Respiratory Research

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Clinical and biologic profiles of patients with acute respiratory distress syndrome by prevalence of chronic obstructive pulmonary disease or emphysema; a cohort study

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Abstract

Introduction Acute respiratory distress syndrome (ARDS) is characterized by diffuse lung injury. The impact of pre-existing chronic obstructive pulmonary disease (COPD) or emphysema on ARDS pathogenesis is not well characterized.

Methods Secondary analysis of ARDS patients enrolled in the Acute Lung Injury Registry and Biospecimen Repository at the University of Pittsburgh between June 2012 and September 2021. Patients were categorized into two mutually exclusive groups by the prevalence of COPD or emphysema at the time of ARDS diagnosis. The COPD/emphysema group comprised ARDS patients with radiological evidence of emphysema, chart diagnosis of COPD, or both. Demographics, lung mechanics, and clinical outcomes were obtained from the electronic medical record. Host-response biomarkers known to have validated associations with ARDS were previously measured in plasma and lower respiratory tract samples using a customized Luminex assay. Continuous and categorical variables were compared between groups with and without COPD/emphysema.

Results 217 patients with ARDS were included in the study, 57 (27%) had COPD/emphysema. Patients with COPD/emphysema were older (median 62 [interquartile range 55–69] versus 53 [41–64] years, $p < 0.01$), more likely to be male (62% vs. 44%, $p = 0.02$) and had a higher prevalence of congestive heart failure (25% vs. 4%, $p < 0.01$) compared to patients without COPD/emphysema. Baseline demographics, laboratory parameters, and mechanical ventilatory characteristics were otherwise similar between the two groups. No difference in 90-day mortality was observed between groups; however, patients with COPD/emphysema had shorter duration of intensive care unit (ICU) stay

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(median 10 [7–18] versus 16 [9–28] days, $p = 0.04$) and shorter duration of mechanical ventilation (median 7 [4–16] vs. 12 [6–20] days, $p = 0.01$). Host response biomarkers in serum and lower respiratory tract samples did not significantly differ between groups.

Conclusion ARDS patients with COPD or emphysema had similar respiratory mechanics, host response biomarker profiles, and mortality compared to those without COPD or emphysema but with a shorter median duration of mechanical ventilation and ICU length of stay. Future studies should address differences in clinical and biological responses by disease severity, and should investigate the impact of severity of COPD and emphysema on mechanical ventilation and targeted therapeutic strategies in ARDS.

Clinical trial number Not applicable

Keywords Acute respiratory distress syndrome, Chronic obstructive pulmonary syndrome, Systemic host immune response, Emphysema

Introduction

Acute respiratory distress syndrome (ARDS) is a common and potentially fatal condition characterized by diffuse lung injury in response to a direct or indirect insult, with an estimated prevalence of 10% among critically ill patients and with a 28-day in-hospital mortality rate approaching 40% [1, 2]. The incidence of ARDS increased sharply during the Coronavirus-19 (COVID-19) pandemic, highlighting the need to better understand pathogenesis and management. Effective clinical treatments for ARDS remain limited, with numerous preclinical interventions yielding minimal success in clinical trials [3, 4]. Notably, preclinical in vivo models of ARDS are often conducted in young and healthy mice, contrasting the clinical ARDS patient population, which is characterized by multiple chronic comorbidities [5]. Understanding the relationship between chronic comorbidities and ARDS pathogenesis is essential for tailoring therapeutic strategies [6].

Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease globally and is the sixth leading cause of death in the United States [7, 8]. The impact of pre-existing COPD on ARDS pathogenesis is not well characterized. Patients with COPD have a higher risk of severe community-acquired pneumonia, the most common cause of ARDS, and once hospitalized with severe pneumonia in the intensive care unit (ICU), have higher mortality and need for mechanical ventilation [9–11]. COPD is common in ARDS patients as the Large observational study to understand the Global impact of Severe Acute respiratory FailurE (LUNG-SAFE) study encompassing 459 ICUs in 50 countries demonstrated that approximately one in five ARDS patients had underlying COPD [1]. The LUNG-SAFE study did not characterize differences in clinical outcomes based on pre-existing COPD and additionally based the diagnosis of COPD on chart reviews. Systematic assessment of radiologic imaging may uncover the presence of anatomic emphysema, which may impact clinical and biologic responses in ARDS.

