

# Risk Factors for Mortality Among Mechanically Ventilated Patients Requiring Pleural Drainage

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**Purpose:** Pleural effusions are common in mechanically ventilated patients. However, the risk factors for poor outcomes after pleural drainage are poorly understood. This study aimed to identify factors that were associated with in-hospital mortality among mechanically ventilated patients who underwent pleural drainage.

**Methods:** This retrospective study evaluated 82 consecutive patients who required chest tubes during mechanical ventilation at two university-affiliated hospitals in Korea between January 2015 and June 2020.

**Results:** The median age was 76 years (interquartile range [IQR]: 64–84 years), and the median SOFA score was 11 (IQR: 7–13). Intensive care unit admission was most commonly because of pneumonia (n = 44, 53.7%) and 60 patients (77.9%) had exudative pleural effusions. During pleural drainage, the PaO<sub>2</sub>/FiO<sub>2</sub> was 210 (IQR: 153–253); 45 patients (54.9%) were receiving vasopressors, and 31 patients (37.8%) were receiving continuous renal replacement therapy (CRRT). The multivariable regression analysis revealed that poor overall survival was independently associated with receiving vasopressors (adjusted hazard ratio [aHR]: 3.81, 95% confidence interval [CI]: 1.65–8.81, p = 0.002) and receiving CRRT (aHR: 5.48, 95% CI: 2.29–13.12, p < 0.001). The PaO<sub>2</sub>/FiO<sub>2</sub> ratio was relatively stable through the third day of pleural drainage among survivors but decreased among non-survivors. The vasopressor dose decreased among survivors but remained relatively stable among non-survivors.

**Conclusion:** Among mechanically ventilated patients who required pleural drainage, use of vasopressors and CRRT was significantly associated with in-hospital mortality. On the third day of pleural drainage, the changes in PaO<sub>2</sub>/FiO<sub>2</sub> and vasopressor dose were associated with in-hospital mortality.

**Keywords:** pleural fluid, drainage, mechanical ventilation, mortality

## Introduction

Pleural effusions are common in patients who are treated in the intensive care unit (ICU). For example, a single-center study revealed that 27% of patients who were admitted to the ICU had pleural effusions that were identified via chest radiography.<sup>1</sup> Another large observational study revealed that 7.7% of critically ill patients had pleural effusions.<sup>2</sup> Furthermore, among critically ill patients, patients with pleural effusions had a higher rate of in-hospital mortality than patients without effusions (38.7% vs 31.3%).<sup>2</sup> Pleural fluid accumulation occurs when there is an imbalance in fluid production and drainage, which can be aggravated by mechanical ventilation (MV).<sup>3</sup> The increase in pleural fluid leads to restrictive ventilatory defects that can cause hypoxemia,<sup>3–6</sup> and is associated with various hemodynamic parameters.<sup>7</sup>

Some studies have evaluated the effects of pleural effusion drainage on oxygenation, respiratory mechanics, diaphragm function, and hemodynamics during MV. Razazi et al suggested that a large amount of pleural drainage (>500 mL) was associated with increases in respiratory system compliance and oxygenation, as the PaO<sub>2</sub>/FiO<sub>2</sub> ratio increased from 191 to 250 at 24 h after effusion drainage.<sup>8</sup> Another observational study revealed that moderate-to-large pleural effusion was associated with failure to achieve MV weaning.<sup>9</sup> Umbrello et al also reported that draining pleural effusion during MV weaning helps improve diaphragmatic function.<sup>10</sup> However, it is unclear whether these positive effects of pleural drainage are associated with survival among mechanically ventilated patients, and remains poorly

understood the risk factor for mortality. Therefore, this study aimed to identify factors that were associated with in-hospital mortality among mechanically ventilated patients who underwent pleural drainage.

## Methods

### Study Design

This retrospective study evaluated 82 consecutive adult patients ( $\geq 18$  years old) who required chest tubes during MV at two university-affiliated tertiary hospitals in the Republic of Korea between January 1, 2015 and December 31, 2020. Pleural effusions were identified based on daily chest radiography screening and were confirmed by a board-certified pulmonologist using ultrasonography. The decision to perform pleural effusion drainage was made by the pulmonologist and attending physician according to the following conditions: for patients with large pleural effusion ( $\geq 1/2$  hemithorax), or for patients with small to moderate effusion ( $> 10$  mm and  $< 1/2$  hemithorax) for which diuretics or renal replacement therapy (RRT) are ineffective.<sup>11</sup> To yield minimal safety margin, pleural drainage was attempted for patients with maximal inter-pleural separation of  $>20$  mm indicated by ultrasonography.<sup>12</sup> Patients were excluded if they had undergone pleural drainage before or after the MV. The retrospective study protocol was approved by the institutional review board of Chung-Ang University Hospital (2011-010-19341), which waived the requirement for informed consent.

