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Pleural effusion and thoracentesis in ICU patients: A longitudinal observational cross-sectional study

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Abstract

Background: Pleural effusion is common among patients in the intensive care unit (ICU) but reported prevalence varies. Thoracentesis may improve respiratory status, however, indications for this are unclear. We aimed to explore prevalence, development, and progression of pleural effusion, and the incidence and effects of thoracentesis in adult ICU patients.

Methods: This is a prospective observational study utilizing repeated daily ultrasonographic assessments of pleurae bilaterally, conducted in all adult patients admitted to the four ICUs of a Danish university hospital throughout a 14-day period. The primary outcome was the proportion of patients with ultrasonographically significant pleural effusion (separation between parietal and visceral pleurae >20 mm) in either pleural cavity on any ICU day. Secondary outcomes included the proportion of patients with ultrasonographically significant pleural effusion receiving thoracentesis in ICU, and the progression of pleural effusion without drainage, among others. The protocol was published before study initiation.

Results: In total, 81 patients were included of which 25 (31%) had or developed ultrasonographically significant pleural effusion. Thoracentesis was performed in 10 of these 25 patients (40%). Patients with ultrasonographically significant pleural effusion, which was not drained, had an overall decrease in estimated pleural effusion volume on subsequent days.

Conclusion: Pleural effusion was common in the ICU, but less than half of all patients with ultrasonographically significant pleural effusion underwent thoracentesis. Progression of pleural effusion without thoracentesis showed reduced volumes on subsequent days.

KEYWORDS

critical illness, intensive care units, observational study, pleural effusion, thoracentesis, ultrasonography

Karen W. Fjæreide and Per L. Petersen contributed equally to this article.

Editorial Comment

This study confirms that pleural effusions are common in the intensive care unit (ICU). The effect of pleural effusions and of thoracocentesis in patients admitted to the ICU are still uncertain. This emphasizes the need for interventional clinical trials in this patient group to assess risk and benefit.

1 | INTRODUCTION

Pleural effusion is common in critical illness with a reported prevalence in patients admitted to the intensive care unit (ICU) between 8% and 62% for radiographically confirmed diagnosis,[1,2] and 37% and 81% for ultrasonographically confirmed diagnosis.[1,3–5] Pleural effusion has been associated with restrictive ventilatory impairment, hypoxaemia,[6] and failure in weaning from mechanical ventilation,[7] but the full clinical implications have not yet been determined. In diagnosing pleural effusion, ultrasonography has the advantages of repeatability and bedside availability, and the sensitivity and specificity approaches that of computed tomography.[8,9] An earlier study utilizing ultrasonography in the ICU setting considered pleural effusion clinically relevant when the separation between the visceral and parietal pleurae was above 45 mm,[10] while a more recent study considered pleural effusion clinically relevant when pleural separation was equal to or greater than 20 mm together with a potential adverse effect on patient progress.[11] Criteria that clearly define clinical significance of pleural effusion in ICU patients, however, are lacking.[12] Pleural drainage of pleural effusion through thoracentesis is frequently conducted in the ICU[13]; the complication rate is low with the most common complication being pneumothorax having an incidence of 0.8%, or even lower with procedural ultrasonographical guiding.[14,15] Observational studies indicate that thoracentesis in patients with pleural effusion improves oxygenation and ventilation with increased post-procedural partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio and end-expiratory lung volumes,[15] although paradoxically, pleural drainage has been associated with increased mortality in ICU patients with pleural effusion.[16] The progression of pleural effusion without thoracentesis in ICU patients has never been quantified, and no randomized clinical trials of thoracentesis in ICU patients with pleural effusion have been conducted.[15] Consequently, indication and timing for when to drain pleural fluid is not yet standardized, nor are the clinical consequences of pleural drainage fully enlightened.[17]

The aim of this study was to investigate the prevalence of ultrasonographically significant pleural effusion, and secondarily, to quantify this over time and to assess the incidence of thoracentesis, in adult patients admitted to the ICU.

2 | METHODS

This is a prospective longitudinal observational quality control study utilizing cross-sectional daily ultrasonographic measurements. The protocol was published on zenodo.org prior to study initiation.[18] See Appendix S1 for full protocol. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.[19] See Appendix S2 for the STROBE checklist.

2.1 | Ethics

According to national Danish legislation, observational quality control studies do not require ethical approval. This was confirmed for the specific study upon query to The Committee on Health Research Ethics in the North Denmark Region (journal number 2021-000438). Approval to obtain data from patient medical journals was obtained from the local head of department as required. The project was registered in the North Denmark Regional research registry (ID: 2021-136) as according to the Danish Data Protection agency.

