change in dyspnoea on VDS from arrival until the last evaluation is made

Secondary outcomes for both groups
- Length of stay (consecutive days in the hospital, including transfer to another ward)
- The proportion of readmissions within 7 and 30 days, 6 and 12 months
- In-hospital all-cause mortality
- 7- and 30-days, 6- and 12-months all-cause mortality after admission
- The proportion of patients correctly diagnosed after the second and third ultrasound examination compared to the controls receiving usual care at the same time points

Secondary outcomes for the serial ultrasound group
- IVC-CI correlated to vital signs and VDS
- B-line count correlated to vital signs and VDS
- The dynamic changes in IVC-CI between the ultrasound examinations
- The dynamic changes in B-line count between the ultrasound examinations

Sample size
The sample size is calculated from the primary outcome – change in dyspnoea on a VDS. In a former study where VDS was used in the ED on patients admitted with dyspnoea, the initial median score for the admitted patients with dyspnoea was 7 on a scale from 0-10.[29,30] After the initial evaluation, and treatment, it was decreased by 1 point. Another study supports that a 1-point decrease is regarded as a minimally clinically important difference (MCID) for the dyspnoeic patient on this scale.[5] It is expected that the patients in the

serial ultrasound group will achieve a greater improvement on the scale compared to the standard care group because the treatment in the ultrasound group is titrated to the ultrasound findings, which is supported by an ongoing systematic review regarding monitoring patients with serial ultrasound conducted by this research group.[35] It is anticipated by the research group that the VDS will decrease by 2 points in the ultrasound group compared to a 1-point improvement in the standard care group. VDS is reported as median and interquartile range (IQR) in the former study because the data was not normally distributed. To calculate sample size, first standard deviation (SD) is estimated to 2.42 from the reported IQR of 6-9 with the Box-Cox methods proposed by McGrath et al.[36] With an assumption of a power of 80%, type 1-error of 5%, and 10% dropouts, the sample size is 103 patients in each group.

Statistical analysis

Baseline characteristics

Demographic and other baseline characteristics of the participants will be summarized and divided into the intervention and control group and will include: age, sex, comorbidity, smoker status, alcoholic usage, medications, and the results of the first clinical assessment of the patients (VDS, lung auscultation, oedema, vitals, blood samples, arterial blood gases, and ultrasound findings). Continuous variables will be summarized as means and SD or medians, and IQR depending on the distribution of the variables. For categorical variables, frequencies and percentages will be reported. Where values are missing, percentages will be calculated for the available cases, and the denominator will be mentioned.

The primary outcome

The primary outcome – change in dyspnoea on VDS – will be compared between the two groups to detect any difference. Pairwise comparisons of VDS will be made at the same time points in both groups.

The secondary endpoints

Length of stay, death, and the number of readmissions will be registered in the follow-up of the patients. Comparisons between the two groups will be made to detect a difference. Time to event (dead or readmission) will be visualized with Kaplan Meier curves. Cox regression will be used to analyse whether there is an association related to the UL findings when adjusting for diagnosis and age. In the case of lost to follow-up or other reasons for missing data, both intention-to-treat and per-protocol analysis of the pre-defined outcomes will be used to allow readers to interpret the effectiveness of the therapy guided by the ultrasound intervention.

The secondary endpoints registered in the serial ultrasound group

The dynamic changes in IVC-CI and sum of B-lines will be expressed as means and SD or median, and IQR depending on the distribution of the data and compared between the different time points where the parameters are registered cf. figure 2. Furthermore, IVC-CI and the sum of B-lines will be compared to vitals and VDS-score to detect a correlation.

The intraobserver and interobserver variability will be assessed with 10% of the included patients. The scans will be stored and anonymized. Afterward, they will be reanalysed by the same investigator with a minimum interval of 30 days and then by a second investigator. The variability will be assessed with Cohen's kappa.

All statistical analyses will be performed with STATA (v. 15.0, Stata Corporation, Texas, USA).

Data management

The registered data on each patient will be directly recorded and securely stored in an encrypted, logged, and password-protected database REDCap. The database is created by the project manager (MDA) together with a data manager from OPEN. All adjustments in the database are logged. In this database, each patient receives a unique identification number securing patient identity. The investigators will gain access to this database to withdraw a randomization number and enter data. All the data reported are linked to each specific investigator. The randomization process is concealed from all the investigators and the database creator.

A data monitoring committee is not appointed because focused ultrasound is radiation and pain-free and carries no potentially harmful consequences for the patients.[37] No interim analyses or endpoint adjustments are planned. The trial is planned to end when the last included patient has been followed for one year. Any decision to end the trial before this point will be made incorporation and full agreement between the project manager (MDA), and the supervisors (ATL, PHG, and CBL).

Patient and public involvement
Patients and the public were not involved in the design and development of the study. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. During and after the trial, the patients are invited to respond to the setup of the trial and to the patient's comfort or discomfort during the interventions. The responses will be taken into consideration for possible adjustments. The trial results will be disseminated to the involved patients by request, which is applied to the informed content material the patients are receiving.