### Data Collection

The patients' electronic medical records were searched to collect the following data from the time of the pleural drainage: age, sex, body mass index, Sequential Organ Failure Assessment (SOFA) score, Charlson comorbidity index, comorbidities, reasons for admission to the medical intensive care unit (MICU), duration of hospital stay, duration of MICU stay, duration of MV, tracheostomy, vital signs, ventilator parameters ( $\text{FiO}_2$ , positive end-expiratory pressure [PEEP], tidal volume, and peak inspiratory pressure), arterial blood gas parameters (pH,  $\text{PaCO}_2$ ,  $\text{PaO}_2$ ,  $\text{HCO}_3$ , and  $\text{SaO}_2$ ),  $\text{PaO}_2/\text{FiO}_2$  ratio, and laboratory results (concentrations of protein, albumin, lactate dehydrogenase [LDH], as well as leukocyte count). The  $\text{PaO}_2/\text{FiO}_2$  ratio and vasopressor dose were recorded on days 1–3 before the pleural fluid drainage, at the time of drainage (baseline), and on days 1–3 after the drainage.

The characteristics of the pleural effusion and intervention were: time from MV to drainage catheter insertion, duration of pleural drainage, need for vasopressors or continuous renal replacement therapy (CRRT), laterality (right, left, or bilateral), 24-h drainage volume, type of pleural drainage (percutaneous pigtail drainage or surgical thoracostomy), operator (interventional radiologist, cardiac surgeon, intensivist, or emergency medicine doctor), location (angiography room, MICU, or emergency room), complications (pneumothorax and subcutaneous emphysema), and pleural effusion findings (appearance, laboratory findings [pH, leukocyte and erythrocyte counts, proportion of neutrophils, and concentrations of protein, albumin, glucose, and LDH], and bacterial smear/culture findings).

Pleural effusions were classified as exudates or transudates using Light's criteria.<sup>13</sup> Exudative pleural effusions fulfilled at least one of the following criteria and transudative effusions fulfilled none of the criteria: ratio of pleural-fluid protein to serum protein  $>0.5$ , ratio of pleural fluid LDH to serum LDH concentration  $>0.6$ , and pleural-fluid LDH concentration of  $>2/3$  the upper limit of normal for serum. Parapneumonic effusion was defined as any pleural effusion secondary to pneumonia or lung abscess, which is characterized as an exudate with a predominance of neutrophils.<sup>14</sup> Parapneumonic effusion was considered complicated effusion if the pleural fluid pH was  $<7.2$ , the glucose concentration was  $<60$  mg/dL, or the LDH concentration was  $>3\times$  the upper limit of normal for serum.<sup>14,15</sup> Empyema was defined based on the presence of bacteria or pus in the pleural space. The vasopressor doses were calculated using the following equation: norepinephrine equivalents = norepinephrine + epinephrine + (phenylephrine/10) + (dopamine/100) + (metaraminol/8) + (vasopressin $\times 2.5$ ) + (angiotensin II $\times 10$ ).<sup>16</sup>

### Statistical Analyses

Categorical variables are presented as numbers (%) and were compared using the Pearson's chi-squared test or Fisher's exact test. Continuous variables are presented as median (interquartile range [IQR]) or mean  $\pm$  standard deviation and were compared using the Student's *t* test or the Mann–Whitney *U*-test. Univariate and multivariable Cox proportional

hazard regression analyses were performed to identify factors that were significantly associated with cumulative survival. Significant variables in the univariate analyses ( $p < 0.05$ ) and clinically significant variables were entered into the multivariable analysis, with the results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Kaplan-Meier curves for cumulative survival were created and compared using the Log rank test. The effects of pleural drainage on oxygenation and hemodynamics were evaluated using one-way analysis of variance for repeated measures to compare the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and vasopressor dose among survivors and non-survivors. Inter-group comparisons at each time point were performed using the paired-samples Student *t* test. Differences were considered statistically significant at  $p$ -values of  $< 0.05$  and all analyses were performed using SPSS software (version 26.0; IBM Corporation, Armonk, NY, USA).

