Radiologically and clinically diagnosed acute pulmonary oedema in critically ill patients: prevalence, patient characteristics, treatments and outcomes

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Acute pulmonary oedema (APO) is a clinical condition that is well described in medical publications.[1,2] Multiple pathophysiological processes can contribute to this clinical syndrome.[2] It can be caused by cardiogenic, neurogenic, induced by volume overload, related to transfusion or other rare factors.[3] As there is no diagnostic gold standard test for APO, its diagnosis rests on the combined presence of suggestive clinical features (known cause or trigger, dyspnoea, orthopnoea, frothy blood-tinged sputum, acute onset of crackles or rales on auscultation, compromised gas exchange) and supportive radiological findings (diffuse haziness of lung fields, acute interstitial alveolar infiltrate, Kerley B lines). Such radiologically and clinically diagnosed pulmonary oedema (RCDPO) in ambulant patients and those presenting to the emergency department is well described in publications on acute heart failure. However, there are few data on patients with RCDPO that is severe enough to require treatment in an intensive care unit (ICU). Moreover, to our knowledge, all reports on patients with RCDPO have described the pulmonary oedema in the context of another diagnosis — for example, as a complication of catastrophic subarachnoid haemorrhage.[4-8]

The lack of data on severe RCDPO requiring ICU treatment stems in part from the difficulties associated with making an APO diagnosis in a general ICU population. Specific conditions such as neurogenic pulmonary oedema, negative pressure pulmonary oedema, and pulmonary oedema associated with myocardial infarction, cardiogenic shock or cardiac arrest have been studied and are often linked with the development of APO.[8-11] However, even in such conditions, in the absence of a diagnostic gold standard, the diagnosis of pulmonary oedema typically rests on the presence of radiological features and results of clinical assessment.[12,13]

ABSTRACT

Background: Acute pulmonary oedema is a life-threatening syndrome diagnosed based on radiological and clinical findings. However, to our knowledge, no studies have investigated this syndrome in critically ill patients.

Objective: To describe the prevalence of radiologically and clinically diagnosed pulmonary oedema (RCDPO) in critically ill patients, characteristics of diagnosed patients, and treatments and outcomes in this patient population.

Methods: We conducted a retrospective study using natural language processing to identify all radiological reports of pulmonary oedema among patients who had been admitted to single tertiary intensive care unit (ICU) over a 1-year period (January 2015 to January 2016). We reviewed clinical data, discharge diagnosis, treatment and outcomes for such patients, and used multivariable logistic regression analysis to identify the association of RCDPO with various outcomes.

Results: Out of 2001 ICU patients, we identified 238 patients (11.9%) with RCDPO. Patients with RCDPO were more acutely ill, had more chronic liver disease and had more chronic renal failure than critically ill patients who did not have RCDPO. They were typically admitted with acute cardiovascular disease; were more likely to receive invasive mechanical ventilation and continuous renal replacement therapy; had longer duration of ICU and hospital stay; were more likely to die in hospital; and, if discharged alive, were more likely to be admitted to a chronic care facility. In total, 46 RCDPO patients (19.3%) died in hospital. On multivariable analysis, only age and continuous renal replacement therapy were independently associated with mortality. In contrast, invasive mechanical ventilation was associated with a 2.5 times greater odds of radiological resolution.

Conclusion: RCDPO affected about one in eight ICU patients. Such patients were sicker and had more comorbidities. The presence of RCDPO was independently associated with higher risk of death. Invasive mechanical ventilation was the only intervention independently associated with greater odds of radiological resolution.

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Accordingly, we used the combination of radiological diagnosis and confirmatory clinical assessment to define the presence of pulmonary oedema in a cohort of critically ill patients admitted to the ICU of a tertiary institution over a 1-year period. In this cohort of critically ill patients, we aimed to describe the prevalence of RCDPO, patient characteristics, and treatments, risk factors and outcomes. In particular, we aimed to test the hypothesis that, compared with patients without RCDPO, those with pulmonary oedema would have a significantly greater mortality rate.

Method

Study population

We conducted a retrospective study of adult patients (> 18 years old) admitted to the intensive care unit of Austin Hospital (a university-affiliated hospital) from January 2015 to January 2016.

