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Clinically Significant Pleural Effusion in Intensive Care: A Prospective Multicenter Cohort Study

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Objectives: The prevalence and optimal management of clinically significant pleural effusion, confirmed by thoracic ultrasound, in the critically ill is unknown. This study aimed to determine: 1) the prevalence, characteristics, and outcomes of patients treated in intensive care with clinically significant effusion and 2) the comparative efficacy and safety of pleural drainage or expectant medical management.

Design: A prospective multicenter cohort study.

Setting: ICUs in four teaching hospitals in Western Australia.

Patients: Consecutive patients with clinically significant pleural effusions (depth ≥ 2 cm on thoracic ultrasound with clinician-determined adverse effects on patient progress).

Interventions: None.

Measurements and Main Results: Primary outcome was the change in Pao_2:FIO_2 (mm Hg) ratio from baseline to 24 hours. Changes in diagnosis and treatment based on pleural fluid analysis and pleural effusion related serious adverse events between those who underwent either drainage within 24 hours or expectant management were compared. Of the 7,342 patients screened, 226 patients (3.1%) with 300 pleural effusions were enrolled. Early drainage of pleural effusion occurred in 76 patients (34%) and significantly improved oxygenation (Pao_2:FIO_2 ratio 203 at baseline vs 263 at 24 hr, +29.6% increment; $p < 0.01$). This was not observed in the other 150 patients who had expectant management (Pao_2:FIO_2 ratio 250 at baseline vs 268 at 24 hr, +7.2% increment; $p = 0.44$). The improvement in oxygenation after early drainage remained unchanged after adjustment for a propensity score on the decision to initiate early drainage. Pleural effusion related serious adverse events were not different between the two groups (early drainage 10.5% vs no early drainage 16.0%; $p = 0.32$). Improvements in diagnosis were noted in 91 initial (nonrepetitive) drainages (76.5% out of 119); treatment strategy was optimized after 80 drainage episodes (59.7% out of 134).

Conclusions: Early drainage of clinically significant pleural effusion was associated with improved oxygenation and diagnostic accuracy without increased complications.

Key Words: intensive care; PaO_2:FIO_2 ratio; pleural drainage; pleural effusion; thoracic ultrasound

Pleural effusion (PLEFF) is common in the critically ill and associated with increased mortality (1). The prevalence of ultrasound-detectable PLEFF has been reported to be as high as 62%, but how frequently PLEFF causes adverse effects on patients' clinical progress is less clear (2). In addition, there is also considerable variability in how PLEFF is managed in the ICU setting (3)—in part related to inadequate evidence on the benefits and risks of pleural drainage (4, 5). Although pleural drainage is safer with ultrasound guidance (6, 7), serious complications including visceral injury, bleeding, and even death have also been reported (8). On the other hand, important and potentially fatal diagnoses—such as pleural infection or empyema (9)—can be missed without pleural fluid analysis, and thoracentesis can

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change the presumptive diagnosis of the cause of effusion in up to 45% of patients (10).

In addition to aiding diagnosis, drainage of PLEFF may also improve respiratory function. The evidence to date is, however, conflicting. Although one study confirmed improved compliance and diaphragmatic thickening after drainage (11), another noted no association between presence or size of PLEFF and ventilation weaning failure (12). A meta-analysis of small studies showed that pleural drainage can improve Pao_2:Fio_2 (P:F) ratio (13). Whether a similar improvement in oxygenation can be achieved with optimizing noninvasive therapy (e.g., diuresis, positive end-expiratory pressure [PEEP]), without drainage of PLEFF is unknown.

Thoracic ultrasound adds value to clinical assessment and chest radiography (14). It can detect even physiologic amounts of pleural fluid and predict the drainable volume (15). However, criteria that define clinical significance of PLEFF in critically ill patients are lacking (5, 16). We hypothesized that clinically significant PLEFF—defined by a depth greater than or equal to 2 cm on thoracic ultrasound in a drainable location together with clinician-determined adverse effects on patient progress—is common in critically ill patients, and early drainage is associated with an improvement in oxygenation and treatment strategy. This prospective, multicenter, cohort study aimed to determine: 1) the prevalence, characteristics, and outcomes of patients treated in intensive care with clinically significant effusion and 2) the comparative efficacy and safety of pleural drainage compared with expectant medical management.