2.2 | Study procedures and population

Bilateral bedside pleural ultrasonography was performed daily on all adult patients (≥18 years) admitted to the four ICUs at Aalborg University Hospital, Denmark (a cardiothoracic ICU, a neuro and trauma ICU, and two multidisciplinary ICUs, for a total of 26 patient beds) in a 14-day period from September 27 to October 10, 2021.

Ultrasonography was performed by two medical students and two physicians who had all previously completed an ultrasonography course including 6 h of e-learning and 6 h of workshop followed by a practical exam. To ensure adequate and equal proficiency with the procedure, a 4-h structured observation and a repeated exam, supervised by a cardiothoracic anaesthesiologist (A.M.) experienced in point-of-care ultrasonography, was conducted prior to study initiation.

Bilateral examinations could be conducted in 15–20 min and were conducted from 08:00 to 15:00 each day. To evaluate protocol adhesion, we report the proportion of patient days, defined as the patient being in the ICU at any time from 08:00 to 15:00 within the inclusion period, where ultrasonographic examinations were conducted.

2.3 | Ultrasonography

The ultrasonographic assessments of pleurae were performed with the patients in supine position and a 15° elevation of the torso.[10]

Bilateral pleural views were obtained according to the Consensus Document ESC/EACVI for Focus Cardiac Ultrasound and Lung Ultrasound.[20] A transverse section perpendicular to the body axis was obtained with the intrapleural fluid visible as an anechoic or hypoechoic layer between the parietal and visceral pleurae. Fluid measurement was performed and recorded at the lung basis along a perpendicular line between the parietal and visceral pleurae at the largest pleural separation (Figure 1). Measurements were conducted at end-expiration for patients on mechanical ventilation, and end-inspiration for non-ventilated spontaneously breathing patients.[10]

To quantify the estimated volume of pleural effusion, the simplified Balik formula was used:

$$\mathrm{Vol}_{(\mathrm{mL})} = \mathrm{Sep}_{(\mathrm{mm})} \times 20.$$

where Vol = estimated volume (mL) of pleural effusion, and Sep = maximal separation between parietal and visceral pleurae (mm).[10]

Ultrasonographically significant pleural effusion was defined as pleural separation >20 mm, equal to an estimated volume >400 mL. Any pleural effusion was defined as pleural separation >5 mm.

All ultrasonographic measurements were conducted using Vivid S5 or S6, GE or SonoSite X-porte ultrasonography units with cardiac transducers (3ScRS).

2.4 | Outcome measures

The primary outcome was the proportion of patients with ultrasonographically significant pleural effusion in either of the pleural cavities on any day in the ICU during the 14 consecutive days. Secondary outcomes included proportion of patients with any pleural effusion in either of the pleural cavities on any day in the ICU, development of pleural effusion over time, maximal estimated volume of pleural effusion, cumulated daily amount of intravenous fluid received, cumulated fluid balance, the incidence of thoracentesis in patients with ultrasonographically significant pleural effusion in the ICU, estimated volume of pleural effusion prior to thoracentesis, and actual volume drained in patients where thoracentesis was performed. Additional clinical outcomes included complications to thoracentesis (haemothorax, pneumothorax, or infection), hospital and ICU mortality rates, and supplementally ICU length of stay and duration of mechanical ventilation. Additionally, a post-hoc defined evaluation of the 24-h PaO_2/FiO_2 ratio prior to and after thoracentesis or identified ultrasonographically significant pleural effusion in undrained patients was conducted, and the duration of pleural catheter in situ was registered. Mechanical ventilation parameters (tidal volume, peak inspiratory pressure, and positive end-expiratory pressure) prior to and after thoracentesis or identified ultrasonographically significant pleural effusion were supplementally reported together with 24-h oxygen supplementation levels (FiO_2 in closed systems and flow of oxygen in open systems).

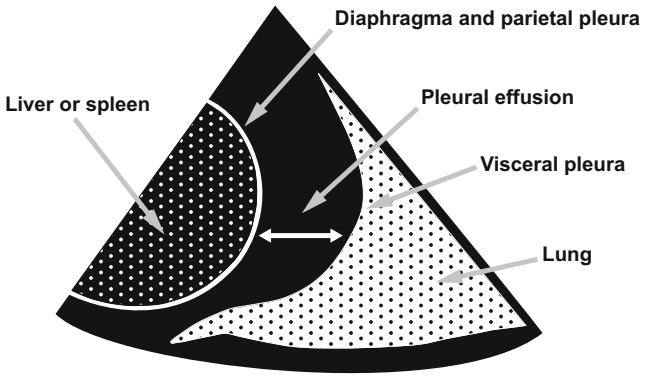

FIGURE 1 Illustration of ultrasonographic measurement of the maximal separation between parietal and visceral pleurae (Sep) in a patient with pleural effusion. The horisontal white arrow indicates Sep.