Four of us (KEK, DR, SLC, HA) screened 2001 patients for the presence of a radiological diagnosis of APO (ie, based on chest x-ray) during their ICU admission by using natural language processing of electronically recorded radiological reports from an electronically searchable database that had been developed in-house. One of us (NY [a radiologist blinded to clinical assessment and outcome]) reviewed the selected patients' chest x-rays and formal reports to confirm or exclude the radiological diagnosis of pulmonary oedema. Subsequently, two of us (AB, TN [clinical investigators]) reviewed the selected patients' medical notes to confirm or refute the clinical diagnosis of pulmonary oedema and exclude potential differential diagnoses such as chronic lung disease, pneumonia, or adult respiratory distress syndrome (ARDS). Two of us (KEK, DR) assessed the resolution of features of pulmonary oedema by reviewing subsequent radiological reports to determine time taken to resolution. We calculated this as the time from the date of the first radiological report to the date of the report on which pulmonary oedema resolution was recorded.

We also collected demographic data for the screened patients, including age, sex, baseline comorbidities and Acute Physiology and Chronic Health Evaluation (APACHE) III score. This information is documented routinely for all ICU patients by trained coders and stored in the ICU database. We also recorded: admission diagnosis; onset and resolution times for pulmonary oedema; cumulative and daily fluid balance; interventions such as invasive mechanical ventilation (MV), non-invasive ventilation and continuous renal replacement therapy (CRRT); use of diuretics including frusemide; and spontaneous diuresis. We used the Australian and New Zealand Intensive Care Society Adult Patient Database to collect baseline patient characteristics. It is the only core registry for Australian and New Zealand ICUs that records detailed data on demographics, interventions, and duration of ICU and hospital care for adult ICU patients.[14]

Control group

Baseline demographics, admission diagnosis and outcomes for patients with RCDPO were compared with those for all other ICU patients who were treated in the same ICU during the same 1-year period (ie, those without the diagnosis of pulmonary oedema).

Ethics approval

This study was approved by Austin Hospital's Human Research Ethics Committee with a waiver of informed consent (LNR/17/Austin/49).

Statistical analysis

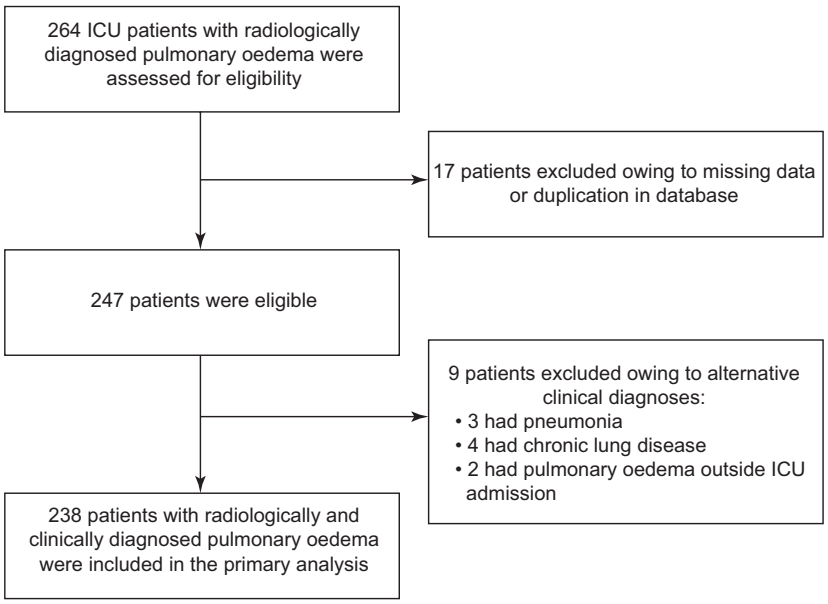
For the study population, we used univariate analysis to compare patients' characteristics according to survival, pulmonary oedema resolution and interventions. We used the $\chi 2$ test to test for equal proportions, the Student *t* test to compare normally distributed data, and the Mann–Whitney *U* test as appropriate. We report results as number (percentage), mean (standard deviation) or median (interquartile range [IQR], 25th to 75th percentile), respectively. We assessed resolution of pulmonary oedema and use of CRRT using the log-rank test, and we present the results as Kaplan–Meier survival curves. Independent predictors of mortality and resolution of pulmonary oedema were determined using multivariable logistic regression and Cox proportional hazards models. The models were constructed using stepwise selection and backward elimination techniques considering potential confounders such as age, chronic comorbidities and APACHE III score, with each of the results presented as odds ratio (95% confidence interval). For statistical tests, a two-sided *P* value of less than 0.05 was taken to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp) and Stata Statistical Software, release 16 (StataCorp).