MATERIALS AND METHODS

Patient Selection

To define clinically significant PLEFF in this study, meetings were held between intensivists from all study centers. A consensus definition of clinically significant PLEFF was agreed when all the following criteria are met: 1) the treating clinician believes that the PLEFF is significantly impacting on clinical progress (e.g., gaseous exchange, weaning of ventilation, resolution of sepsis) and 2) interpleural separation on end-expiration of greater than or equal to 20 mm was detectable in a safe drainage location (without incursion of visceral structures throughout the respiratory cycle) on thoracic ultrasound with the patient lying supine with 30° head elevation.

Consecutive patients admitted to medical and surgical ICUs of four teaching hospitals (total 80 beds) in Perth, Australia, between December 1, 2015, and March 31, 2018, were assessed for PLEFF every day by treating clinicians. Potentially eligible patients were referred to investigators every day of the week. Investigators also reviewed all thoracoabdominal radiological investigations twice weekly during the study period, prompting ultrasound scanning in cases of suspected clinically significant PLEFF, if not already performed. Clinicians performing thoracic ultrasound had attended nationally accredited training courses. All drainage procedures performed in the ICU were guided by ultrasound in accordance with international guidelines (17). In this study, patients under 18 years old were excluded.

No power calculation to define recruitment targets was possible, as no study had included expectant-management groups previously. Feasibility assessments projected recruitment rates of 100 patients per year. A prespecified target of 300 clinically significant PLEFF was therefore set based on a maximum study length of three years. A minimum number of 100 patients requiring drainage procedures was also set to ensure an adequate sample to assess drainage complication rates.

Demographic (age, gender) clinical (reason for ICU admission, comorbidities, rationale for drainage, or expectant management), and physiologic parameters (arterial blood gas, ventilatory mode, and settings) were recorded prospectively at the time of confirming clinically significant PLEFF, at baseline prior to interventions targeting the PLEFF, and at 24, and 48 hours after enrollment. Management decisions were left up to treating clinicians. In this study, early drainage was defined as chest tube insertion or thoracentesis performed within 24 hours of confirming clinically significant PLEFF. Patients managed with medical means for greater than 24 hours (including diuresis, renal replacement therapy, and/or increased ventilator pressures as well as treating the underlying illness) without drainage were considered to have expectant or conservative management.

Comparative Efficacy and Safety Outcomes

Changes in oxygenation within 24 hours of enrollment was the primary outcome of interest. A minimum clinically important difference (MCID) in P:F ratio (mm Hg) between baseline and 24 or 48 hours was defined a priori by a 20% increment from the baseline P:F ratio (18).

Pleural drainage was considered successful if the procedure resulted in at least one or more of the following benefits without any adverse event: 1) significant improvement in P:F ratio at 24 hours compared with baseline; 2) ability to wean and/or extubate within 48 hours of treatment; or 3) a change in diagnosis or treatment plan as a result of pleural fluid analyses.

Adverse events and serious adverse events (SAEs) were recorded prospectively at the time points above and also at ICU, hospital discharge, and 90 days after enrollment unless patients died prior to 90 days, using data from the clinical records including ICU nursing charts, medical records, hospital discharge summaries, and radiological investigations. SAEs were defined as any adverse event that caused death or irreversible harm or required treatment to prevent these outcomes. SAEs were discussed with treating clinicians and decisions made unanimously in all cases between the lead clinician and principal investigator to define whether a SAE was pleural effusion related (PERSAEs).

Mortality was censored at 90 days. Changes in diagnosis/treatment were recorded up to ICU discharge as a result of pleural drainage, as reported by treating physician. Hospital stay and hospital-free days were recorded up to 90 days or death.

All variables except pleural drainage success were collected and analyzed in the same way, at the same time points in both the early drainage and the control groups.

Statistical Analyses

In calculating prevalence, a maximum of one PLEFF per patient was counted (i.e., bilateral PLEFF was counted as one and recurrent PLEFF were discounted). Potential predictors for the decision to drain PLEFF within 24 hours of diagnosis rather than expectant

management were defined a priori, provided missing data were less than 25%. Logistic regression was used to determine predictors of early pleural drainage and the statistically significant predictors were then used to generate a propensity score (i.e., probability of having an early pleural fluid drainage). The propensity score was then used as a continuous covariate in the sensitivity analyses to reduce the effect of potential selection bias in determining the comparative efficacy of pleural drainage on the two main efficacy outcomes—achieving MCID improvement (20% increment from baseline) in P:F ratio or treatment success (defined by point two 1) to 3) above) without any adverse event.