ETHICS AND DISSEMINATION

The ultrasound examination is safe to use.[37] The study will be conducted in accordance with the Declaration of Helsinki.[38] Patient autonomy is respected, and written consent is obtained before enrolment in the study. The patients can at any point withdraw their consent. The study is approved by The Regional Committee on Health Research Ethics for Region Zealand, Denmark (identifier SJ-744). A data handling agreement with OPEN, University of Southern Denmark, has been signed. The centres participating in the project have approved the data handling process. The study has been approved for data storage by Region Zealand, Denmark, and is registered on the Region Zealand Register of Trials (identifier REG-056-2019). All data are stored, secured, and managed according to the laws and regulations in the General Data Protection Regulation (GDPR)[39] and the Danish Data Protection Act.[40] The trial is registered on ClinicalTrials.gov (identifier NCT04091334). In the event of important modifications or adjustments to the trial protocol, the relevant institutions will be informed, and amendments will be registered on ClinicalTrials.gov.
The results of this trial will be conducted following the Consolidated Standards of Reporting Trials (CONSORT) statement[41] in peer-reviewed scientific journals regardless of the outcomes and will have the following order of authors: MDA, ATL, PHG, and CBL. The investigators involved in the trial will be offered authorship if they are interested and are fulfilling all the ICMJE authorship requirements. Furthermore, the results will be communicated at conferences in emergency medicine and in EDs nationally and internationally.

DISCUSSION

It is anticipated that the results of the study will provide clinical information from the serial ultrasound examinations together with the standard evaluation to further reduce the severity of dyspnoea of the admitted patients and thereby determine in which clinical scenarios a serial ultrasound assessment is clinically relevant to perform. This is, to our knowledge, the first multicentre trial investigating the value of serial ultrasound examinations in monitoring patients with acute dyspnoea.

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AUTHOR CONTRIBUTIONS

MDA is the principal investigator and is in charge of all aspects of database management, education, and information of the trial to the involving investigators. MDA conceived the trial and received inputs and feedback from ATL, PHG, and CBL. MDA drafted the study protocol manuscript. All co-authors read and approved the final manuscript.

ETHICS APPROVAL
The study has been approved by The Regional Committee on Health Research Ethics for Region Zealand, Denmark (identifier SJ-744). Data storage is approved and listed on the Region Zealand Register of Trials (identifier REG-056-2019).

PATIENT CONSENT FOR PUBLICATION
Not required.

DATA SHARING PLAN
Raw data (deidentified participant data) may be made available upon request to the corresponding author if data sharing is in accordance with applicable legislation on the processing of personal data (GDPR and the Danish Data Protection Act). Data will be provided through a secured mailing address. Data can only be reused after acceptance from the project manager.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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APPENDIX S2 Protocol alterations

The alteration was made in full agreement between the trial project manager (MDA) and the supervisors (ATL, PHG, and CBL).

Study settings
The trial was planned to take place in five different EDs. Patients were screened at all sites, but only three of these were able to include patients, and most of them were at one site due to other assignments for the investigators.

Primary outcome
In order to explain a possible effect of the serial ultrasound intervention on VDS, we planned to analyse the treatment provided in the two groups.

Secondary outcomes
The included patients were originally planned to be followed for one year regarding the secondary outcomes mortality and number of readmissions. However, the intervention in the trial was applied during the initial five hours in the ED and therefore was not expected to have any influence on the prognosis of the patients after 30 days. Furthermore, time to event (dead or readmission) was planned to be visualized with Kaplan Meier curves and Cox regression to analyse whether there was an association related to the ultrasound findings when adjusting for diagnosis and age. Instead, we decided to visualize all the secondary outcomes in a single table with proportions, percentages, risk differences, and CI and to treat mortality and readmission as categorical variables within two timespans (0-7 and 8-30 days).

APPENDIX S3 Diagnostic criteria for the point-of-care ultrasound (PoCUS) examination

Focused cardiac ultrasound (FoCUS)
The FoCUS is performed according to principles described in the International Evidence-Based Recommendations for Focused Cardiac Ultrasound, which is elaborated in a European Respiratory Society monograph regarding thoracic ultrasound.[1,2] All pathological findings should be confirmed in at least two views.

Pericardial effusion
Anechoic/hypoechoic pericardial free space between the pericardium and the heart. Have to be distinguished from pericardial fat.

Left ventricle (LV) dysfunction
It is estimated by eyeballing and subdivided according to the American College of Cardiology.[3]

- Hyperdynamic: Ejection fraction (EF) > 70%
- Normal: EF 50-70%
- Mild: EF 40-49%
- Moderate: EF 30-39%
- Severe: EF < 30%

Right ventricle (RV) dysfunction
RV dilation: RV dilated compared to LV with a ratio of ≥ 1/1 when assessed in the apical four-chamber (A4C) view.

Tricuspid annular plane systolic excursion (TAPSE): Estimated with M-mode and subdivided according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging:[4]

- TAPSE ≥ 17 mm: Normal
- TAPSE < 17 mm: Abnormal

Other pathology
Findings of other pathology are also registered if the investigator has the expertise, e.g., valve disease, cor pulmonale, and cardiomyopathy.

Focused lung ultrasound (LUS)
The principles of the FLUS examination are based on the International Recommendations for Lung Ultrasound.[1]

Pleural effusion
Anechoic/hypoechoic zone separating the two pleural layers.

Interstitial syndrome (IS)
IS is defined as the presence of B-line artefacts which are vertical lines with the same echogenicity as the pleural line (typically hyperechoic) arising from the pleural line and moving synchronously with respiration/lung sliding and extending to the bottom of the screen without fading (partially depending on the machine setting). The B-lines can both be distributed diffusely or focally. The total and maximum number of B-lines in each zone is registered, and the sum of B-lines in all zones is calculated. Only one B-line rules out congestion, and three or more B-lines in one zone and/or the presence of pleural effusions are suggestive of congestion.[5]

Pneumothorax
A pneumothorax is present when:

- Presence of lung point(s)
- Absence of lung sliding
- Absence of B-lines
- Absence of lung pulse

A pneumothorax is suspected when:

- Absence of lung point(s)
- Absence of lung sliding
- Absence of B-lines
- Absence of lung pulse

Other pathology

If other pathology is visualized by an investigator with the expertise, it should also be registered. Examples are signs of pneumonia, pulmonary embolism, and unspecific consolidations.