## Results

The study included 82 consecutive patients who underwent pleural drainage catheter insertion during MV. The baseline patient characteristics are shown in Table 1. The median age was 76 years (IQR: 64–84 years) and 52 patients (63.42%) were male. The median SOFA score was 11 (IQR: 7–13) and 90.2% of the patients had comorbidities. The common reasons for admission to the ICU were pneumonia ( $n=44$ , 53.7%), cardiovascular disorders ( $n=14$ , 17.1%), and post-cardiac arrest care ( $n=10$ , 12.2%). The median duration of ICU stay was 42 days (IQR: 16–44 days) and tracheostomy was performed in 39 patients (47.6%). The median FiO<sub>2</sub> was 0.40 (IQR: 0.35–0.50) with a median PEEP of 8 cmH<sub>2</sub>O (IQR: 5–8 cmH<sub>2</sub>O) (Table 2). The median PaO<sub>2</sub> was 85 mmHg (IQR: 73–98 mmHg) and the median PaO<sub>2</sub>/FiO<sub>2</sub> was 210 (IQR: 153–253).

**Table 1** Baseline Patient Characteristics

Variables	Total (n=82)	Survivors (n=40)	Non-Survivors (n=42)	P-value
Age (years)	76 (64–84)	77 (64–85)	73 (64–82)	0.263
Male sex	52 (63.4)	25 (62.5)	27 (64.3)	1.000
Body mass index (kg/m <sup>2</sup> )	20.7 (18.7–24.8)	22.0 (19.5–25.2)	20.0 (18.3–23.5)	0.092
SOFA score	11 (7–13)	10 (6–14)	11 (8–13)	0.421
Charlson comorbidity index	5 (4–7)	6 (4–7)	5 (3–8)	0.737
Comorbidities	74 (90.2)	35 (87.5)	39 (92.9)	0.477
Diabetes mellitus	31 (37.8)	13 (32.5)	18 (42.9)	0.334
Hypertension	44 (53.7)	22 (55.0)	22 (52.4)	0.812
Chronic lung disease	10 (12.2)	5 (12.5)	5 (11.9)	1.000
Chronic kidney disease	11 (13.4)	5 (12.5)	6 (14.3)	0.813
Chronic liver disease	5 (6.1)	3 (7.5)	2 (4.8)	0.672
Cardiovascular disorders	22 (26.8)	13 (32.5)	9 (21.4)	0.258
Neurological disorders	23 (28.0)	14 (35.0)	9 (21.4)	0.262
Malignancy	21 (25.6)	9 (22.5)	12 (28.6)	0.529
Reasons for ICU admission				0.411
Pneumonia	44 (53.7)	22 (55.0)	22 (52.4)	
Sepsis	5 (6.1)	1 (2.5)	4 (9.5)	
Respiratory disorders	7 (8.5)	5 (12.5)	2 (4.8)	
Cardiovascular disorders	14 (17.1)	7 (17.5)	7 (16.7)	
Post-cardiac arrest care	10 (12.2)	5 (12.5)	5 (11.9)	
Neurological disorders	2 (2.4)	0 (0.0)	2 (4.8)	
Length of stay, days	42 (25–74)	53 (35–87)	33 (22–53)	0.006
ICU stay, days	25 (16–44)	25 (14–46)	27 (18–43)	0.553
Duration of MV, days	21 (11–40)	19 (8–41)	24 (15–39)	0.172
Tracheostomy	39 (47.6)	21 (52.5)	18 (42.9)	0.507