D'Agostino and Pearson tests were used to check normality of data. Paired and unpaired *t* tests were used for comparisons of continuous, normally distributed, data. Mann-Whitney *U* test (unpaired) and Wilcoxon signed rank test (paired data e.g., intra-group P:F ratio comparisons) were used to analyses non-normally distributed data. Tukey multiple comparisons test was performed for multiple comparisons for the P:F ratio data. Proportions and univariate analyses were compared using Fisher exact or chi-square tests. Variables with a *p* value of less than 0.2 in univariable analyses with a missing data rate of less than 25% were included in multivariable analyses. Results are given as median (interquartile range [IQR]) unless otherwise stated. Statistical tests were performed using Prism Version 8 (GraphPad Software, San Diego, CA) except the logistic regression analyses, which were performed using SAS/STAT (SAS Institute, Cary, NC). All statistical tests were two-tailed and an alpha-error less than 5% was considered significant. Ethical approval for this study was provided by the Sir Charles Gairdner and Osborne Park Group Ethics Committee in November 2015 (HREC number 2015-085).

RESULTS

Prevalence of Clinically Significant PLEFF

Of the 7,342 patients admitted to the four study ICUs during the study period, 1,870 patients (25.5%) had PLEFF reported on chest radiographs; 479 patients (6.5%) had ultrasound confirmation of PLEFF. Three hundred clinically significant PLEFF met the inclusion criteria in 226 patients, representing 3.1% (95% CI, 2.7–3.5%) of all ICU admissions (**Fig. 1**). No patients were lost to follow-up and median follow-up time was 90 days (IQR, 36.5–90.0 d).

Early drainage (three therapeutic thoracenteses, the remainder intercostal catheter insertions, no low volume diagnostic aspirations) occurred in 76 patients (34%) within 24 hours of a diagnosis of clinically significant PLEFF. Volume drained at 48 hours was 1180 mL (IQR, 550–1,910 mL). Four patients had bilateral early drainage. Nine patients (11.8%) had recurrence of clinically significant PLEFF at 0 to 43 days (median = 2 d) after the initial drainage procedure. Twelve repeat drainage procedures were performed in eight of these patients, resulting in a total of 92 drainage procedures. One patient with re-accumulation of lymphomatous effusion after 4 days underwent palliative care.

Among those who did not receive early drainage within 24 hours of a diagnosis of clinically significant PLEFF (n = 150, 66.4%), 27 patients (18.0%) (38 effusions) required a total of 45 drainage procedures after a median of 4 days of expectant management.

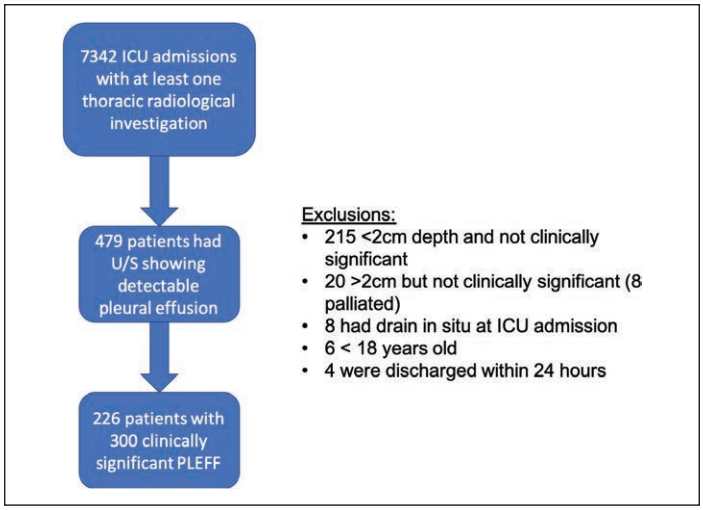

Figure 1. Screening and eligibility flow chart. PLEFF = pleural effusion, U/S = thoracic ultrasound.

Contraindications to drainage were noted in 26 patients (17.3%) (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A127). Documentation of reasoning behind treatment choice and nature of expectant management strategy of PLEFF was missing in 22 patients. In the remainder, 41 of 128 (32.0%) had likely transudative causes with 28 presumed due to cardiac failure, seven presumed hepatic hydrothoraces and six fluid overload with known renal insufficiency. Specific PLEFF treatments in the first 24 hours included initiation of diuresis (27.3%), renal replacement therapy (4.7%), and increase in PEEP (4.7%). The remaining patients all underwent treatment of the underlying illness with optimization of fluid balance.