2.5 | Data

Ultrasonographically collected data were compared to data from the patients' medical journals in relation to the cause of ICU admittance, type of respiratory support and ventilator parameters, PaO_2, presence of chronic or acute cardiac failure, surgical status, infections, Sequential Organ Failure Assessment score,[21] Simplified Acute Physiology Score 3,[22] fluid balance, pleural fluid culture tests, and thoracentesis performed.

2.6 | Blinding

The examinations performed were not part of the daily clinical practice in the ICUs. Treating physicians were kept unaware of results of the ultrasonographic examinations. However, for safety reasons, if ultrasonographically significant pleural effusion was identified in patients with severe or progressing respiratory failure, as evaluated by one of the physicians responsible for the study conduct, the treating physicians were informed. Study examiners were aware of any thoracentesis performed.

2.7 | Statistical analyses

No power estimation was conducted, the inclusion period was defined by feasibility and therefore the number of patients should be considered a convenience sample.

Categorical data are presented as numbers and percentages, continuous data as means with standard deviations or 95% confidence intervals, or medians with interquartile ranges (IQR) as appropriate. Normality of data was assessed by histograms and quantile–quantile plots supplemented with Shapiro–Wilks tests. Supplemental statistical comparisons were conducted using Wilcoxon rank-sum tests for non-parametric continuous unpaired data and Wilcoxon signed-rank tests

TABLE 1 Baseline characteristics.

	All patients [$N = 81$]	Group 1: Ultrasonographically significant pleural effusion[a] [$n = 25$]	Group 2: No ultrasonographically significant pleural effusion[a] [$n = 56$]
Age, years—median (IQR)	66 (58–75)	66 (59–75)	67 (57–75)
Female gender—no. (%)	33 (41%)	11 (44%)	22 (39%)
Height, cm—mean ± SD	173 ± 1 [$n = 78$]	171 ± 3 [$n = 25$]	174 ± 1 [$n = 53$]
Comorbidities at ICU admittance—no. (%)			
COPD	10 (12%)	5 (20%)	5 (9%)
Hypertension	39 (48%)	9 (36%)	30 (54%)
Atrial fibrillation[b]	11 (14%)	2 (8%)	9 (16%)
Ischaemic heart disease	12 (15%)	2 (8%)	10 (18%)
Chronic cardiac insufficiency[c]	3 (4%)	1 (4%)	2 (4%)
Diabetes	20 (25%)	6 (24%)	14 (25%)
Chronic dialysis	2 (2%)	1 (4%)	1 (2%)
Type of admittance—no. (%)			
Medical	40 (49%)	14 (56%)	26 (46%)
Surgical	41 (51%)	11 (44%)	30 (54%)
Causes for ICU admission—no. (%)			
Acute abdomen[d]	12 (15%)	6 (24%)	6 (11%)
Pneumonia	34 (42%)	15 (60%)	19 (34%)
Sepsis	19 (24%)	14 (56%)	5 (9%)
Cardiac failure[e]	13 (16%)	3 (12%)	10 (18%)
Resuscitated from cardiac arrest	5 (6%)	0 (0%)	5 (9%)
Pulmonary embolism	5 (6%)	3 (12%)	2 (4%)
Intracranial hemorrhage	6 (7%)	1 (4%)	5 (9%)
Planned postoperative ICU stay[f]	15 (19%)	3 (12%)	12 (21%)
SAPS 3 at admission—median (IQR)	52 (39–69)	60 (51–70)	44 (32.5–64.5)
SOFA score at day of inclusion—median (IQR)	7 (4–9) [$n = 63$]	7 (6–9) [$n = 21$]	6 (4–9) [$n = 42$]
PaO_2/FiO_2 ratio at first scan, kPa—mean ± SD[g]	36.8 ± 1.9 [$n = 69$]	31.8 ± 3.5 [$n = 21$]	39.0 ± 2.3 [$n = 48$]
Mechanical ventilation at first scan—no. (%)			
Yes	42 (55%)	16 (64%)	26 (51%)
No	34 (45%) [$n = 76$]	9 (36%) [$n = 25$]	25 (49%) [$n = 51$]
If Yes:			
CPAP	0 (0%)	0 (0%)	0 (0%)
NIV	1 (1%)	1 (4%)	0 (0%)
Invasive	41 (54%)	15 (60%)	26 (51%)
Patients with pleural catheter in situ at ICU admission—no. (%)	14 (17%)	7 (28%)	7 (13%)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; PaO_2, partial pressure of arterial oxygen; SAPS 3, simplified acute physiology score 3; SD, standard deviation; SOFA score, sequential organ failure assessment score.

[a]Defined as maximal separation between parietal and visceral pleurae >20 mm at any side on any day in the ICU in the inclusion period.

[b]Chronic or paroxysmal atrial fibrillation.

[c]Defined as ejection fraction ≤40% and in habitual anticongestive treatment.

[d]Gastrointestinal perforation or hemorrhage, or acute pancreatitis.