**Note:** Values are presented as median (interquartile range) or number (%).

**Abbreviations:** SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; MV, mechanical ventilation.

**Table 2** Ventilator Parameters and Laboratory Findings at the Pleural Effusion Drainage

Variables	Total (n=82)	Survivors (n=40)	Non-Survivors (n=42)	P-value
Vital signs				
MAP (mmHg)	79 (72–89)	79 (72–91)	79 (72–87)	0.784
Heart rate (/min)	91 (76–104)	86 (75–102)	96 (79–108)	0.161
Respiratory rate (/min)	23 (20–25)	23 (20–24)	22 (20–27)	0.724
Body temperature (°C)	36.6 (36.2–37.1)	36.9 (36.5–37.2)	36.4 (36.1–36.8)	0.001
Oxygen saturation (%)	98 (96–100)	99 (96–100)	98 (96–100)	0.277
Ventilation parameters				
FiO <sub>2</sub>	0.40 (0.35–0.50)	0.43 (0.35–0.50)	0.40 (0.40–0.53)	0.579
PEEP (cmH <sub>2</sub> O)	8 (5–8)	7 (5–9)	8 (6–8)	0.806
Tidal volume (mL)	400 (330–458)	394 (326–459)	400 (330–458)	0.788
Peak inspiratory pressure (cmH <sub>2</sub> O)	19 (16–23)	19 (15–23)	20 (16–24)	0.507
Arterial blood gases				
pH	7.41 (7.36–7.45)	7.44 (7.39–7.45)	7.39 (7.35–7.44)	0.140
PaCO <sub>2</sub> (mmHg)	40 (35–45)	39 (36–49)	41 (34–44)	0.565
PaO <sub>2</sub> (mmHg)	85 (73–98)	85 (74–97)	84 (73–105)	0.770
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	24 (21–28)	25 (23–31)	23 (21–27)	0.063
SaO <sub>2</sub> (%)	96 (95–98)	96 (95–98)	96 (94–98)	0.824
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	210 (153–253)	210 (156–253)	211 (144–253)	0.919
Laboratory results				
White blood cells (×10 <sup>9</sup> /L)	11.4 (7.3–15.7)	10.0 (6.7–14.2)	12.5 (8.5–16.6)	0.109
Hemoglobin (g/dL)	9.0 (8.2–10.1)	9.0 (7.9–9.9)	9.0 (8.3–10.2)	0.183
Platelets (×10 <sup>9</sup> /L)	149 (64–210)	169 (107–247)	88 (57–161)	0.001
Total protein (g/dL)	5.3 (4.6–5.7)	5.4 (4.7–5.9)	5.0 (4.6–5.6)	0.061
Albumin (g/dL)	2.4 (2.1–2.7)	2.4 (2.1–2.7)	2.4 (2.0–2.7)	0.331
Total bilirubin (mg/dL)	0.7 (0.5–1.4)	0.6 (0.3–0.9)	1.0 (0.6–2.5)	0.003
Aspartate aminotransferase (IU/L)	37 (23–96)	29 (22–64)	47 (31–171)	0.017
Alanine aminotransferase (IU/L)	28 (13–53)	26 (11–45)	30 (14–90)	0.371
Blood urea nitrogen (mg/dL)	27 (18–38)	25 (18–38)	28 (17–41)	0.766
Serum creatinine (mg/dL)	1.01 (0.63–1.59)	1.05 (0.64–1.59)	0.98 (0.63–1.60)	0.886
Serum sodium (mmol/L)	138 (134–141)	138 (134–142)	138 (134–140)	0.488
Serum potassium (mmol/L)	3.9 (3.6–4.2)	3.8 (3.7–4.2)	4.0 (3.5–4.3)	0.933
C-reactive protein (mg/dL)	101 (47–172)	72 (45–120)	130 (67–198)	0.018
Lactic dehydrogenase (IU/L)	306 (233–379)	300 (233–345)	308 (231–580)	0.253

**Note:** Values are presented as median (interquartile range) or number (%).

**Abbreviations:** MAP, mean arterial pressure; FiO<sub>2</sub>, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; HCO<sub>3</sub><sup>-</sup>, bicarbonate; SaO<sub>2</sub>, oxygen saturation.

The pleural drainage-related variables and pleural effusion findings are shown in Table 3. At the time of pleural drainage, 45 patients (54.9%) were receiving vasopressors and 31 patients (37.8%) were receiving CRRT. The median 24-h drainage volume was 1000 mL (IQR: 644–1463 mL). Procedure-related complications occurred in 3 patients (3.7%), which involved pneumothorax in 2 patients and subcutaneous emphysema in 1 patient. The effusions were classified as exudative in 60 patients (77.9%) and complicated pleural effusions in 17 patients (22.1%). Relative to survivors, non-survivors were significantly more likely to receive vasopressors (66.7% vs 42.5%,  $p=0.028$ ) and CRRT (59.5% vs 15.0%,  $p<0.001$ ).

Table 4 shows the multivariable regression analysis of factors that were associated with death. Significantly shorter overall survival was independently associated with use of vasopressors (aHR: 3.81, 95% CI: 1.65–8.81,  $p=0.002$ ) and CRRT (aHR: 5.48, 95% CI: 2.29–13.12,  $p<0.001$ ). Figure 1 shows the Kaplan-Meier curves, which revealed that non-use of CRRT was associated with significantly longer median overall survival, relative to CRRT use (non-CRRT: 147 days [95% CI: 62–232 days] vs CRRT: 36 days [95% CI: 27–45 days],  $p<0.001$ ). Furthermore, transudative effusion