Predictors for Early Drainage of PLEFF

In the univariable analyses, a larger size PLEFF on thoracic ultrasound and suspected pleural infection were the only two factors significantly associated with early drainage of PLEFF (**Table 1**). In the multivariable analysis, a larger size PLEFF (odds ratio [OR] 2.79 per cm increment; 95% CI, 1.86–3.72), suspected pleural infection (OR, 3.41; 95% CI, 2.58–4.04), and positive-pressure ventilation (including noninvasive ventilation [NIV]) (OR, 1.64; 95% CI, 1.07–2.26) were independent predictors of clinicians' decision to initiate early pleural drainage (**Table 2**).

Primary Efficacy and Safety Outcomes

Oxygenation and Treatment Success. Drainage significantly improved P:F ratio from baseline (203 mm Hg; IQR, 148–285 mm Hg) by an average of 60 mm Hg to 263 mm Hg (IQR, 217–352 mm Hg) ($p < 0.01$, n = 59, 22% missing) at 24 hours after drainage, with 29.6% meeting the MCID of 20% improvement criterion. Conversely, P:F ratio was not significantly different between baseline and at 24 hours after enrollment in patients who received expectant management without drainage (250 mm Hg, IQR 176–325 vs 268 mm Hg, IQR 190–323, respectively; p = 0.44, only 7.2% met MCID criterion, n = 124, 17% missing) (**Fig. 2**). Adjusting for multiple comparisons within each management strategy confirmed significant improvement in oxygenation at both 24 and 48 hours

TABLE 1. Characteristics of the Study Patients at the Time of the Diagnosis of Clinically Significant Pleural Effusion

Characteristic	Early Pleural Drainage ($n = 76$)	Conservative Management ($n = 150$)	p
Age, yr	60 (45–72)	60 (48–72)	0.96
Female, %	27.6	36.8	0.17
Acute Physiology and Chronic Health Evaluation II score	20 (14–25)	20 (14–25)	0.89
ICU admission source, %			
Operating theatre	14.5	19.7	0.58
Emergency department	21.1	28.3	0.26
Primary reason for intensive care admission, %			
Septic shock	27.6	26.7	0.88
Respiratory failure	21.1	18.0	0.59
Renal replacement	1.3	2.6	0.51
End-expiratory interpleural separation at lung base on thoracic ultrasound scan (cm)	4.6 (3.5–5.8)	3.4 (2.5–4.5)	< 0.01
Pao_2:FIO_2 ratio (mm Hg)	223.0 (153.3–292.5)	250.0 (176.0–325.0)	0.18
Ventilation requirement, %			
Invasive ventilation	52.6	45.3	0.30
Noninvasive ventilation	6.6	4.0	0.39
Suspected pleural infection, %	56.6	13.3	< 0.01

Continuous data are the median (interquartile range).

TABLE 2. Logistic Regression Analysis Showing the Predictors of Early Pleural Drainage As the Initial Treatment Strategy at the Diagnosis of Clinically Significant Pleural Effusion (Odds Ratio > 1 Means More Likely to Undergo Early Pleural Drainage)

Predictors	Predictor Cut Point[a]	Univariable OR (95% CI); p	Multivariable OR (95% CI); p
Age, yr	≥ 60 yr old (vs < 60)	0.96 (0.73–1.24); $p = 0.78$	NA
Gender	Male (vs female)	1.1 (0.90–1.32); $p = 0.38$	NA
ICU stay prior to diagnosis of pleural effusion	≥ 1 d (vs ≤ 1)	0.69 (0.52–0.89); **$p < 0.01$**	0.70 (0.42–1.05); $p = 0.09$
Baseline Pao_2:FIO_2 ratio, mm Hg (baseline)	≥ 246.5 (vs < 246.5)	0.81 (0.56–1.12); $p = 0.25$	NA
Positive pressure (including noninvasive ventilation and continuous positive airway pressure)	Yes (vs no)	1.28 (1.00–1.62); $p = 0.07$	1.64 (1.07–2.26); **$p = 0.03$**
Acute Physiology and Chronic Health Evaluation II score	≥ 20 (vs ≤ 20)	1.01 (0.76–1.32); $p > 0.99$	NA
Bilateral pleural effusion	Yes (vs no)	0.85 (0.55–1.29); $p = 0.54$	NA
Depth of pleural effusion on ultrasound scan, cm	≥ 3.6 (vs ≤ 3.6)	1.82 (1.44–2.31); **$p < 0.01$**	2.79 (1.86–3.72); **$p < 0.01$**
Suspected pleural infection	Yes (vs no)	4.23 (2.72–6.65); **$p < 0.01$**	3.41 (2.58–4.04); **$p < 0.01$**

NA = not applicable, OR = odds ratio.
[a]Continuous variables were dichotomized using the median as the cut point.
Boldface values are $p < 0.05$ to indicate statistical significance.

occurred after drainage compared with baseline (both adjusted $p < 0.01$), but not after expectant management (adjusted $p > 0.99$). P:F ratio between the two groups at baseline, 24 or 48 hours were, however, not significantly different (adjusted $p = 0.18$, $p = 0.92$, $p = 0.81$, respectively). Details of further outcomes regarding oxygenation are shown in **Supplemental Table 2** (Supplemental Digital Content 1, http://links.lww.com/CCX/A127).