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APPENDIX S4 Diagnostic criteria used in the audit of the medical records

The final diagnosis is established by an audit of the medical records by two independent physicians. Disagreement will be resolved by a third reviewer making a consensus agreement. The allocation and extra ultrasound examinations done in the intervention group will not be journalized.
By the final diagnosis is meant the diagnosis which was the primary cause of the patient's dyspnoea which caused the admission.
The following diagnostic criteria are used in the audit:

Acute myocardial infarction
The diagnostic criteria are based on the guideline from the European Society of Cardiology.[1]

- Detection of a rise and/or fall of troponin values with at least one value above the 99th percentile and
- Evidence of acute myocardial ischemia with at least one of the following:
    - Symptoms of acute myocardial ischemia, e.g., chest pain, dyspnoea, or arrhythmia
    - New ischemic ECG changes
    - Development of pathological Q waves
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
    - Identification of a coronary thrombus by angiography, including intracoronary imaging or by autopsy

Acute decompensated heart failure
The diagnosis is in general agreement with the 2016 European Society of Cardiology[2], and the 2013 American College of Cardiology/American Heart Foundation guidelines.[3]

- Diagnosed with heart failure (before admission or during the admission)
- Worsening of pre-existing dyspnoea or new-onset dyspnoea
- Radiologic findings suggestive of fluid retention (chest radiography, lung ultrasound)

Noncardiogenic pulmonary oedema
Both criteria have to be fulfilled:

- Heart failure is excluded as a cause of the pulmonary oedema
- Radiologic confirmation of fluid retention

Pulmonary embolism
This diagnosis should be confirmed either on

- Computed tomographic pulmonary angiography (CTPA)
- Magnetic resonance pulmonary angiography (MRPA)
- Ventilation-perfusion (V/Q) scanning
- Catheter-based pulmonary angiography

Exacerbation of chronic obstructive lung disease (COPD)
The diagnostic criteria are based on the Global Initiative for Chronic obstructive lung disease guideline[4] and are defined as:

- Acute worsening of respiratory symptoms in a patient diagnosed with COPD results in additional therapy. Prominent respiratory symptoms are: Dyspnoea, increased sputum and volume, cough, and wheezing.

Exacerbation of asthma
The diagnostic criteria are based on the 2019 GINA (global initiative for asthma) report.[5]

- A patient diagnosed with asthma

- Progressive worsening in symptoms of dyspnoea, cough, wheezing, or chest tightness
- A progressive decrease in lung function (peak expiratory flow or forced expiratory volume in 1 second) with a change from the patient's usual status that requires a change in treatment

Pneumonia
Different diagnostic criteria exist, but in this trial, the diagnostic criteria for community-acquired pneumonia are based on the Guidelines for the Management of Adult Lower Respiratory Tract Infections.[6]

- Acute symptoms and presence of signs of lower respiratory tract infection (dyspnoea, cough, fever, and new focal chest signs (e.g., decreased chest expansion, dullness on percussion, reduced entry of air, bronchial breathing, and crackles)) and
- New pulmonary infiltrate on chest radiograph or ultrasound

Sepsis
Based on the 2016 Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SCCM/ESICM) task force.[7]

- Suspected infection (later confirmed by positive microbiologic cultures, response to antibiotics, signs, and symptoms of infection, or supporting radiologic findings) and
- Fulfilling two or more criteria on the quick Sepsis-related Organ Failure Assessment (qSOFA) or with an increase of two or more points in the SOFA score.

Pleural effusion
Radiological imaging confirmation either by chest x-ray, lung ultrasound, or chest CT.
The cause of the pleural effusion can have different aetiologies, e.g., cancer, infection, and heart failure.

Pneumothorax
Pneumothorax is diagnosed by one of the following radiological imaging modalities:

- Chest X-ray
- Chest CT
- Lung ultrasonography

Anaemia
The diagnostic criteria are based on the World Health Organization criteria.[8]

- Men: Hb < 8.1 mmol/l
- Women: Hb < 7.5 mmol/l

Primary or secondary lung cancer
Pathological confirmation or relevant diagnostic imaging of the presence of cancer in the lung.

Acute kidney injury (AKI)
Define according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI) as any of the following:[9]

- Increase in p-creatinine by ≥ 26.5 µmol/l within 48 hours or
- Increase in p-creatinine by ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days or
- Urine volume < 0.5 ml/kg/h for 6 hours

Other diagnoses
If the patient is admitted because of another diagnosis not fulfilling the criteria mentioned above; if the patients have two or more concomitant diagnoses, or if the patients have one of the above-mentioned diagnoses according to the auditing physician but are not precisely fulfilling the criteria, the final diagnosis is made by consensus with the third reviewer.

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Table S1 Additional baseline characteristics of the patients in the serial ultrasound and control group