**Table 3** Factors Related to Pleural Drainage and Characteristics of Pleural Effusion

Variables	Total (n=82)	Survivors (n=40)	Non-Survivors (n=42)	P-value
Time from MV to pleural drainage (days)	8 (3–17)	8 (3–12)	8 (3–26)	0.322
Duration of pleural drainage (days)	14 (8–21)	17 (7–28)	13 (8–17)	0.129
Need for vasopressors	45 (54.9)	17 (42.5)	28 (66.7)	0.028
CRRT	31 (37.8)	6 (15.0)	25 (59.5)	<0.001
Laterality of pleural drainage				0.818
Right	32 (39.0)	15 (37.5)	17 (40.5)	
Left	22 (26.8)	12 (30.0)	10 (23.8)	
Bilateral	28 (34.1)	13 (32.5)	15 (35.7)	
24-h drainage volume (mL)	1000 (644–1463)	995 (618–1353)	1020 (665–1533)	0.420
Type of pleural drainage				0.474
Percutaneous pigtail drainage	70 (85.4)	33 (47.1)	37 (52.9)	
Surgical thoracostomy	12 (14.6)	7 (58.3)	5 (41.7)	
Operator				0.622
Interventional radiologist	50 (61.7)	23 (59.0)	27 (64.3)	
Cardiac surgeon	12 (14.8)	7 (17.9)	5 (11.9)	
Intensivist	18 (22.2)	8 (20.5)	10 (23.8)	
Emergency medicine doctor	1 (1.2)	1 (2.6)	0 (0.0)	
Location				0.325
Angiography room	50 (61.7)	23 (59.0)	27 (64.3)	
ICU	29 (35.8)	14 (35.9)	15 (35.7)	
Emergency room	2 (2.5)	2 (5.1)	0 (0.0)	
Complications				0.227
Pneumothorax	2 (2.4)	0 (0)	2 (4.8)	
Subcutaneous emphysema	1 (1.2)	1 (2.5)	0 (0)	
Exudate vs transudate <sup>†</sup>				0.151
Exudate	60 (77.9)	27 (71.1)	33 (84.6)	
Transudate	17 (22.1)	11 (28.9)	6 (15.4)	
Complicated pleural effusion <sup>‡</sup>	17 (22.1)	6 (15.8)	11 (28.2)	0.189
Empyema	6 (7.9)	1 (2.7)	5 (12.8)	0.201
Pleural effusion findings				
pH	7.38 (7.18–7.62)	7.42 (7.22–7.68)	7.36 (7.13–7.56)	0.234
RBCs (mm <sup>3</sup> )	3000 (1000–8425)	2275 (1000–7558)	3300 (1000–27,000)	0.504
WBC (mm <sup>3</sup> )	367 (114–863)	369 (89–1434)	367 (151–620)	0.951
Neutrophils (%)	42 (15–79)	31 (15–73)	53 (14–90)	0.204
Lymphocyte (%)	26 (11–51)	29 (13–69)	20 (8–42)	0.142
Protein (g/dL)	2.4 (1.5–3.2)	2.4 (1.5–3.6)	2.3 (1.9–3.1)	0.643
Albumin (g/dL)	1.2 (0.8–1.6)	1.3 (0.9–1.8)	1.2 (0.8–1.4)	0.327
LDH (IU/L)	192 (127–345)	160 (113–270)	253 (139–511)	0.066
Glucose (mg/dL)	140 (110–175)	138 (120–175)	142 (100–176)	0.585
Pleural fluid/serum protein ratio	0.53 (0.36–0.70)	0.56 (0.30–0.68)	0.51 (0.41–0.74)	0.840

**Notes:** Values are presented as median (interquartile range) or number (%). <sup>†</sup>Exudate fulfilled at least one of the following criteria and transudate did not fulfill any of the criteria: a >0.5 ratio of pleural-fluid protein to serum protein, a >0.6 ratio of pleural fluid LDH to serum LDH, and pleural-fluid LDH concentration >2/3 the upper limit of normal for serum. <sup>‡</sup>Parapneumonic effusion is considered complicated effusion if the pleural fluid pH is <7.2, the glucose concentration is <60 mg/dL, or the LDH concentration is >3× the upper limit of normal for serum.

**Abbreviations:** MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ICU, intensive care unit; RBC, red blood cell; WBC, white blood cell; LDH, lactate dehydrogenase.

was associated with significantly longer median overall survival, relative to exudative effusion (transudative: 85 days [95% CI: 0–314 days] vs exudative: 24 days [95% CI: 6–100 days],  $p=0.039$ ).

Figure 2 shows the changes in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and vasopressor dose before and after pleural drainage (Supplementary Materials Tables S1 and S2). After 24 h of pleural drainage, the mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio had risen from 206 to 245 ( $p<0.001$ , Figure 2A) and the vasopressor dose had decreased from 0.10 µg/kg/min to 0.07 µg/kg/min