Early drainage was also associated with an increased likelihood of treatment success without any adverse event (OR, 1.74; 95 CI, 1.02–3.60) compared with expectant management without early drainage, independent of Acute Physiology and Chronic Health Evaluation II score and age (**Table 3**). No baseline characteristics at the time of treatment decisions (including larger size effusion, suspected pleural infection, or positive-pressure ventilation) were associated with a successful pleural drainage treatment without adverse events (Table 3).

Adverse Events. Of the 76 patients who had early pleural drainage, eight patients (10.5%) had PERSAEs from 91 procedures (8.8% of procedures) and one patient (1.3%) had a non-PERSAE serious adverse event. A further six patients had seven non-SAEs (7.9%). Of the 150 patients who were treated with expectant management, 24 patients (16.0%) had 29 PERSAEs and 11 had non-PERSAE serious adverse events. Two other patients had non-SAEs. Detailed descriptions of adverse events are their relative incidence rates are shown in **Supplemental Table 3** (Supplemental Digital Content 1, http://links.lww.com/CCX/A127).

Mortality. No patients died in direct relation to their PLEFF management. There was no significant difference in hospital mortality between those treated with early drainage (27.3%) and expectant management (27.3%) ($p > 0.99$).

Diagnostic Impact. Eighteen repeat procedures were performed for purely therapeutic reasons in patients that had already undergone ipsilateral effusion drainage and were excluded from the analysis of change in diagnosis. Ninety-one out of 119 (76.5%) nonrepetitive procedures improved the predrainage diagnosis and 62 (52.1%) resulted in a complete change in the diagnosis (Supplementary file, Supplemental Digital Content 1, http://links.lww.com/CCX/A127).

Therapeutic Impact. Eighty out of 137 procedures (58.4%) resulted in a change in treatment. Fifteen procedures were duplicate ipsilateral procedures that did not significantly alter treatment and 42 initial procedures did not directly alter management strategy (Supplementary file, Supplemental Digital Content 1, http://links.lww.com/CCX/A127).

Weaning and Extubation. Neither the rates of extubation (7/40 [17.5%] and 21/68 [30.9%]; $p = 0.13$) nor of weaning from NIV (2/5 [20.0%] and 4/6 [66.7%]; $p = 0.38$) were significantly different at 48 hours between treatment groups.

ICU Stay and Days in Hospital Within 90 Days of Enrollment. Median ICU stay after diagnosis of PLEFF was not significantly different at 6 days (IQR, 4.0–10.5 d) and 5.5 days (IQR, 2.3–11.0 d) in the early drainage and control groups, respectively ($p = 0.41$). Hospital stay and hospital-free days after diagnosis of clinically significant PLEFF were also no different at 18 days (IQR, 8–37 d) and 14.5 days (IQR, 7–29 d) ($p = 0.21$) and the median hospital-free days were 54.5 and 55.5 ($p = 0.68$), respectively.

Propensity Score Analyses

Early pleural drainage remained significantly associated with higher odds of having a MCID improvement in oxygenation at 24 hours after enrollment compared to baseline (OR, 2.4; 95% CI, 1.1–5.3; $p = 0.029$) after adjusting for the propensity score of having an early drainage procedure. The propensity score was not significantly associated with the MCID improvement in oxygenation ($p = 0.93$). After adjusting for the propensity score of the decision to use early drainage, early drainage also remained associated with

TABLE 3. Predictors of Successful Drainage (Achieving Clinical Benefit Without Any Adverse Event, $n = 107$[a])