Results

Out of 2001 ICU patients, 264 were identified as having radiologically diagnosed pulmonary oedema. Of them, 238 were included in the primary analysis; 17 patients were excluded owing to missing data or duplications, and nine were excluded because of an alternative clinical diagnosis (Figure 1).

Demographics and baseline characteristics of patients with and without RCDPO are shown in Table 1. Patients with RCDPO were more severely ill. They also had more comorbidities and were more commonly admitted with

Figure 1. Screening and exclusion of patients with radiologically and clinically diagnosed pulmonary oedema



ICU = intensive care unit.

acute cardiovascular disease. They were more likely to receive invasive MV and CRRT; had longer duration of ICU and hospital stay; were more likely to die in hospital; and, if discharged alive, they were more likely to be admitted to a chronic care facility.

Major treatments

Invasive MV was used in 175 patients with RCDPO (73.5%). Those who received invasive MV were more likely to also receive CRRT and were treated with CRRT for longer. They received less non-invasive ventilation, received a lower median daily dose of frusemide and achieved a less negative median daily fluid balance. Although patients given invasive MV cleared their RCDPO more often, they stayed in the ICU longer and had a significantly higher ICU mortality rate (Table 2).

CRRT was used in 69 patients with RCDPO (29.0%). These patients were more severely ill, more likely to receive invasive MV and had longer duration of mechanical ventilation. They were also more likely to have chronic liver disease and to receive a larger total dose of frusemide. In addition, they had longer ICU and hospital length of stay and greater ICU and hospital mortality (Figure 2; Supporting Information, Table S1).

Diuretics were administered in 214 patients (89.9%). The most commonly used diuretic was frusemide. The online Supporting Information (Table S2) shows a summary of the characteristics of patients receiving diuretics versus those who did not receive diuretics. The patients who did not receive diuretics all received CRRT and, did not achieve a negative fluid balance; they also were more likely to have chronic liver disease, and had significantly higher in-hospital mortality compared with those who did receive diuretics.

Pulmonary oedema resolution and mortality

Radiological resolution of pulmonary oedema occurred in 177 patients (74.4%). Patients who achieved RCDPO resolution were more likely to be male and more likely to receive invasive MV. However, they also had a less negative median daily fluid balance. Such patients had higher rates of ICU and hospital survival (Figure 3), but longer length of stay in ICU and hospital (Table 3).

Multivariable analysis for the prediction of radiological pulmonary oedema resolution showed that invasive MV was independently associated with a 2.5-fold increased odds of resolution (Supporting Information, Table S3). Moreover, receiving CRRT and having a higher APACHE III score were associated with a decreased hazard ratio for resolution of pulmonary oedema (Supporting Information, Table S4).

In total, 46 RCDPO patients died (19.3%). Non-survivors were older, more acutely ill, more likely to have chronic liver disease, more likely to receive invasive MV, more likely to receive CRRT, more likely to receive a smaller dose of frusemide, less likely to achieve a substantial negative fluid balance, and less likely to achieve radiological resolution (Supporting Information, Table S5).

Multivariable logistic regression analysis for baseline predictors of mortality across all patients adjusted for RCDPO, age, chronic liver disease, chronic renal failure, chronic respiratory disease and chronic cardiovascular disease showed that RCDPO, chronic liver disease and age were independently associated with increased risk of death (Supporting Information, Table S6). RCDPO was independently associated with a 59% increase in the risk of death.