[e]Cardiogenic pulmonary oedema, myocardial infarction, arrhythmogenic cardiac failure, resuscitated from cardiac arrest, or endocarditis.

[f]Elective cardiac surgery, elective surgery for intracranial tumors, or elective surgery for cancer of the gastric cardia.

[g]FiO_2 for open systems was estimated through standardized tables.

for nonparametric continuous paired data, Chi-squared tests for mortalities, and paired *t*-tests for PaO_2/FiO_2 ratios. A *p*-value below .05 was considered statistically significant. No adjustments for multiple testing or imputations of missing data were conducted as all analyses are considered exploratory only. Graphs of development of pleural effusions by day in the ICU were conducted. The association between estimated volume of pleural effusion prior to thoracentesis, and 24-h volume drained in patients where thoracentesis was performed was illustrated with a scatter plot supplemented with Spearman's rank correlation coefficients. All calculations and statistical analyses were performed using Stata statistical software, release 17 (StataNordic).

3 | RESULTS

A total of 81 patients were included during the 14-day observation period. Of these, 21 patients (25.9%) were already admitted to the ICU before study initiation. Right-sided ultrasonography was conducted on 291/298 patient days (97.7%) and left-sided on 290/298 patient days (97.3%). In five patients, no ultrasonography was conducted at all, as they were admitted outside the time of the daily ultrasonographic assessments, and their ICU admissions were of short durations due to early discharge or death (all within 11 h after admission).

3.1 | Baseline parameters

The types of ICU admittance were evenly distributed between medical and surgical admissions. The most common reasons for ICU admission were pneumonia and sepsis. See Table 1 for baseline characteristics.

3.2 | Outcomes

Of the 81 patients included, 25 patients (31%) had ultrasonographically significant pleural effusion in either of the pleural cavities at any day in the ICU during the observation period. Of these 25 patients, 13 (52%) had ultrasonographically significant pleural effusion upon their first ultrasonography. Ultrasonographically significant pleural effusions seemed most prevalent in patients with pneumonia and

TABLE 2 Pleura effusions and thoracentesis-related outcomes.

	Total [$N = 81$]	Right side	Left side	Bilateral
Ultrasonographically significant pleural effusion (Sep >20 mm)[a]—no. (%)	25 (31%)	1 (1%)	14 (17%)	10 (12%)
Maximal estimated volume (mL) of pleural effusion—median (IQR)[b]	-	680 (600–920)	560 (520–770)	-
Number of patients with new ultrasonographically significant pleural effusion (Sep >20 mm)[c]—no. (%)	12 (15%)	1 (1%)	10 (12%)	1 (1%)
Days with ultrasonographically significant pleural effusion (Sep >20 mm)/cumulated patient-days assessed—no. (%)		18/291 (6%)	41/290 (14%)	
Patients with any pleural effusion (Sep >5 mm)[a]—no. (%)	38 (47%)	2 (2%)	12 (15%)	24 (30%)
Patients undergoing thoracentesis in the ICU[d]—no. (%)	15 (19%)	13 (16%)	9 (11%)	7 (9%)
Sep >20	8 (10%)	5 (6%)	5 (6%)	
Sep >5, ≤20	4 (5%)	2 (2%)	2 (2%)	-
Sep ≤5	3 (4%)	3 (4%)	1 (1%)	-
Missing scan[e]	3 (4%)	3 (4%)	1 (1%)	-
Duration of pleural catheter, days—median (IQR)	2 (2–4) [$n = 23$]	3 (2–6) [$n = 11$]	2 (2–2) [$n = 12$]	-
Estimated volume (mL) of pleural effusion prior to drainage in all patients undergoing thoracentesis[f]—median (IQR)	-	420 (0–920) [$n = 10$]	730 (250–1080) [$n = 8$]	-
24-h volume (mL) drained after thoracentesis—median (IQR)[f,g]	-	813 (585–1500) [$n = 12$]	950 (665–1760) [$n = 9$]	-

Abbreviations: ICU, intensive care unit; IQR, interquartile range; Sep, maximal separation between pleura parietalis and pleura visceralis.

[a]With no pleural catheter in situ at inclusion.

[b]In pleural effusions with Sep >20 mm, volumes estimated according to the Balik formula.[10]

[c]Developed after the first ultrasonography, that is, in-ICU.

[d]In case of bilateral thoracenteses, patients will appear in both Right side and Left side columns across categories and patients may be represented in two rows if receiving bilateral thoracenteses with pleural effusions belonging to separate categories. Thus, patient numbers do not add up.

[e]Three patients underwent thoracentesis with no study ultrasonography performed prior to this.

[f]Regardless of Sep.