**Table 4** Univariate and Multivariable Regression Analyses of Factors Associated with Death

Variables	Univariate HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Age (years)	0.99 (0.97–1.01)	0.166		
Sex		0.475		0.050
Male	Reference		Reference	
Female	0.79 (0.40–1.52)		0.43 (0.19–1.00)	
Body mass index (kg/m <sup>2</sup> )	0.96 (0.89–1.04)	0.313		
SOFA score	1.04 (0.96–1.12)	0.362		
Charlson comorbidity index	1.06 (0.95–1.19)	0.287		
Tracheostomy	0.35 (0.18–0.68)	0.002		
Reasons for ICU admission		0.410		0.024
Pneumonia	Reference		Reference	
Sepsis	0.35 (0.12–1.03)		0.32 (0.10–1.08)	
Respiratory disorders	0.56 (0.15–2.11)		1.77 (0.36–8.66)	
Cardiovascular disorders	0.48 (0.14–1.64)		0.15 (0.03–0.66)	
Post-cardiac arrest care	0.20 (0.04–1.14)		0.53 (0.07–3.86)	
Neurological disorders	0.45 (0.08–2.68)		0.79 (0.11–5.59)	
Exudate vs transudate		0.048		
Transudate	Reference			
Exudate	2.62 (1.01–6.80)			
PaO <sub>2</sub> /FiO <sub>2</sub> ratio		0.728		
>200	Reference			
≤200	0.78 (0.40–1.51)			
≤100	1.04 (0.36–3.02)			
Vasopressors		0.003		0.002
No	Reference		Reference	
Yes	2.78 (1.41–5.47)		3.81 (1.65–8.81)	
CRRT		<0.001		<0.001
No	Reference		Reference	
Yes	3.11 (1.66–5.81)		5.48 (2.29–13.12)	

**Notes:** The multivariable Cox regression analysis was adjusted for age, sex, body mass index, SOFA score, Charlson comorbidity index, tracheostomy, reasons for ICU admission, exudate vs transudate, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, vasopressors, and CRRT.

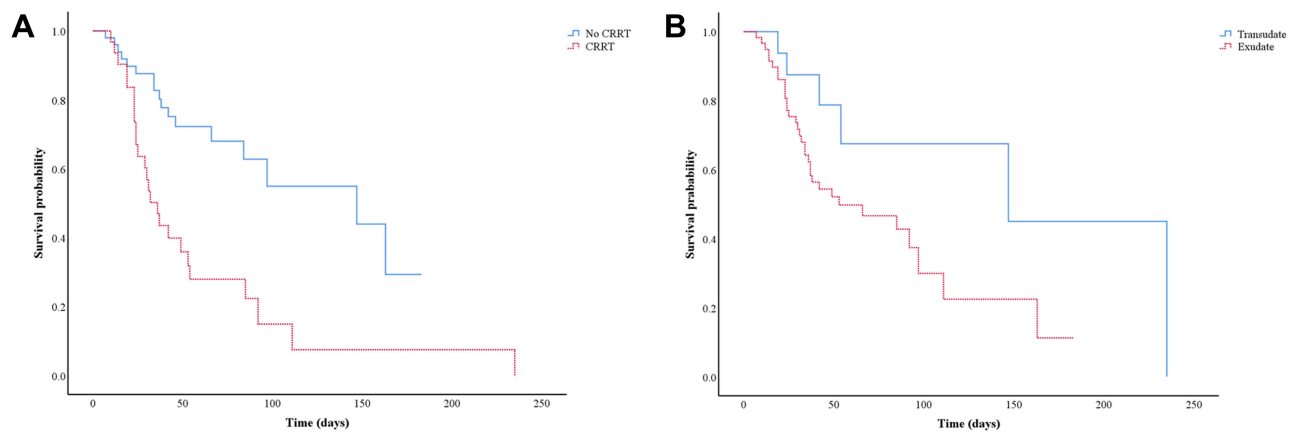
**Abbreviations:** HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; CRRT, continuous renal replacement therapy.

( $p=0.03$ , [Figure 2B](#)). After day 3 of pleural drainage, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio tended to decrease among non-survivors, relative to among survivors (survivors:  $263\pm 100$  vs non-survivors:  $229\pm 104$ ,  $p=0.102$ ) ([Figure 2C](#)). However, the vasopressor dose decreased among survivors but not among non-survivors (survivors:  $0.01\pm 0.04$   $\mu\text{g}/\text{kg}/\text{min}$  vs non-survivors:  $0.08\pm 0.18$   $\mu\text{g}/\text{kg}/\text{min}$ ,  $p=0.011$ ) ([Figure 2D](#)).