	Serial ultrasound group n=102		Control group n=104	
Patient characteristics				
Alcoholic drinks per week				
Never	26	(25.5)	29	(27.9)
<7 drinks	37	(36.3)	48	(46.2)
7-14 drinks	22	(21.6)	18	(17.3)
>14 drinks	17	(16.7)	9	(8.7)
Home medications				
Inhaled bronchodilators	53	(52.0)	42	(40.4)
Inhaled corticosteroids	41	(40.2)	35	(33.7)
Oral corticosteroids	13	(12.7)	11	(10.6)
Antibiotics	11	(10.8)	7	(6.7)
Immunosuppressants	0	(0.0)	4	(3.8)
Antiplatelets	18	(17.6)	19	(18.3)
Anticoagulants	33	(32.4)	36	(34.6)
Beta-blockers	39	(38.2)	38	(36.5)
Calcium channel blockers	30	(29.4)	25	(24.0)
Diuretics	42	(41.2)	46	(44.2)
Nitrates	17	(16.7)	15	(14.4)
Digoxin	6	(5.9)	4	(3.8)
Antidepressants	15	(14.7)	21	(20.2)
Opioids	21	(20.6)	16	(15.4)
ACE inhibitors/ARBs	39	(38.2)	43	(41.3)
NSAIDs	7	(6.9)	3	(2.9)
PPIs	42	(41.2)	30	(28.8)
Antidiabetic drugs	18	(17.6)	14	(13.5)
Statins	33	(32.4)	42	(40.4)
Other	77	(75.5)	76	(73.1)
None	5	(4.9)	6	(5.8)
Physical examination				
Ronchi	27	(26.5)	21	(20.2)
Crackles	53	(52.0)	39	(37.5)
Rhythmic	73	(71.6)	83	(79.8)
Arrhythmic	28	(27.5)	20	(19.2)
Murmur	13	(12.7)	7	(6.7)
Oxygen delivery method				
Nasal cannula	30	(29.4)	21	(20.2)
Mask	4	(3.9)	13	(12.5)
Other	2	(2.0)	1	(1.0)
Laboratory results				
Blood samples				

Haemoglobin, mmol/l	7.9 (6.8-8.7)	7.9 (6.9-8.6)
Platelets, x10E9/l	250 (184-298)	252 (198-304)
WBC, x10E9/l	9 (7-12)	8 (7-10)
CRP, mg/l	14 (5-50)	11 (3-35)
Sodium, mmol/l	138 (136-140)	138 (136-139)
Potassium, mmol/l	4 (4-4)	4 (4-4)
Creatinine, micromol/l	76 (61-98)	78 (60-100)
D-dimer		
Elevated	13 (12.7)	11 (10.6)
Normal	8 (7.8)	20 (19.2)
Not ordered	81 (79.4)	73 (70.2)
Troponin I		
Elevated	8 (7.8)	5 (4.8)
Normal	13 (12.7)	16 (15.4)
Not ordered	81 (79.4)	83 (79.8)
Arterial blood gas		
PaO2, kPa	9 (8-11)	9 (8-11)
pH	7.46 (7.42-7.48)	7.44 (7.42-7.47)
PaCO2, kPa	5 (4-5)	5 (4-6)
$HCO3^{-}$, mmol/l	26 (23-28)	26 (24-28)
Saturation, %	95 (94-97)	96 (93-98)
Lactate, mmol/l	1.1 (0.8-1.6)	1.2 (0.8-1.7)
Chest X-ray		
Pulmonary vascular congestion	40 (39.2)	23 (22.1)
Pulmonary oedema	1 (1.0)	0 (0.0)
Pleural effusion	35 (34.3)	24 (23.1)
Pneumothorax	1 (1.0)	1 (1.0)
Normal	19 (18.6)	32 (30.8)
Not ordered	10 (9.8)	10 (9.6)
CT	89 (87.3)	84 (80.8)
Lung scintigraphy	2 (2.0)	0 (0.0)
Echocardiography	61 (59.8)	63 (60.6)
Other imaging	28 (27.5)	26 (25.0)

Data are n (%) or median (IQR).

Table S2 The administered treatment in the two groups at different time points

	Inclusion*				2 hours from inclusion†				4 hours from inclusion‡				5 hours from the inclusion§			
	Serial ultrasound group (n=102)	**Control group (n=104)**	**Risk difference (95% CI)**	***P* value**	**Serial ultrasound group (n=102)**	**Control group (n=104)**	**Risk difference (95% CI)**	***P* value**	**Serial ultrasound group (n=102)**	**Control group (n=104)**	**Risk difference (95% CI)**	***P* value**	**Serial ultrasound group (n=102)**	**Control group (n=104)**	**Risk difference (95% CI)**	***P* value**
Medications																
Antibiotics	10 (9.8)	11 (10.6)	-0.8 (-9.0 to 7.5)	0.85	15 (14.7)	9 (8.7)	6.0 (-2.7 to 14.8)	0.18	6 (5.9)	4 (3.8)	2.0 (-3.8 to 7.9)	0.50	0	3 (2.9)	-2.9 (-6.1 to 0.3)	0.08
Antiarrhythmics	8 (7.8)	4 (3.8)	4.0 (-2.3 to 10.4)	0.22	3 (2.9)	0	2.9 (-0.3 to 6.2)	0.08	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31
Diuretics	46 (45.1)	32 (30.8)	14.3 (1.2 to 27.4)	0.03	43 (42.2)	9 (8.7)	33.5 (22.5 to 44.5)	<0.0001	35 (34.3)	4 (3.8)	30.5 (19.6 to 39.4)	<0.0001	8 (7.8)	2 (1.9)	5.9 (0.1 to 11.8)	0.05
Furosemid, mg ‖	18.0 (21.2)	16.0 (19.6)	2.1 (-3.5 to 7.7)	0.47	16.7 (20.3)	2.7 (9.7)	14.0 (9.6 to 18.3)	<0.0001	13.5 (20.3)	1.7 (9.7)	11.8 (7.4 to 16.2)	<0.0001	2.9 (11.7)	0.8 (5.5)	2.2 (-0.3 to 4.7)	0.09
Antiplatelets	1 (1.0)	3 (2.9)	-1.9 (-5.6 to 1.8)	0.32	0	0	0	0	1 (1.0)	2 (1.9)	-0.9 (-4.2 to 2.3)	0.57	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32
Anticoagulants	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	0	0	0	0	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	0	0	0	0
Inhaled anticholinergics	33 (32.4)	32 (30.8)	1.6 (-11.1 to 14.3)	0.81	27 (26.5)	24 (23.1)	3.4 (-8.3 to 15.2)	0.57	20 (19.6)	17 (16.3)	3.2 (-7.2 to 13.7)	0.54	8 (7.8)	9 (8.7)	-0.8 (-8.3 to 6.7)	0.83
Inhaled Beta2-adrenergic agonists	36 (35.3)	33 (31.7)	3.6 (-9.3 to 16.4)	0.59	29 (28.4)	25 (24.0)	4.4 (-7.6 to 16.4)	0.47	21 (20.6)	17 (16.3)	4.2 (-6.3 to 14.8)	0.43	8 (7.8)	10 (9.6)	-1.8 (-9.5 to 5.9)	0.65
Nitrates	1 (1.0)	4 (3.8)	-2.9 (-7.0 to 1.3)	0.18	0	0	0	0	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32
Oral corticosteroids	16 (15.7)	22 (21.2)	-5.5 (-16.0 to 5.1)	0.31	3 (2.9)	4 (3.8)	-0.9 (-5.8 to 4.0)	0.72	2 (2.0)	2 (1.9)	0.0 (-3.7 to 3.8)	0.98	2 (2.0)	0	2.0 (-0.7 to 4.7)	0.15
Antivirals	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	0	0	0	0	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31