Predictors	Predictor Cut Point[b]	Univariable OR (95% CI); *p*	Multivariable OR (95% CI); *p*
Early drainage (within 24 hr of diagnosis)	Yes (vs no)	1.42 (1.05–2.11); **0.03**	1.74 (1.02–3.60); **0.04**
Age, yr	≥ 60 (vs < 60)	1.52 (0.94–2.73); 0.13	0.82 (0.40–1.06); 0.11
Gender	Male (vs female)	1.10 (0.82–1.58); 0.65	NA
Pao_2:Fio_2 ratio, mm Hg (at baseline)	≥ 220 (vs < 220)	0.86 (0.58–1.39); 0.63	NA
Positive pressure (including noninvasive ventilation and continuous positive airway pressure)	Yes (vs no)	0.77 (0.30–1.95); 0.58	NA
Acute Physiology and Chronic Health Evaluation II score	≥ 21 (vs < 21)	0.78 (0.58–1.13); 0.19	0.85 (0.57–1.06); 0.20
Bilateral effusion	Yes (vs no)	0.71 (0.41–1.31); 0.34	NA
Depth of pleural effusion on ultrasound scan, cm	≥ 4.4 (vs < 4.4)	1.33 (0.87–2.24); 0.28	NA
Suspected pleural infection	Yes (vs no)	1.27 (0.82–2.14); 0.39	NA
Suspected pneumonia	Yes or no	0.89 (0.58–1.47); 0.65	NA

NA = not applicable, OR = odds ratio.

[a]Seventy-six early drainage patients, four of whom underwent bilateral drainage at the same time, and 27 late drainage patients.

[b]Median values of the 136 patients who had the pleural effusion drained were used to set the cut points to dichotomize continuous predictors. OR > 1 means drainage was more likely to be successful.

Boldface values are $p < 0.05$ to indicate statistical significance.

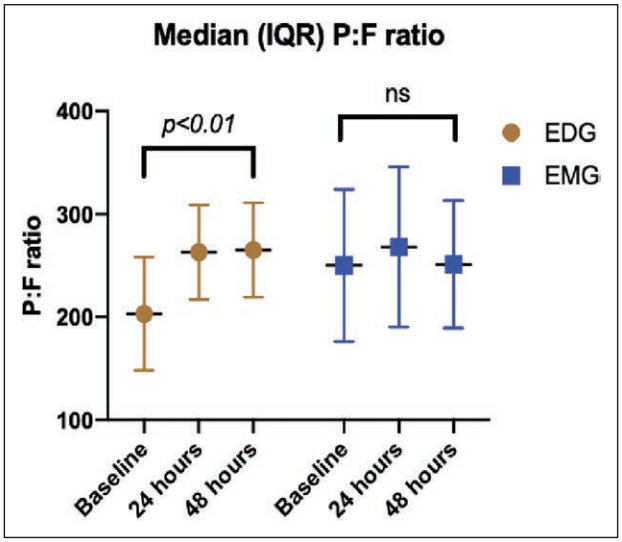

Figure 2. Pao_2:FIo_2 (P/F) ratio increased significantly from baseline at 24 and 48 hr in the early drainage group (EDG). There was no change in the expectant management group (EMG). *p* values were < 0.01 at 24 and 48 hr in the EDG and not significant (ns) at any timepoint in the EMG. IQR = interquartile range.

an increased likelihood of drainage success without any adverse event compared with delayed drainage after failed expectant management (OR, 2.7; 95% CI, 1.1–7.1; $p = 0.049$).

DISCUSSION

This study is the first to have prospectively examined treatment of clinically significant PLEFF, comparing early pleural drainage with expectant management, the treatment option chosen in two-thirds of patients. The study population was pragmatically selected to ensure generalizable outcomes and baseline characteristics were consistent with the expected severity of illness and gender balance.

Patients selected for drainage had clinically significant improvements in P:F ratio at 24 and 48 hours compared with baseline, whereas those undergoing expectant management did not. Drainage improved diagnostic accuracy in 77% of patients and 52% had a change in primary diagnosis with 19% resulting in completely unsuspected diagnoses. In addition, 58% of drainage procedures resulted in major changes to patient treatment. These benefits were without apparent cost in terms of SAEs compared with expectant management and the only significant predictor of successful drainage without an adverse event in patients undergoing a drainage procedure was the decision to drain within 24 hours of diagnosis. There were no differences, however, in other clinical outcomes such as ability to extubate or wean off NIV, nor ICU or hospital length of stay or crude mortality rates.

In this clinician-choice, nonrandomized study, it is impossible to say whether early drainage in the expectantly managed group would have resulted in the same benefits since it is possible that clinicians were able to select those patients that were able to improve with drainage and the treatment groups were not entirely matched at baseline. Factors associated with the decision to drain early were increased effusion depth, positive-pressure ventilation, and suspected pleural infection, all reasonable clinical reasons for opting for drainage—a treatment that is safer in the presence of large PLEFF, that seems to improve oxygenation and is the optimal treatment for pleural infection. However, when correcting for these factors with propensity score analyses these were not associated with clinically significant improvements in oxygenation or safe drainage success.