We performed this study to investigate the impact of COPD and emphysema on ARDS pathogenesis. Our specific objectives were (1) to determine the prevalence of COPD and emphysema in ARDS using both chart review and systemic review of radiologic testing and (2) to investigate differences between ARDS patients by the prevalence of COPD or emphysema in mechanical ventilation parameters, host response biomarkers, and clinical outcomes.

Methods

Description of cohort

We performed a secondary analysis of patients prospectively enrolled in the Acute Lung Injury and Biospecimen Repository (ALIR) at the University of Pittsburgh between June 2012 to September 2021. Details of the ALIR have previously been published, and all patients were enrolled after obtaining informed consent [12, 13]. ALIR protocols have been approved by the Human Research Office at the University of Pittsburgh (protocol# STUDY19050099).

ALIR enrolls adult patients with acute respiratory failure, with most requiring invasive mechanical ventilation. For this study, we included patients with a diagnosis of ARDS as determined by a consensus committee meeting of at least three board-certified pulmonary and critical care physicians following a review of all available clinical and radiographic data and adjudicated based on Berlin Criteria [14]. We classified patients in our study cohort into two mutually exclusive groups based on the prevalence or absence of COPD or emphysema (COPD/emphysema). All ARDS patients with a chart diagnosis of COPD were included in the COPD/emphysema group. Chart diagnosis was based on a review of history and physical examination notes on admission to the intensive care unit and was not dependent on specific diagnosis or procedure codes. ARDS patients with a chart diagnosis of COPD underwent a review of computed tomography (CT) chest reports and/or imaging, if available, during the incident admission or within the 2 years preceding

admission to determine presence and extent of anatomic emphysema as described below. ARDS patients without a chart diagnosis of COPD were only included in our study if a CT chest had been performed during or in the 2 years prior to admission— if review of chest imaging revealed anatomic emphysema, then patients were classified in the COPD/emphysema group, if not, then patients were classified in the ARDS without COPD/emphysema group.

Emphysema scoring

Electronic records of all ARDS patients were reviewed for the presence of CT chest imaging with or without intravenous contrast performed as part of their clinical care up to 2 years prior to the incident hospitalization. All CT scans had previously been interpreted by a board-certified radiologist. All CT images that were available in the electronic record were independently reviewed by a board-certified pulmonologist (SN) for visual assessment of the presence of emphysema without knowledge of the radiologist's report. The extent of emphysema was graded from 0 to 3, using a semiquantitative visual scoring system to define emphysema severity (0 none; 1 mild; 2 moderate; 3 severe), which corresponded to 0%, less than 25%, 26–50%, and greater than 75% visual emphysema respectively [15]. For this study, patients with a score≥1 were classified as having anatomic emphysema. In patients with multiple CT scans of the chest available for review, the CT scan most proximal to the day of admission for respiratory failure due to ARDS was used for emphysema assessment. Agreement between the radiology report and independent review for the visual assessment of emphysema was assessed by the κ coefficient for interrater reliability. In cases of discrepancy, images were independently reviewed and scored by a second reviewer (FS). In a subset of patients, a CT chest had been performed but images were not available for independent review. In this subset, the radiologist's interpretation was used to determine the presence or absence of emphysema.

Clinical data collection

Baseline demographics, chronic comorbidities, outpatient use of inhaler therapies for COPD, parameters of mechanical ventilation, laboratory variables, and calculated sequential organ failure assessment (SOFA) scores were abstracted from the electronic medical record. Driving pressure (ΔP) on the day of study enrollment was calculated as the difference between the positive end-expiratory pressure (PEEP) and the plateau pressure (Pplat) during volume-controlled ventilation or between PEEP and the maximum airway pressure (Pmax) during pressure-controlled ventilation. Ventilatory ratio (VR) was calculated by using the formula VR = [minute ventilation (ml/min) × PaCO2 (mmHg)]/(predicted body weight(kg) × 100×37.5). Respiratory system compliance (CRS) was calculated by dividing the tidal volume(ml) by ΔP(cmH20) [16].