Heparin	0	2 (1.9)	-1.9 (-4.6 to 0.7)	0.16	2 (2.0)	0	2.0 (-0.7 to 4.7)	0.15	0	4 (3.8)	-3.8 (-7.5 to -0.2)	0.046	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32
Opioids	2 (2.0)	0	2.0 (-0.7 to 4.7)	0.15	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	0	0	0	0
Alpha and beta-blockers	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	0	0	0	0	0	0	0	0	0	0	0	0
Potassium chloride	12 (11.8)	6 (5.8)	6.0 (-1.7 to 13.7)	0.13	13 (12.7)	2 (1.9)	10.8 (3.8 to 17.8)	0.0028	14 (13.7)	0	13.7 (7.0 to 20.4)	0.0001	3 (2.9)	1 (1.0)	2.0 (-1.8 to 5.8)	0.30
Fluid																
Fluid volume, mean (SD), ml ||	72.1 (254.5)	86.5 (282.5)	-14.5 (-88.4 to 59.4)	0.70	45.1 (244.8)	9.6 (98.1)	35.5 (-15.6 to 86.5)	0.17	20.6 (139.5)	43.3 (221.5)	-22.7 (-73.7 to 28.3)	0.38	1.0 (9.9)	9.6 (98.1)	-8.6 (-27.9 to 10.6)	0.37
Normal saline	8 (7.8)	7 (6.7)	1.1 (-6.0 to 8.2)	0.76	4 (3.9)	1 (1.0)	3.0 (-1.2 to 7.2)	0.17	2 (2.0)	3 (2.9)	-0.9 (-5.1 to 3.2)	0.67	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31
Ringers acetate	0	2 (1.9)	-1.9 (-4.6 to 0.7)	0.16	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	1 (1.0)	1 (1.0)	0.0 (-2.7 to 2.7)	0.99	0	0	0	0
Lactated Ringers solution	1 (1.0)	0	1.0 (-0.9 to 2.9)	0.31	0	0	0	0	0	0	0	0	0	0	0	0
Other treatment																
Red blood cells	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	0	0	0	0	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32	0	0	0	0
Oxygen therapy	40 (39.2)	37 (35.6)	3.6 (-11.3 to 14.5)	0.59	44 (43.1)	38 (36.5)	6.6 (-6.7 to 19.9)	0.33	40 (39.2)	34 (32.7)	6.5 (-6.5 to 19.6)	0.33	39 (38.2)	33 (31.7)	6.5 (-6.5 to 19.5)	0.33
Oxygen, l/min	0 (0-2)	0 (0-2)	1.6 (-9.6 to 16.8)	0.81	0 (0-2)	0 (0-1.5)	7.6 (-5.8 to 21.0)	0.27	0 (0-2)	0 (0-2)	8.5 (-4.7 to 21.8)	0.21	0 (0-2)	0 (0-1)	8.5 (-4.7 to 21.8)	0.21
Pleurocentesis	0	3 (2.9)	-2.9 (-6.1 to 0.3)	0.08	1 (1.0)	1 (1.0)	0.0 (-2.7 to 2.7)	0.99	3 (2.9)	0	2.9 (-0.3 to 6.2)	0.078	0	1 (1.0)	-1.0 (-2.8 to 0.9)	0.32

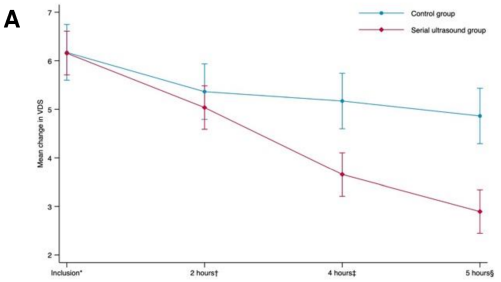
Data are n (%) or median (IQR) unless otherwise noted.
*Inclusion: Same standard diagnostics in both groups, including LUS and FoCUS.
†2 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
‡4 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
§5 hours: Same standard care in both groups. No ultrasound examinations.
||Furosemid (mg) and fluid volume (ml) is in mean despite a non-normal distribution in order to get an estimate of the amount otherwise in median in would not show the difference.
FoCUS, focused cardiac ultrasound; LUS, lung ultrasound.