Nevertheless, the inaccuracy of presumptive diagnoses in large numbers of patients and the failure of reasonable influencers of patient selection to predict successful treatment raise questions over whether early drainage may have improved outcomes in patients that were expectantly managed. Randomized studies are now needed to ascertain whether this is the case and to develop guidelines that can improve treatment selection.

British Thoracic Society (BTS) guidelines suggest that symptom-inducing unilateral effusions or bilateral effusions that persist despite treating likely transudative causes should be sampled (19). However, these guidelines are not based on the clinical context of critical illness during which development of PLEFF is common and a drainage procedure will have a different risk to benefit ratio compared with patients in the outpatient clinics or hospital wards (18, 20). Intensive care populations are increasingly complex with multiple interacting pathologies and comorbidities (21, 22). Individual patients can also have multiple, significant etiologies concurrently (23). In addition, symptomatology is almost useless to guide the need for drainage in critically ill patients especially when they are sedated and ventilated. In this study, the presence of bilateral vs unilateral effusions had no impact on treatment success, assumption of the nature of the effusion without drainage was shown to be inaccurate and delayed drainage was less likely to be successful, so the utility of the BTS guidelines in our population is questionable.

Larger volume PLEFFs have long been thought to offer the best chance of drainage success and estimated volume has been used to determine clinical significance. Balik et al (24) proposed a formula for calculating pleural fluid volume in critical care patients that is widely used, but the authors state their formula may not be "clinically important" below 17 mm (340 mL). Lichtenstein et al (25) proposed a minimal interpleural distance of 1.5 cm over greater than or equal to 3 intercostal spaces as a safe cutoff for attempting drainage, and Soni et al (26) described five essential structures that must be visible on ultrasound to safely diagnose PLEFF and guide pleural drainage in critically ill patients. However, using these ultrasound criteria alone to select patients who may benefit from drainage has clear drawbacks. Loculated parapneumonic effusions, for example, may only meet depth criteria at one intercostal space but may yet yield significant benefits with drainage (19).

This study has limitations. As previously highlighted, it was nonrandomized and while identified selection biases did not appear to influence the main outcomes, unidentified factors may have confounded the results. Second, although one study suggested a prevalence of PLEFF of 62% in the critical care population and another that 8% were suitable for thoracentesis, in this study only 26% developed evident PLEFF on chest radiograph and 3% PLEFF that met ultrasound size criteria and was considered significant by treating clinicians (2, 10). Ultrasonography was reserved for suspected cases, and chest radiography alone can miss even a large-volume PLEFF, so it is possible that some patients with clinically significant PLEFF were missed in the screening process. Third, the primary outcome of oxygenation has not been shown to be a successful surrogate of

clinical outcomes in critical care research. However, this observational cohort study was designed in the absence of quality data testing any other well validated and generalizable outcomes, with the intent of generating enough data on safety and physiologic benefit to be able to safely design large randomized studies, powered to answer important clinical questions. The MCID of a 20% increase in P:F ratio has previously been considered clinically significant in itself (18) and corresponds to weaning the FIO_2, for example, from 0.5 to 0.42 to keep a PaO_2 of ~70 mm Hg which the investigators believe to be of potential clinical significance justifying further investigation.

CONCLUSIONS

Clinically significant PLEFF—defined by a depth greater than or equal to 2 cm in a drainable location on thoracic ultrasound together with a potential adverse effect on patient progress—was detected in 3.1% of patients admitted to intensive care, and one third of them were managed with early drainage. In selected patients without contraindications, early drainage resulted in improved oxygenation, diagnostic accuracy, and treatment optimization, without apparent SAEs compared with expectant management. Our results support further evaluation by adequately powered randomized controlled trials of when, and in whom, clinically significant PLEFF should be drained.

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Dr. Fysh is the guarantor of the article. Drs. Fysh, Ho, and Lee conceived and designed the study. Drs. Fysh, Litton, Wibrow, and Ho were involved as center coordinators. Drs. Fysh, Smallbone, Mattock, McCloskey, and Wibrow performed data collection. Drs. Fysh and Ho performed statistical analyses. All authors were involved in article drafting, revision, and final approval of the article.