Table 1. Characteristics of patients with and without RCDPO in the ICU*

Characteristics	All ICU patients	Patients with RCDPO	Patients without RCDPO	*P*
Patients	2001	238	1763	
Mean (SD) baseline age, years	63.0 (17.0)	62.3 (14.3)	60.35 (17.4)	0.12
Sex, female	1239	92 (38.7%)	670 (38.0%)	0.99
Mean (SD) APACHE III score†	50.4 (24.6)	64.0 (26.6)	48.6 (23.7)	< 0.01
Comorbidities				
Chronic liver disease/cirrhosis	145 (7.2%)	38 (16.0%)	106 (6.0%)	< 0.01
Chronic respiratory disease	179 (8.9%)	25 (10.5%)	156 (8.8%)	0.67
Chronic cardiovascular disease	78 (3.9%)	18 (7.6%)	62 (3.5%)	0.02
Immunosuppression	128 (6.4%)	20 (8.4%)	108 (6.1%)	0.18
Chronic renal failure	122 (6.1%)	28 (11.8%)	96 (5.4%)	< 0.01
Diagnosis				
Cardiovascular	630 (31.5%)	95 (39.9%)	536 (30.6%)	< 0.01
Respiratory	284 (14.2%)	32 (13.4%)	253 (14.3%)	0.58
Gastrointestinal	424 (21.2%)	52 (21.8%)	369 (20.9%)	0.44
Neurological	191 (9.5%)	9 (3.8%)	180 (10.1%)	< 0.01
Sepsis	130 (6.5%)	22 (9.2%)	111 (6.3%)	0.32
Trauma	86 (4.3%)	9 (3.8%)	78 (4.4%)	0.45
Other	256 (12.8%)	19 (8.0%)	236 (13.5%)	0.04
Intervention				
Continuous renal replacement therapy	159 (7.9%)	69 (29.0%)	97 (5.5%)	< 0.01
Invasive mechanical ventilation	1072 (53.6%)	175 (73.5%)	904 (51.3%)	< 0.01
Mortality and morbidity				
ICU mortality	129 (6.4%)	23 (9.7%)	108 (6.1%)	0.095
Hospital mortality	220 (11%)	46 (19.3%)	178 (10.1%)	< 0.01
Chronic care facility discharge	293 (14.6%)	47 (19.7%)	247 (14%)	0.03
Median (IQR) hospital length of stay, days	9 (5–18)	18.6 (10.3–33.2)	9 (5–16)	< 0.01
Median (IQR) ICU length of stay, days	2 (1–4)	5 (2.3–9.9)	1 (1–3)	< 0.01

APACHE III = Acute Physiology and Chronic Health Evaluation III. ICU = intensive care unit. IQR = interquartile range. RCDPO = radiologically and clinically diagnosed pulmonary oedema. SD = standard deviation. * Data are number (%) unless otherwise indicated. † APACHE III scores range from 0 to 299, with higher scores indicating more severe disease and a higher risk of death. Scores were calculated with the values recorded for each variable during the first 24 hours of ICU admission.

Multivariable analysis for the prediction of mortality among RCDPO patients adjusted for CRRT, MV, APACHE III score and age showed that only age and CRRT were independently associated with mortality in this group. CRRT was associated with a 3.9-fold increased risk of death, while age was associated with an increased risk of death of 4.8% per year of age (Supporting Information, Table S7).

A Cox regression proportional hazards model for mortality adjusted for age, MV, CRRT, APACHE III score and chronic liver disease (Supporting Information, Table S8) confirmed that each 1-year increase in age was independently associated with an increased risk of death of 4.0%.

Discussion

Key findings

RCDPO occurred in about one in eight ICU patients. Such patients were sicker and had more comorbidities than other ICU patients. They were often treated with invasive MV, CRRT and diuretics. Radiological resolution of pulmonary oedema was common (three in four patients), especially when patients received invasive MV, and was associated with a higher chance of survival. However, outcomes for ICU patients with RCDPO were poor; one in five died in hospital, and one in four survivors were discharged to a chronic

Table 2. Comparison of patients with radiologically and clinically diagnosed pulmonary oedema (*n* = 238) treated with or without invasive mechanical ventilation*