Table S3 Presumptive diagnoses at the different time points and the final audit diagnoses

Diagnosis	Inclusion*		2 hours from inclusion†		4 hours from inclusion‡		5 hours from the inclusion§		Final audit diagnosis	
	Serial ultrasound group (n= 102)	Control group (n=104)	Serial ultrasound group (n= 102)	Control group (n=104)	Serial ultrasound group (n= 102)	Control group (n=104)	Serial ultrasound group (n= 102)	Control group (n=104)	Serial ultrasound group (n= 102)	Control group (n=104)
Acute myocardial infarction	2 (2.0%)	4 (3.8%)	1 (1.0%)	3 (2.9%)	2 (2.0%)	3 (2.9%)	0 (0.0%)	4 (3.8%)	0 (0.0%)	2 (1.9%)
Acute decompensated heart failure	42 (41.2%)	40 (38.5%)	42 (41.2%)	40 (38.5%)	42 (41.2%)	40 (38.5%)	41 (40.2%)	40 (38.5%)	37 (36.3%)	35 (33.7%)
Non-cardiogenic pulmonary edema	7 (6.9%)	8 (7.7%)	5 (4.9%)	5 (4.8%)	5 (4.9%)	5 (4.8%)	6 (5.9%)	5 (4.8%)	5 (4.9%)	2 (1.9%)
Pulmonary embolism	7 (6.9%)	16 (15.4%)	5 (4.9%)	12 (11.5%)	2 (2.0%)	5 (4.8%)	2 (2.0%)	2 (1.9%)	0 (0.0%)	4 (3.8%)
Exacerbation of chronic obstructive lung disease	22 (21.6%)	26 (25.0%)	23 (22.5%)	27 (26.0%)	22 (21.6%)	27 (26.0%)	22 (21.6%)	26 (25.0%)	21 (20.6%)	22 (21.2%)
Exacerbation of asthma	8 (7.8%)	0 (0.0%)	8 (7.8%)	0 (0.0%)	6 (5.9%)	1 (1.0%)	6 (5.9%)	1 (1.0%)	6 (5.9%)	2 (1.9%)
Pneumonia	36 (35.3%)	28 (26.9%)	35 (34.3%)	28 (26.9%)	35 (34.3%)	27 (26.0%)	34 (33.3%)	28 (26.9%)	30 (29.4%)	18 (17.3%)
Sepsis	0 (0%)	0 (0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0.0%)
Pleural effusion	6 (5.9%)	7 (6.7%)	6 (5.9%)	7 (6.7%)	5 (4.9%)	8 (7.7%)	5 (4.9%)	7 (6.7%)	4 (3.9%)	5 (4.8%)
Pneumothorax	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)
Anemia	1 (1.0%)	5 (4.8%)	1 (1.0%)	5 (4.8%)	1 (1.0%)	5 (4.8%)	1 (1.0%)	6 (5.8%)	2 (2.0%)	5 (4.8%)
Lung cancer	2 (2.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (1.9%)
Acute kidney injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)	1 (1.0%)
Atrial fibrilliation/flutter	13 (12.7%)	8 (7.7%)	13 (12.7%)	7 (6.7%)	13 (12.7%)	7 (6.7%)	13 (12.7%)	7 (6.7%)	13 (12.7%)	12 (11.5%)
Covid-19	12 (11.8%)	14 (13.5%)	11 (10.8%)	14 (13.5%)	10 (9.8%)	14 (13.5%)	9 (8.8%)	10 (9.6%)	4 (3.9%)	3 (2.9%)
Anxiety	1 (1.0%)	3 (2.9%)	1 (1.0%)	5 (4.8%)	1 (1.0%)	5 (4.8%)	1 (1.0%)	5 (4.8%)	1 (1.0%)	3 (2.9%)
Hypertension	1 (1.0%)	2 (1.9%)	1 (1.0%)	2 (1.9%)	1 (1.0%)	2 (1.9%)	1 (1.0%)	3 (2.9%)	1 (1.0%)	1 (1.0%)
Viral pneumonia	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	3 (2.9%)
Ascites	2 (2.0%)	2 (1.9%)	2 (2.0%)	2 (1.9%)	1 (1.0%)	4 (3.8%)	1 (1.0%)	2 (1.9%)	0 (0%)	0 (0%)
Obesity	2 (2.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0%)	0 (0%)
Other diagnosis	3 (2.9%)	8 (7.7%)	3 (2.9%)	9 (8.7%)	5 (4.9%)	13 (12.5%)	5 (4.9%)	14 (13.5%)	10 (9.8%)	24 (23.1%)
Total number of diagnoses	168	174	163	170	154	170	151	163	136	144

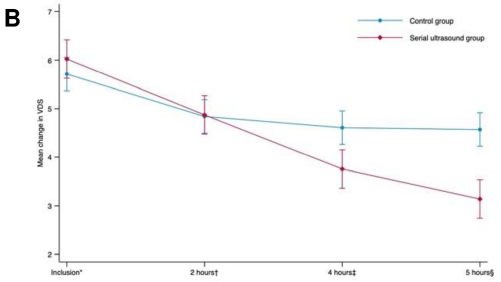
Data are n (%).
*Inclusion: Same standard diagnostics in both groups, including LUS and FoCUS.

†2 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
‡4 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
§5 hours: Same standard care in both groups. No ultrasound examinations.