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REFERENCES

1. Azoulay E: Pleural effusions in the intensive care unit. *Curr Opin Pulm Med* 2003; 9:291–297
2. Mattison LE, Coppage L, Alderman DF, et al: Pleural effusions in the medical ICU: Prevalence, causes, and clinical implications. *Chest* 1997; 111:1018–1023
3. Azoulay E, Fartoukh M, Similowski T, et al: Routine exploratory thoracentesis in ICU patients with pleural effusions: Results of a French questionnaire study. *J Crit Care* 2001; 16:98–101
4. Maslove DM, Chen BT, Wang H, et al: The diagnosis and management of pleural effusions in the ICU. *J Intensive Care Med* 2013; 28:24–36
5. Ball J: A pseudo-rumsfeldian approach to pleural effusions in mechanically ventilated patients. *Crit Care* 2011; 15:132
6. Mayo PH, Goltz HR, Tafreshi M, et al: Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. *Chest* 2004; 125:1059–1062
7. Wrightson JM, Fysh E, Maskell NA, et al: Risk reduction in pleural procedures: Sonography, simulation and supervision. *Curr Opin Pulm Med* 2010; 16:340–350
8. Cantey EP, Walter JM, Corbridge T, et al: Complications of thoracentesis: Incidence, risk factors, and strategies for prevention. *Curr Opin Pulm Med* 2016; 22:378–385
9. Fysh ET, Yogendran A, Rosenstengel A, et al: Pleural infections in intensive care. *Chest* 2016; 150:1419–1420
10. Fartoukh M, Azoulay E, Galliot R, et al: Clinically documented pleural effusions in medical ICU patients: How useful is routine thoracentesis? *Chest* 2002; 121:178–184
11. Umbrello M, Mistraletti G, Galimberti A, et al: Drainage of pleural effusion improves diaphragmatic function in mechanically ventilated patients. *Crit Care Resusc* 2017; 19:64–70
12. Dres M, Roux D, Pham T, et al: Prevalence and impact on weaning of pleural effusion at the time of liberation from mechanical ventilation: A multicenter prospective observational study. *Anesthesiology* 2017; 126:1107–1115
13. Goligher EC, Leis JA, Fowler RA, et al: Utility and safety of draining pleural effusions in mechanically ventilated patients: A systematic review and meta-analysis. *Crit Care* 2011; 15:R46
14. Xirouchaki N, Magkanas E, Vaporidi K, et al: Lung ultrasound in critically ill patients: Comparison with bedside chest radiography. *Intensive Care Med* 2011; 37:1488–1493
15. Brogi E, Gargani L, Bignami E, et al: Thoracic ultrasound for pleural effusion in the intensive care unit: A narrative review from diagnosis to treatment. *Crit Care* 2017; 21:325
16. Gryminski J, Krakówka P, Lypacewicz G: The diagnosis of pleural effusion by ultrasonic and radiologic techniques. *Chest* 1976; 70:33–37
17. Havelock T, Teoh R, Laws D: BTS guidelines for pleural procedures – pleural aspiration, chest drain insertion and thoracic ultrasound. *Thorax* 2010; 65:i61–i76
18. Walden AP, Jones QC, Matsa R, et al: Pleural effusions on the intensive care unit; hidden morbidity with therapeutic potential. *Respirology* 2013; 18:246–254
19. Hooper C, Lee YCG, Maskell N: Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010; 65(Suppl 2):ii4–ii17
20. Mayo PH, Doelken P: Pleural ultrasonography. *Clin Chest Med* 2006; 27:215–227
21. Creagh-Brown B, Green S: Increasing age of patients admitted to intensive care, and association between increased age and greater risk of post-ICU death. *Crit Care* 2014; 18(Suppl 1):P56
22. Azoulay E; Groupe de Recherche en Réanimation Onco-Hématologique (Grrr-OH): A new standard of care for critically ill patients with cancer. *Chest* 2014; 146:241–244
23. Fysh ETH, Shrestha RL, Wood BA, et al: A pleural effusion of multiple causes. *Chest* 2012; 141:1094–1097
24. Balik M, Plasil P, Waldauf P, et al: Ultrasound estimation of volume of pleural fluid in mechanically ventilated patients. *Intensive Care Med* 2006; 32:318–21
25. Lichtenstein D, Hulot JS, Rabiller A, et al: Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. *Intensive Care Med* 1999; 25:955–958
26. Soni NJ, Franco R, Velez MI, et al: Ultrasound in the diagnosis and management of pleural effusions. *J Hosp Med* 2015; 10:811–816