Characteristics	Invasive mechanical ventilation used	Invasive mechanical ventilation not used	*P*
Patients	175 (73.5%)	63 (26.5%)	
Mean (SD) baseline age, years	62.8 (13)	62.8 (17.5)	0.98
Sex, female	61 (34.9%)	31 (49.2%)	0.04
Mean (SD) APACHE III score†	65.9 (27.9)	62.4 (20.5)	0.36
Comorbidities			
Chronic liver disease/cirrhosis	31 (17.7%)	7 (11.1%)	0.22
Chronic respiratory disease	17 (9.7%)	8 (12.7%)	0.51
Chronic cardiovascular disease	8 (4.6%)	10 (15.9%)	< 0.01
Immunosuppression	11 (6.3%)	9 (14.3%)	0.05
Chronic renal failure	18 (10.3%)	10 (15.9%)	0.24
Intervention			
Frusemide	140 (80.0%)	44 (69.8%)	0.10
Non-invasive ventilation	16 (9.1%)	14 (22.2%)	< 0.01
CRRT	59 (33.7%)	10 (15.9%)	< 0.01
Median (IQR) cumulative fluid balance, mL,)	–1259 (–4516 to 750)	–1670 (–4075 to –0.50)	0.34
Median (IQR) daily fluid balance, mL	–177.2 (–554.7 to 147.8)	–439.5 (–1060.7 to –6.8)	< 0.01
Total (IQR) frusemide dose, mg	180 (80–360)	120 (50–290)	0.20
Median (IQR) daily frusemide dose, mg	28.3 (12.3–47.9)	39 (16.7–92.2)	< 0.01
Outcome			
ICU mortality	23 (13.1%)	0	< 0.01
Hospital mortality	37 (21.1%)	9 (14.3%)	0.24
Chronic care facility discharge	34 (19.4%)	13 (20.6%)	0.81
Radiological pulmonary oedema clearance	139 (79.4%)	38 (60.3%)	< 0.01
Median (IQR) CRRT time, h	172.5 (71.5–274.6)	51.8 (0–93.0)	< 0.01
Median (IQR) hospital length of stay, days	19.9 (10.7–35.2)	14.8 (7.5–27.4)	0.06
Median (IQR) ICU length of stay, days	6.7 (2.9–12.3)	3.4 (1.7–5.5)	< 0.01

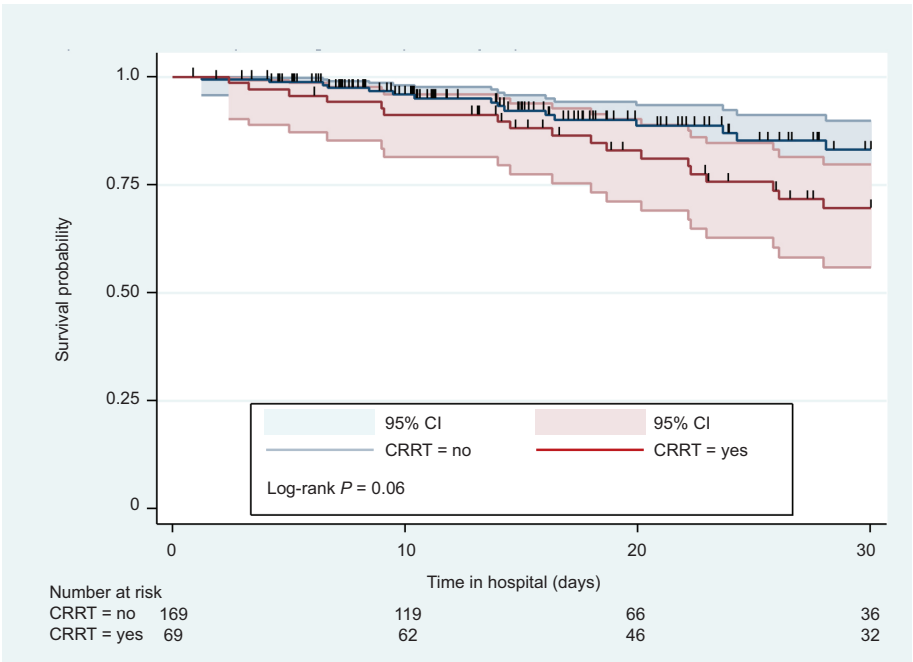
APACHE III = Acute Physiology and Chronic Health Evaluation III. CRRT = continuous renal replacement therapy. ICU = intensive care unit. IQR = interquartile range. SD = standard deviation. * Data are number (%) unless otherwise indicated. † APACHE III scores range from 0 to 299, with higher scores indicating more severe disease and a higher risk of death. The score was calculated with the values recorded for each variable during the first 24 hours of ICU admission.

health care facility. Finally, RCDPO was an independent risk factor for mortality.