Differences between groups and within groups at different time points

Between groups	**VDS difference (95% CI)**
Serial ultrasound vs control group at inclusion	-0.02 (-0.74 to 0.72)
Serial ultrasound vs control group +2 hours	-0.33 (-1.06 to 0.40)
Serial ultrasound vs control group +4 hours	-1.52 (-2.25 to -0.78)
Serial ultrasound vs control group +5 hours	-1.97 (-2.70 to -1.23)
Within the control group	
Control group at +2 hours vs control group <1 hour	-0.81 (-1.42 to -0.19)
Control group at +4 hours vs control group at +2 hours	-0.19 (-0.81 to 0.42)
Control group at +5 hours vs control group +4 hours	-0.31 (-0.92 to 0.31)
Within the serial ultrasound group	
Serial ultrasound group at +2 hours vs serial ultrasound group <1 hours	-1.12 (-1.60 to -0.64)
Serial ultrasound group at +4 hours vs serial ultrasound group at +2 hours	-1.38 (-1.86 to -0.90)
Serial ultrasound group at +5 hours vs serial ultrasound group at +4 hours	-0.76 (-1.25 to -0.28)



Differences between groups and within groups at different time points

Between groups	**VDS difference (95% CI)**
(Serial ultrasound vs control group) at inclusion	0.31 (-0.22 to 0.85)
(Serial ultrasound vs control group) +2 hours	0.03 (-0.50 to 0.57)
(Serial ultrasound vs control group) +4 hours	-0.85 (-1.39 to -0.32)
(Serial ultrasound vs control group) +5 hours	-1.43 (-1.97 to -0.90)
Within the control group	
(Control at +2 hours) vs (control <1 hour)	-0.87 (-1.23 to -0.52)
(Control at +4 hours) vs (control at +2 hours)	-0.23 (-0.59 to 0.12)
(Control at +5 hours) vs (control +4 hours)	-0.04 (-0.39 to 0.32)
Within the serial ultrasound group	
(Serial ultrasound at +2 hours) vs (serial ultrasound <1 hours)	-1.15 (-1.56 to -0.74)
(Serial ultrasound at +4 hours) vs (serial ultrasound at +2 hours)	-1.12 (-1.52 to -0.71)
(Serial ultrasound at +5 hours) vs (serial ultrasound at +4 hours)	-0.62 (-1.02 to -0.21)

Figure S1 Change in the primary outcome (VDS) in patients with (A) and without a presumptive diagnosis of AHF (B).
*Inclusion: Same standard diagnostics in both groups, including LUS and FoCUS.
†2 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
‡4 hours: Standard care in both groups. In the serial ultrasound group, an extra LUS and FoCUS.
§5 hours: Same standard care in both groups. No ultrasound examinations.
AHF, acute heart failure; FoCUS, focused cardiac ultrasound; LUS, lung ultrasound; VDS, verbal dyspnoea scale.

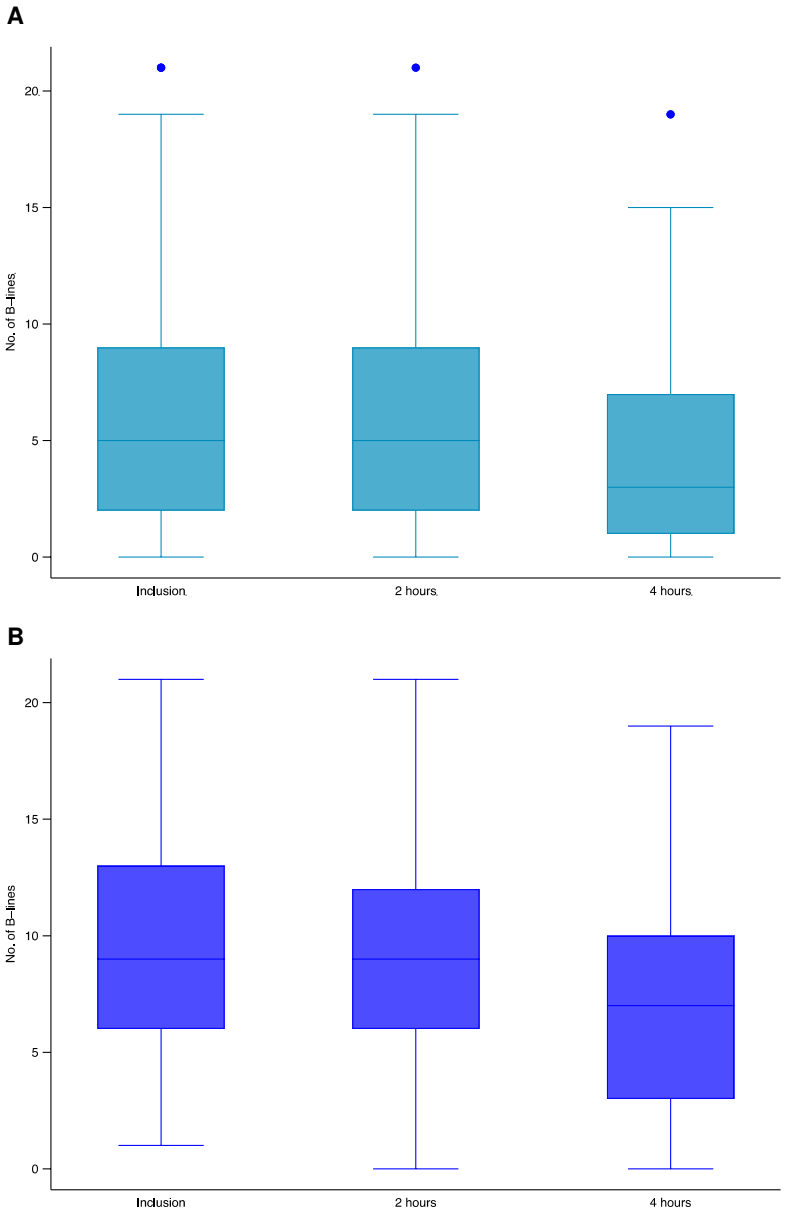


Figure S2 Number of B-lines between the lung ultrasound scans in the serial ultrasound group overall (A) and in patients with AHF (B).
AHF, acute heart failure.