[g]Cumulated volume drained within 24 h after thoracentesis, depending on time for thoracentesis in relation to the three daily volume assessments at 06.00, 14.00, and 22.00 recorded (thus cumulated over 16 to 24 h).

sepsis (see Table 1). Thoracentesis was performed during ICU stay in 10 of the 25 patients (40%) with pleural separation >20 mm, in 3 of 13 patients (23%) with pleural separation >5 mm and ≤20 mm, and additionally, in three patients without any pleural fluid (pleural separation = 0 mm) in the last pre-procedural study ultrasonography conducted. In total, 15 patients (19%) underwent thoracentesis in the ICU regardless of ultrasonographically identified pleural effusion. See Table 2 for pleural effusion and thoracentesis-related outcomes.

The development of ultrasonograpichally significant undrained pleural effusion showed an overall decrease in estimated volumes in both pleural cavities on subsequent days until thoracentesis (on either side), discharge, death, or end of the observation period: Right-sided pleural effusion of 640 mL (IQR: 600–680 mL) on the first day with ultrasonographically significant pleural effusion versus 280 mL (0–380 mL) on the last day measured ($n = 5$, $p = .125$) and left-sided pleural effusion of 520 (482–540 mL) versus 220 mL (0–320 mL) ($n = 9$, $p = .004$). See Figure 2.

The indication for thoracentesis in the ICU after inclusion was hydrothorax for all 15 patients, that is, no patients were drained due to pneumo- or haemothorax. No direct complications to thoracentesis (bleeding or pneumothorax) were observed. Pathogens were cultured from pleural fluid in five patients of which four cultures were assumed to be contamination from skin flora (Staphylococcus epidermidis and other coagulase-negative staphylococci) and a single patient had widespread infection with Enterococcus faecium.

There was no significant difference in the intravenous fluid input during ICU admission between patients with ultrasonographically significant pleural effusion and patients without. Patients who had or developed ultrasonographically significant pleural effusion had significantly longer ICU stays and significantly more days with mechanical ventilation. See Table 3 for clinical outcomes.

We found no correlation between estimated volume of pleural effusion prior to thoracentesis and cumulated drained volume in 24 h after thoracentesis, as illustrated by Figure 3.

No significant differences were found in neither the 24-h PaO_2/FiO_2 ratios of patients with ultrasonographically significant pleural effusion prior to and after pleural drainage, nor in the 24-h PaO_2/FiO_2 ratios prior to and after verified ultrasonographically significant pleural effusion in patients who were never drained. See Table 4 for an overview of oxygenation-related parameters, including mechanical ventilation parameters, prior to and after thoracentesis or identified ultrasonographically significant pleural effusion.

4 | DISCUSSION

In this observational repeated cross-sectional study utilizing daily ultrasonography in patients admitted to the ICU, we found that 31% of patients had ultrasonographically significant pleural effusion (estimated pleural effusion >400 mL) on any day in either pleural cavity in the 14-day inclusion period. Of these, 40% had thoracentesis performed during their ICU stay. Development of ultrasonographically significant pleural effusion without drainage showed reduced pleural effusion volumes on subsequent days.