Comparison with previous studies

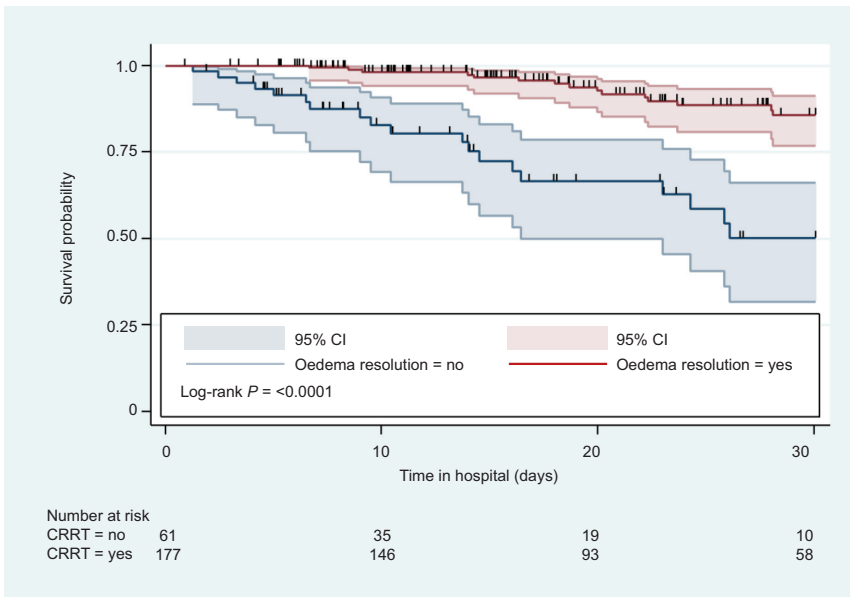
Previous studies have described pulmonary oedema in patients with decompensated heart failure in non-ICU populations, as a possible complication of iatrogenic fluid overload, or as the radiological domain of the diagnosis of ARDS.[15-17] In 2000, authors of a single centre study described 150 patients admitted to an internal medicine department with the diagnosis of APO; they reported 12% overall hospital mortality and 55% mortality among patients who received MV.[18] A more recently published single centre study assessed the severity of radiologically diagnosed pulmonary oedema in 107 out-of-hospital cardiac arrest survivors, and the authors reported that the degree of severity of such pulmonary oedema was associated with worse long term outcomes.[8] Finally, another recent single centre study assessed 108 patients with neurogenic pulmonary oedema following non-traumatic intracerebral haemorrhage, and this was found to be associated with higher 1-year mortality.[5] To our knowledge, no previous study has attempted to

Figure 2. Kaplan–Meier plot of survival probability to Day 30 for patients with RCDPO treated with or without CRRT



CRRT = continuous renal replacement therapy. RCDPO = radiologically and clinically diagnosed pulmonary oedema.

Figure 3. Kaplan–Meier plot of survival probability to Day 30 for patients with RCDPO for whom pulmonary oedema did or did not resolve



RCDPO = radiologically and clinically diagnosed pulmonary oedema.

characterise all types of ICU patients with RCDPO, describe the prevalence of RCDPO in this patient population, and describe treatments and measure outcomes for these patients.

Implications for clinicians

Our results indicate that RCDPO is a common condition in ICU patients. Moreover, it shows that, even though radiological resolution can be achieved in most patients, short term outcomes are poor. Finally, it implies that even with advanced ICU-based therapy such as invasive MV and CRRT (with the theoretical ability to remove fluid as needed) RCDPO is associated with a mortality rate of one in five, and that one in four RCDPO survivors need admission to a chronic health care facility.

Strengths and limitations

This study has several strengths. To our knowledge, it is the only study to establish the prevalence of RCDPO among a large cohort of critically ill patients, and the only one to characterise all such patients with detailed information on interventions, outcomes and predictors of outcomes. As such, it provides novel information on an important and common group of critically ill patients, who have not been formally studied previously, including their characteristics and interventions that might influence their outcomes.