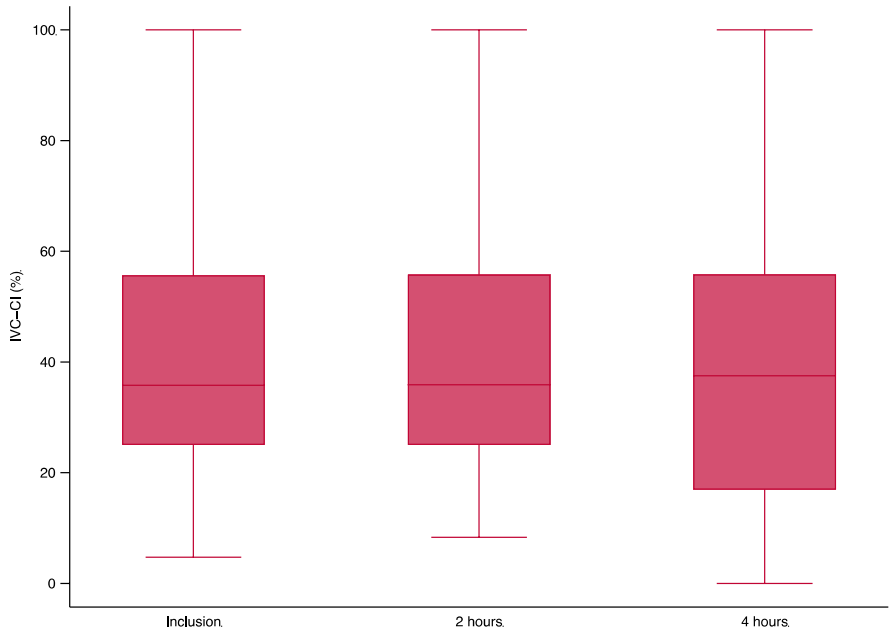


Figure S3 IVC-CI between the ultrasound scans in the serial ultrasound group.
IVC-CI, inferior vena cava collapsibility index.

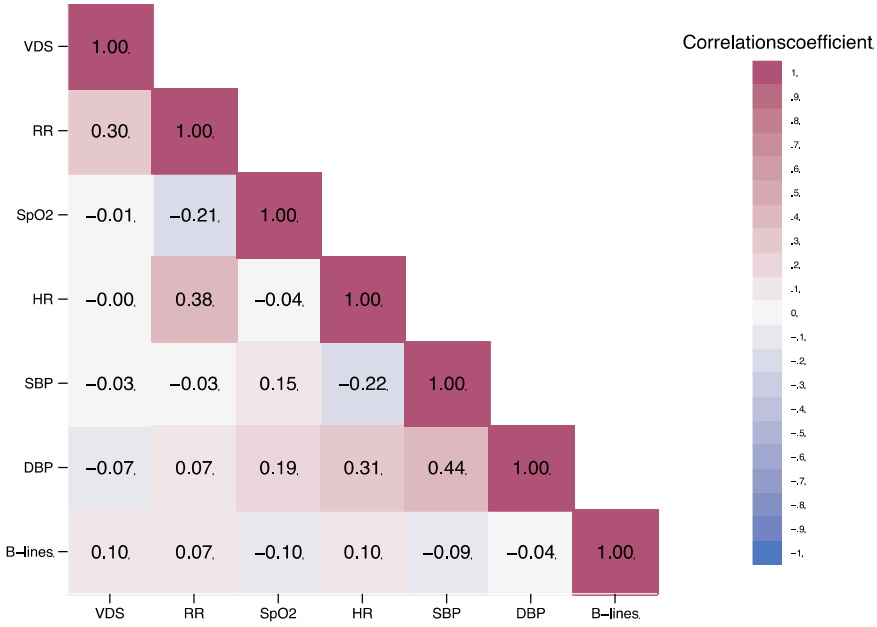


Figure S4 Correlation between B-lines and vital signs and verbal dyspnoea scale.
DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO2, saturation of peripheral oxygen; VDS, verbal dyspnoea scale.

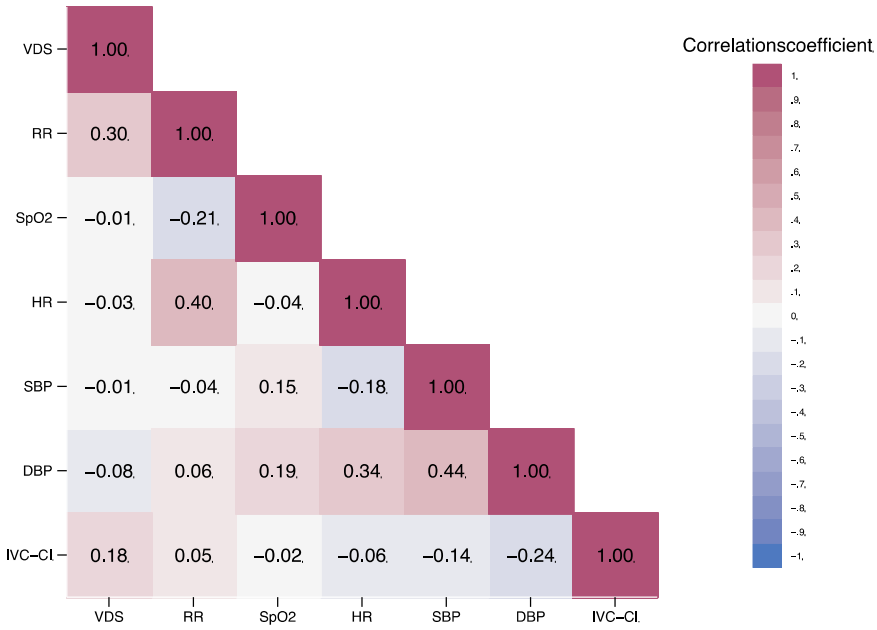


Figure S5 Correlation between the IVC-CI and vital signs and verbal dyspnoea scale.
DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SpO2, saturation of peripheral oxygen; VDS, verbal dyspnoea scale.