## Discussion

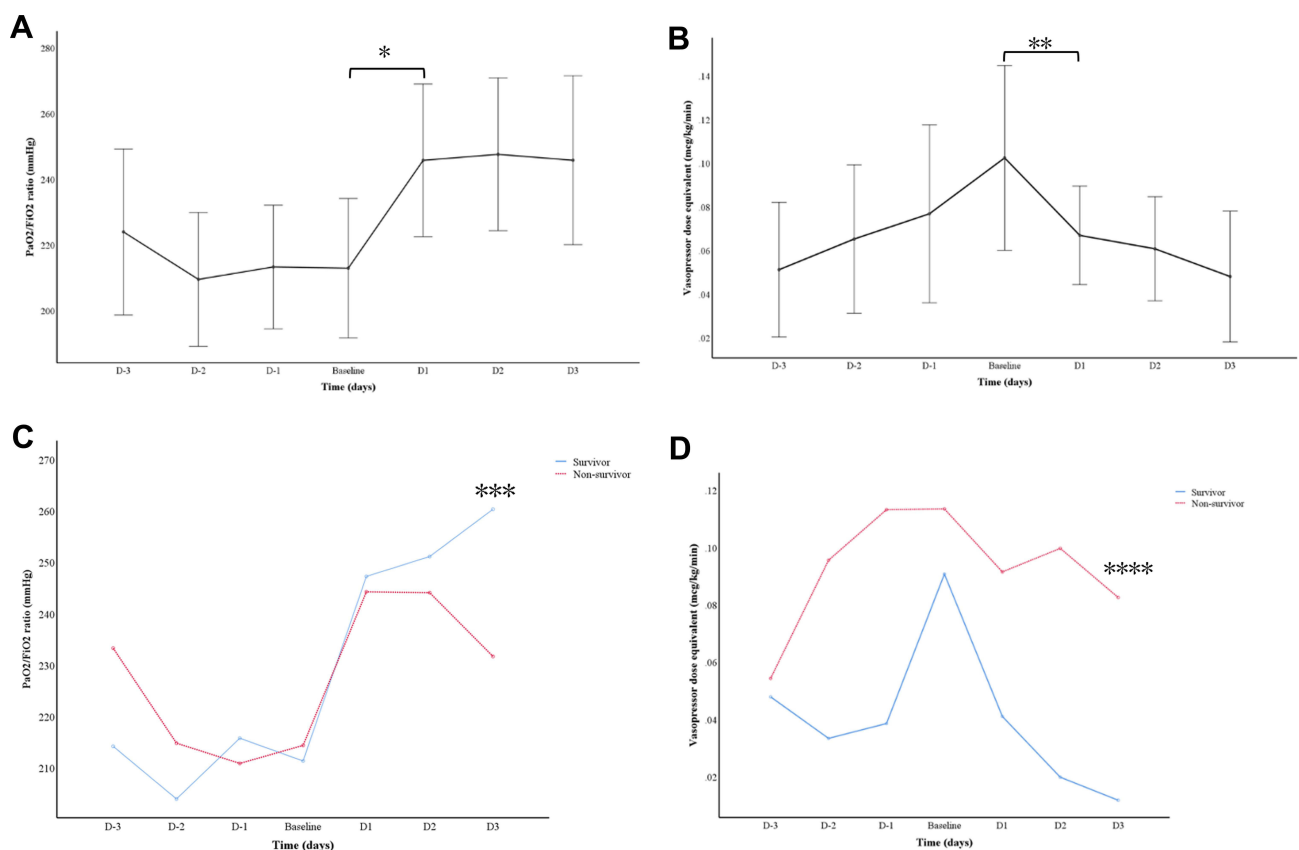
This multicenter study revealed that among mechanically ventilated patients, pleural drainage was typically performed for patients with greater morbidity and was associated with a high mortality rate. In this patient population, mortality was related to the use of CRRT and vasopressors at the time of the drainage procedure, and exudative effusions were associated with poorer outcomes than transudative effusions. Furthermore, survival could be predicted by the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and vasopressor dose on the third day of pleural drainage. Therefore, changes in oxygenation parameters and the vasopressor dose should be carefully monitored among mechanically ventilated patients who require pleural drainage.

Pleural effusion may be a marker of disease severity and may predict mortality.<sup>17</sup> For example, patients undergoing thoracentesis for malignant pleural effusion have a 30-day mortality rate of 37%.<sup>18</sup> In addition, patients with cirrhosis and



**Figure 1** Kaplan-Meier survival analyses **(A)** according to continuous renal replacement therapy (CRRT,  $p < 0.001$ ) and **(B)** the presence of transudate or exudate ( $p = 0.039$ ).

pleural effusion have a higher 30-day mortality rate if they undergo catheter drainage instead of thoracentesis (23.5% vs 18.6%).<sup>19</sup> We also found that pleural drainage was associated with a high mortality rate among patients who required MV. Another study of 133 patients (MV was used for 82% of patients) revealed an in-hospital mortality rate of 49%,<sup>20</sup> which is similar to our result (51%). In this setting, pleural drainage during MV is performed with the expectation of improvements in oxygenation or hemodynamic parameters, although its association with a high mortality rate suggests that pleural drainage during MV should be considered an indicator of serious comorbidity.