We acknowledge several limitations. This is a retrospective single centre study with the known limitations of all such

Table 3. Comparison of patients with radiologically and clinically diagnosed pulmonary oedema (*n* = 238) for whom the condition did or did not resolve*

Characteristics	No resolution	Resolution	*P*
Patients	61 (25.6%)	177 (74.4%)	
Mean (SD) baseline age, years	64.8 (15.3)	62.0 (13.9)	0.19
Sex, female	32 (47.8%)	61 (33.9%)	0.045
Mean (SD) APACHE III score†	68.2 (29.4)	63.8 (24.9)	0.26
Comorbidities			
Chronic liver disease/cirrhosis	9 (14.8%)	29 (16.4%)	0.76
Chronic respiratory disease	8 (13.1%)	17 (9.6%)	0.44
Chronic cardiovascular disease	6 (9.8%)	12 (6.8%)	0.44
Immunosuppression	4 (6.6%)	16 (9.0%)	0.55
Chronic renal failure	5 (8.2%)	23 (13.0%)	0.32
Intervention			
Frusemide	45 (73.8%)	139 (78.5%)	0.44
Non-invasive ventilation	8 (13.1%)	22 (12.4%)	0.89
Invasive mechanical ventilation	36 (59.0%)	139 (78.5%)	< 0.01
CRRT	16 (26.2%)	53 (29.9%)	0.58
Median (IQR) cumulative fluid balance, mL	–1578 (–3145 to 381)	–1384 (–4795 to 734)	0.89
Median (IQR) daily fluid balance, mL	–339.3 (–812.0 to 27.5)	–177.1 (–583.6 to 170.0)	0.04
Total (IQR) frusemide dose, mg	120 (40–260)	160 (80–340)	0.21
Median (IQR) daily frusemide dose, mg	33.2 (14.5–65.4)	30.7 (12.6–53.4)	0.62
Outcome			
ICU mortality	11 (18.0%)	12 (6.8%)	0.01
Hospital mortality	21 (34.4%)	25 (14.1%)	< 0.01
Chronic care facility discharge	10 (16.4%)	37 (20.9%)	0.44
Median (IQR) CRRT time, h	131.7 (40.0–186.0)	159.0 (70.0–296.2)	0.13
Median (IQR) invasive mechanical ventilation time, h	70.0 (31.0–174.0)	52.3 (15.4–181.7)	0.72
Median (IQR) hospital length of stay, days	13.7 (6.5–23.6)	21.7 (12.8–36.5)	< 0.01
Median (IQR) ICU length of stay, days	3.6 (1.9–6.8)	5.9 (2.8–10.9)	< 0.01

APACHE III = Acute Physiology and Chronic Health Evaluation III. CRRT = continuous renal replacement therapy. ICU = intensive care unit. IQR = interquartile range. SD = standard deviation. * Data are number (%) unless otherwise indicated. † APACHE III scores range from 0 to 299, with higher scores indicating more severe disease and a higher risk of death. Scores were calculated with the values recorded for each variable during the first 24 hours of ICU admission.

studies. However, it has a large sample size (twice that of the largest specific subgroup of patients that we identified in previous publications). In addition, our comparison with all other ICU patients who did not have RCDPO during the same period provides a detailed understanding of treatment and outcomes for this condition. The diagnosis of pulmonary oedema is difficult. It may be confused with inflammatory lung conditions such as ARDS. However, to minimise such possible misdiagnosis, all patients identified as having radiological APO had the diagnosis of APO confirmed or refuted and the diagnosis of ARDS confirmed or excluded by a detailed clinical assessment. Such assessment included review of medical notes and of the final discharge diagnosis as documented by the treating clinicians at the time of the patient's discharge. Such assessment was by its very nature unbiased for or against APO versus ARDS, and represented the considered clinical diagnosis of a full treating team. Moreover, whether another team of clinicians might have come to another diagnosis and whether such diagnosis would have been more or less likely to be correct cannot

be tested in the absence of a gold standard diagnostic test. As our study was not a randomised controlled trial, it does not identify therapies that might affect outcomes in these patients. However, the association of invasive MV with greater resolution of pulmonary oedema after adjustment for illness severity and the fact that such resolution was associated with higher chance of survival suggests that invasive MV may be a therapeutic priority in such patients.

Conclusion

RCDPO appears to affect one in eight ICU patients. Such patients were sicker and had more comorbidities than critically ill patients who did not have RCDPO. The presence of such pulmonary oedema was associated with higher risk of death. However, invasive MV of such patients was independently associated with greater odds of radiological resolution of pulmonary oedema, and such resolution and invasive MV were both associated with higher chance of survival. These insights may help guide prognostic and therapeutic decisions by critical care physicians and estimate sample size for controlled interventional trials. In particular, our results justify controlled trials of early invasive MV in critically ill patients with RCDPO.

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Competing interests

No relevant disclosures.

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