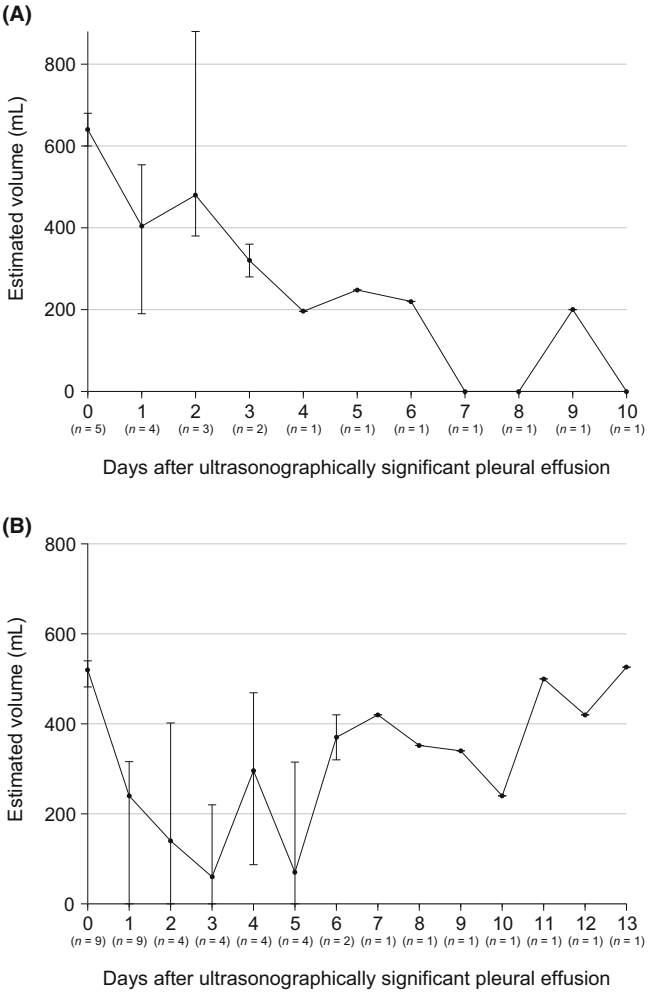

FIGURE 2 Development of ultrasonographically estimated pleural effusions from the first day with ultrasonographically significant pleural effusion (maximal separation between parietal and visceral pleurae >20 mm) until thoracentesis (on either side), ICU discharge, death, or end of the observation period. The data are presented as a median of calculated volumes for consecutive days. Volumes are calculated using the Balik formula.[10] Bars represent interquartile ranges. (A) Right-sided pleural effusions; (B) Left-sided pleural effusions.

The prevalence of any pleural effusion in ICU patients in the current study was with 47% identical to what has previously been found in an unselected medical ICU cohort,[1] whereas studies selecting ICU patients with cardiorespiratory illnesses or according to indication for chest radiography consequently find higher proportions of 60% to 88%,[4,5,23] consistent with our results indicating that patients with pneumonia and sepsis as reasons for ICU admittance seemed more likely to have or develop pleural effusions than other patient populations. The 34% of patients with any pleural effusion who underwent thoracentesis in the ICU in the current study could be considered high, when compared to a previously investigated medical ICU cohort with similar pleural effusion prevalence where only 21% had thoracentesis attempted.[1] However, in a large cohort with similar cut-off for significant pleural effusion, 52% of patients received pleural

TABLE 3 Fluid balance and clinical outcomes.

	All patients [$N = 81$]	Group 1: Ultrasonographically significant pleural effusion[a] [$n = 25$]	Group 2: No ultrasonographically significant pleural effusion[a] [$n = 56$]	p Values[b]
Mean daily IV fluid input, mL—median (IQR)	2232 (1331–3395) [$n = 77$]	2232 (1276–3300)	2218 (1488–3438) [$n = 52$]	.800
Mean daily fluid balance, mL—median (IQR)	657 (−341–1720) [$n = 77$]	261 (−765–983)	940 (81–1916) [$n = 52$]	.065
Length of ICU stay, days—median (IQR)	3 (2–14)	13 (4–23)	2 (2–8)	<.001
ICU days with mechanical ventilation[c], days—median (IQR)	2 (1–12)	9 (1–20)	1 (1–8)	.013
Hospital mortality—no. (%)	20 (25%)	9 (36%)	11 (20%)	.197
ICU mortality—no. (%)	12 (15%)	3 (12%)	9 (16%)	.080

Note: Lower *n* values than at the top of column signify patients with missing data.
Abbreviations: ICU, intensive care unit; IQR, interquartile range.
[a]Defined as maximal separation between parietal and visceral pleurae >20 mm at any side on any day in the ICU in the inclusion period.
[b]Comparison between patients with and without ultrasonographically significant pleural effusion, Wilcoxon rank-sum tests for continuous data and Chi-squared tests for mortalities.
[c]Number of days with any mechanical ventilation defined as invasive ventilation, noninvasive ventilation and non-intermittent continuous positive airway pressure in the ICU, including patients with 0 days of mechanical ventilation.

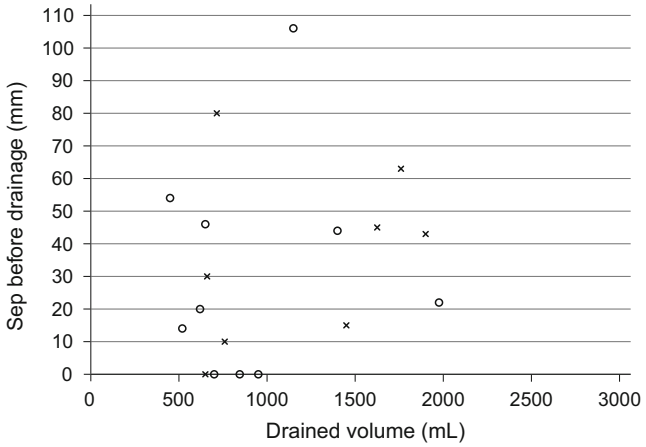

FIGURE 3 Correlation between ultrasonographic measurement of the maximal separation between parietal and visceral pleurae (Sep) in the last scan prior to thoracentesis and the cumulated volume drained within 24 h after thoracentesis, depending on time for thoracentesis in relation to the three daily volume assessments at 06:00, 14:00, and 22:00 recorded (thus cumulated over 16 to 24 h). ○: Right-sided scan and thoracentesis; X: Left-sided scan and thoracentesis. Registrations from three patients who received thoracentesis (three right-sided and one left-sided) in the ICU are missing from the graphs, since no study ultrasonography was conducted in these patients prior to thoracentesis. Spearman's rank correlation coefficient showed no significant correlations between Sep and the cumulated volume drained on either side; right-sided effusions: Spearman's rho = 0.0061, $p = .996$, left-sided effusions: Spearman's rho = 0.4524, $p = .260$.

drainage as compared to 40% in the current study.[11] Since the cut-off for ultrasonographical significant pleural effusion has been proposed to be the level which is clinically relevant when combined with potential adverse effect on patient progress,[11] the 40% drained may indeed be considered low, as large proportions of our patients were mechanically ventilated, or had pneumonia or other cardiopulmonary pathology, that is, conditions in which patient progress would likely be negatively affected by pleural effusion.