**Figure 2** Changes in the  $\text{PaO}_2/\text{FiO}_2$  ratio and vasopressor dose after pleural drainage. Changes are shown for **(A)** the  $\text{PaO}_2/\text{FiO}_2$  ratio ( $p = 0.931$ ), **(B)** the vasopressor dose ( $p = 0.011$ ), **(C)** the  $\text{PaO}_2/\text{FiO}_2$  ratio according to mortality, and **(D)** the vasopressor dose according to mortality.  $*p < 0.001$ , the  $\text{PaO}_2/\text{FiO}_2$  ratio was significantly different between baseline and day 1 (D1).  $**p = 0.03$ , the vasopressor dose was significantly different between baseline and D1.  $***p = 0.102$ , the  $\text{PaO}_2/\text{FiO}_2$  ratios on day 3 were 263 ( $\pm 100$ ) among survivors and 229 ( $\pm 104$ ) among non-survivors.  $***p = 0.011$ , the vasopressor doses on day 3 were 0.01 ( $\pm 0.04$ )  $\mu\text{g}/\text{kg}/\text{min}$  among survivors and 0.08 ( $\pm 0.18$ )  $\mu\text{g}/\text{kg}/\text{min}$  among non-survivors.

Mortality after a diagnosis of pleural effusion is reportedly associated with the Acute Physiology And Chronic Health Evaluation II (APACHE II) score and malignancy.<sup>21</sup> Previous studies of patients who were treated in the ICU, with/without MV, have revealed mean APACHE II scores of 17–21,<sup>20,22,23</sup> which is approximately consistent with the median SOFA score of 11 in the present study. Thus, patients with severe illness who require CRRT and/or vasopressors at the time of pleural drainage may have a high risk of mortality. Similarly, pleural effusion is associated with an increased risk of mortality among patients who are undergoing maintenance hemodialysis,<sup>24</sup> and fluid overload is an important contributor to the increased risk of mortality at RRT initiation.<sup>25</sup> Therefore, CRRT use at the time of pleural drainage for patients who require MV indicates a poor prognosis. Patients with exudative pleural effusions also had a higher mortality rate (vs transudative effusions), which suggests that it is important to determine whether pleural effusions are exudative or transudative in this setting.

The PaO<sub>2</sub>/FiO<sub>2</sub> ratio significantly improves at 24 h after starting pleural drainage,<sup>6,8,26</sup> and our findings revealed no significant change in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio before starting pleural drainage. Thus, the significant improvement in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio is likely a result of pleural drainage. It is also interesting that the PaO<sub>2</sub>/FiO<sub>2</sub> ratio remained relatively constant among survivors, but decreased by day 3 among non-survivors. The vasopressor dose also decreased significantly after 24 h of drainage, which might be related to improvements in hemodynamic parameters, including stroke volume.<sup>7</sup> In critically ill patients, the maintenance of fluid balance is often achieved using diuretics or volume removal during CRRT. As pleural drainage can reduce the need for volume removal, which can lead to hypotension, dose of vasopressors can be reduced. Decline of dose of vasopressors was more remarkable among survivors. Therefore, it may be possible to predict outcomes among these patients based on changes in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and vasopressor dose after starting pleural drainage. Therefore, maintenance of oxygenation and hemodynamic improvement by day 3 is more important than those by 24h improvement in predicting mortality after pleural drainage in mv patients.

This study has several limitations. First, the retrospective nature of the study precluded collection of data regarding the reasons for performing pleural drainage. Second, although vasopressors and CRRT were important factors for mortality among mechanically ventilated patients who required pleural drainage, there is a possibility that non-survivors might have had greater severity, regardless of pleural drainage. Thrombocytopenia and higher C-reactive protein levels were common among the non-survivors and the length of hospital stay was significantly shorter in the non-survivors. Third, some results from the pleural fluid analysis were missing, which precludes a more comprehensive assessment of the removed pleural fluid. Therefore, well-designed prospective studies are needed to clarify whether the etiology of pleural effusions influences the risk of mortality among mechanically ventilated patients who require pleural drainage.

In conclusion, the present study revealed that among patients who required pleural drainage during MV, mortality was associated with the use of vasopressors, use of CRRT, and exudative pleural effusions. Furthermore, changes in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and vasopressor dose by the third day of pleural drainage may be helpful for predicting the in-hospital mortality. Therefore, considering these factors may guide better prognostication and patient management.

## Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethical Approval Statement

This study was approved by the institutional review board of Chung-Ang University Hospital (2011-010-19341), and Ewha Womans University Mokdong Hospital (EUMC2021-02-004). The need for informed consent was waived due to the retrospective design.

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## Disclosure

The authors declare that they have no competing interests.

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