We identified no significant effect of thoracentesis on the 24-h PaO_2/FiO_2 ratio, which stands in contrast to previous studies pooling larger patient numbers,[15] and so, this finding may likely represent a type 2 statistical error. Nevertheless, the point estimates of 24-h PaO_2/FiO_2 ratios in patients with ultrasonographically significant pleural effusion who never received thoracentesis showed higher, albeit insignificant, increases than patients receiving thoracentesis, and additionally, development of ultrasonographically significant pleural effusion showed reduced volumes on subsequent days without drainage. As evaluations of ICU patients with undrained pleural effusion have not been conducted before, these are novel findings that might question the clinical effects of thoracentesis in patients with pleural effusion. Alternatively, it may represent confounding by indication. That is, since no information on clinicians' reasons for thoracentesis in specific patients are known, patients selected for drainage may specifically be those who would benefit. Evaluations of pleural effusions without drainage, lack of significant correlation between ultrasonographically estimated pleural effusion volumes and actually drained volumes in 24 h after thoracentesis, and the fact that three patients without any pleural effusion in our examinations received thoracentesis with pleural effusion volumes >500 mL drained consistent with significant build-up of pleural effusions in these patients in the up to 24 h between study ultrasonography and thoracentesis conducted, indicate that pleural effusions in ICU patients may be rather fluctuating. This may be explained by possible shifts in pleural pressures, changes in capillary permeability or plasma oncotic pressure, increased extrapulmonary lung water caused by cardiac congestion or pulmonary inflammation, and treatment options such as albumin

TABLE 4 Oxygenation-related parameters prior to and after thoracentesis or first scan with ultrasonographically significant pleural effusion[a].

				Mechanical ventilation								Oxygen on open systems	
	PaO_2/FiO_2[b] ratio (kPa)—mean (95% CI)			FiO_2 (fraction)—median (IQR)		Tidal volume per kg[c] (mL/kg)—median (IQR)		Peak pressure ($cm\ H_2O$)—median (IQR)		PEEP ($cm\ H_2O$)—median (IQR)		Oxygen flow[d] (L/min)—median (IQR)	
	Prior[e]	Post[e]	*p* Value[f]	Prior[e]	Post[e]	Prior[g]	Post[g]	Prior[g]	Post[g]	Prior[g]	Post[g]	Prior[e]	Post[e]
Patients drained [$n = 9$][h]	26.8 (15.7–37.8) [$n = 8$]	26.7 (20.1–33.2) [$n = 9$]	.697	0.4 (0.4–0.5) [$n = 5$]	0.4 (0.3–0.4) [$n = 5$]	7.4 (6.9–10.5) [$n = 4$]	11.4 (2.9–12.9) [$n = 3$]	25.0 (14.0–28.0) [$n = 3$]	16.0 (13.0–24.0) [$n = 3$]	8.0 (7.0–9.0) [$n = 4$]	6.0 (6.0–8.0) [$n = 3$]	8 (6–10) [$n = 5$]	4 (3–11) [$n = 7$]
Patients not drained [$n = 16$][i]	29.4 (22.8–36.0) [$n = 15$]	32.3 (26.2–38.4) [$n = 14$]	.055	0.5 (0.4–0.6) [$n = 10$]	0.4 (0.3–0.5) [$n = 8$]	8.1 (7.2–8.7) [$n = 8$]	7.4 (7.2–8.8) [$n = 8$]	21.0 (17.5–24.5) [$n = 8$]	20.0 (16.5–24.5) [$n = 8$]	8.0 (7.5–11.0) [$n = 8$]	8.0 (7.0–11.0) [$n = 8$]	6 (3–6) [$n = 9$]	4 (1–5) [$n = 6$]

Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a]Only patients with ultrasonographically significant pleural effusion defined as maximal separation between parietal and visceral pleurae >20 mm at any side on any day in the ICU in the inclusion period are included in the table.

[b]In open systems, the FiO_2 was estimated through standardized tables.

[c]Predicted body weight, calculated as 50 kg + 0.91 kg/cm × (height−152.4 cm) for men and 45.5 kg + 0.91 kg/cm × (height−152.4 cm) for women.

[d]Flow of pure oxygen in open systems including high-flow systems, regardless of concomitant flow of atmospheric air.

[e]24-h patient means, prior and post event, indicating either thoracentesis for drained group or first scan with ultrasonographically significant pleural effusion for patients who were never drained.

[f]Paired *t*-test between prior and post PaO_2/FiO_2 values.

[g]Measurements at 8 am prior and post event, indicating either thoracentesis for drained group or first scan with ultrasonographically significant pleural effusion for patients who were never drained.

[h]One patient had no data prior to the event. Four patients are represented in both the mechanically ventilated subgroup and the oxygen on open systems subgroup, as they received both mechanical ventilation and oxygen on open systems within the 24-h window.

[i]One patient had no data prior to the event and two different patients had no data after the event. Four patients are represented in both the mechanically ventilated subgroup and the oxygen on open systems subgroup, as they received both mechanical ventilation and oxygen on open systems within the respective 24-h windows.

substitution, diuretics and other anticongestive drugs.[17,24] Nevertheless, this fluctuating nature may also question the efficacy of thoracocentesis. Unfortunately, current evidence is insufficient to evaluate effects of thoracentesis on clinical patient-important outcomes such as ICU length-of stay or duration of mechanical ventilation.[15]

4.1 | Strengths and limitations

The current study has several strengths. These include a pre-published protocol,[18] inclusion of a broad selection of ICU patients across specialties, which heightens external validity, a systematic and stringent implementation of ultrasonographical examinations following current recommended consensus,[20] implementation of a standardized and generally widely used formula for estimation of pleural effusion volume,[10] and an overall very good compliance with the pre-specified protocol with bilateral pleural ultrasonography conducted on more than 97% of included patient days. Nevertheless, the study has several limitations as well. First, the cross-sectional study design may be considered a limitation as this means that patients were not necessarily scanned on all ICU admission days as they may have been admitted prior to or discharged after the 14-day inclusion period. This means that the prevalence of pleural effusion may not represent the true prevalence during ICU stay in the cohort. However, it does represent the minimal prevalence. Second, we found no significant correlation between the estimated volume of pleural effusion and the accumulated volume drained within 24 h after thoracentesis, which may be considered a limitation. However, since patients did not receive thoracentesis immediately after our ultrasonographical measurements but may have been drained at any time-point before the next ultrasonographical study assessment, there may have been up to 24 h between assessments and thoracentesis, in which effusion volumes could increase or decrease. Additionally, pleural fluid production could have occurred between drain insertion and pleural effusion assessment, possibly in combination with higher elevation of the torso by clinicians than our standard 15°, thus increasing the amounts of pleural fluid visible allowing for drain insertion at lower fluid volumes. Furthermore, despite its easy and widespread use, validation studies have found the Balik formula to be less precise than other more complex formulae in estimating pleural effusion volume.[25,26] Fourth, despite ultrasonographical results not being shared, the sole presence of the examiners in the ICU could have affected the focus given to pleural effusion in the patient assessments made by attending physicians. This could both have led to a higher or lower incidence of thoracentesis. Fifth, clinicians' indications for thoracentesis were not assessed as they were not unambiguously noted in the patient files. However, in the ICU in most cases pleural effusions are drained for therapeutic reasons, that is, to improve respiratory failure. Finally, the observational design of the study limits causal inference, and given the lack of a power calculation, the low patient numbers, and the number of comparisons conducted without adjustments for multiplicity, the risk of type I and type II statistical errors are prevalent. Therefore, it cannot be concluded that changes seen in outcomes are causally linked to pleural effusions or to thoracentesis.

5 | CONCLUSIONS

This observational study found that 31% of all patients admitted to the ICU had or developed ultrasonographically significant pleural effusion, of which 40% had thoracentesis. In patients without thoracentesis, the pleural effusion volumes decreased on subsequent days. No significant reductions in 24-h PaO_2/FiO_2 ratio after thoracentesis were found. The current study found that pleural effusions were prevalent but adds to the uncertainty of the effects of pleural effusions and of thoracentesis in patients admitted to the ICU. This underlines the need for interventional clinical trials.

AUTHOR CONTRIBUTIONS

Idea and conceptualisation: Angela Mahdi, Bodil S. Rasmussen, and Olav L. Schjørring; *protocol and study design*: Karen W. Fjæreide, Per L. Petersen, Angela Mahdi, Bodil S. Rasmussen, and Olav L. Schjørring; *ultrasonography and data retrieval*: Karen W. Fjæreide, Per L. Petersen, Elena Crescioli, and Frederik M. Nielsen; *data handling and statistical analyses*: Karen W. Fjæreide and Per L. Petersen. The primary manuscript was drafted by Karen W. Fjæreide and Per L. Petersen, and critically revised by all authors.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research, supporting data is not available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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