Host response biomarkers

Biospecimens are collected from ALIR patients within 72 h of intubation, including blood samples and endotracheal aspirates (ETA), and processed as previously described [12, 13]. Ten host-response biomarkers shown to have validated associations with ARDS were previously characterized in blood and ETA samples with a customized Luminex assay (R&D Systems, Minneapolis) [17]. Host-response biomarkers included markers of innate immune response (interleukin (IL)-6, IL-8, IL-10, fractalkine, soluble tumor necrosis factor receptor-1 [sTNFR-1], suppressor of tumorigenicity-2 [ST-2]); epithelial injury (receptor of advanced glycation end-products [RAGE]); endothelial injury (angiopoietin-2 [Ang-2]); and response to bacterial infections (procalcitonin and pentraxin-3).

Host response subphenotype assignments

We classified patients into host response subphenotypes (hyperinflammatory versus hypoinflammatory) using a parsimonious logistic regression model based on plasma levels of Ang-2, procalcitonin, sTNFR1, and bicarbonate that have been previously validated in this cohort [18].

Receipt of ARDS treatments

Electronic records of patients were reviewed for the use of common ARDS treatments, including glucocorticoids (dexamethasone, hydrocortisone, methylprednisolone, prednisone by oral or intravenous routes), prone positioning, neuromuscular blockade, inhaled vasodilators, extracorporeal membranous oxygenation (ECMO), and tracheostomy. Glucocorticoids are used not only in ARDS management (with potential mortality benefit demonstrated in several randomized clinical trials and metanalyses) [19–21] but also in COPD exacerbations [22] or COVID-19 infections [23], highlighting a need to understand the type of glucocorticoid administered. We focused on early glucocorticoid use within the first week after enrollment [24, 25].

Statistical analyses

In our primary analyses, we compared continuous and categorical variables between ARDS patients with and without COPD/emphysema by nonparametric tests (Kruskal-Wallis or Fisher's tests, as appropriate). We report variables as median and interquartile range [IQR] for continuous variables and number (proportion) for categorical variables. We constructed Kaplan Meier survival curves to visually investigate differences in the duration of mechanical ventilation and 90-day survival and compared between groups. We compared differences in

90-day mortality in logistic regression analyses adjusted for age, history of congestive heart failure by review of the electronic medical record, and COVID-19 diagnosis.

Since ARDS patients with COPD/emphysema in our cohort may have had a chart diagnosis of COPD or evidence of anatomic emphysema on a CT scan (or both), we performed two sensitivity analyses to ensure the robustness of the results. First, we compared differences between ARDS patients with no COPD to the subset of patients who had a documented diagnosis of COPD on chart review. Second, we compared differences between ARDS patients with no COPD to the subset of patients who had evidence of emphysema on CT imaging.

We performed all analyses with STATA version 17 and considered a p-value of less than 0.05 as statistically significant. Analyses were not adjusted for multiple testing. All findings are reported consistent with the STROBE statement for observational studies.

Results

Cohort description

From January 2012 to January 2022, 783 patients with acute respiratory failure were prospectively enrolled from medical ICUs in the UPMC Health System in Western Pennsylvania in the Acute Lung Injury Registry and Biospecimen Repository. In our study, we excluded patients who did not have a CT scan of the chest within 2 years prior to hospitalization for respiratory failure unless they had a chart review diagnosis of COPD ($n=258$) and we excluded patients without ARDS ($n=308$) (Fig. 1). The remaining ARDS patients ($n=217$) were classified into two mutually exclusive groups: those with COPD/emphysema ($n=57$) and without COPD/emphysema ($n=160$). The COPD/emphysema group comprised 28 patients with radiologic evidence of emphysema and 41 patients with a preexisting diagnosis of COPD; 12 ARDS patients had both evidence of emphysema and a chart diagnosis

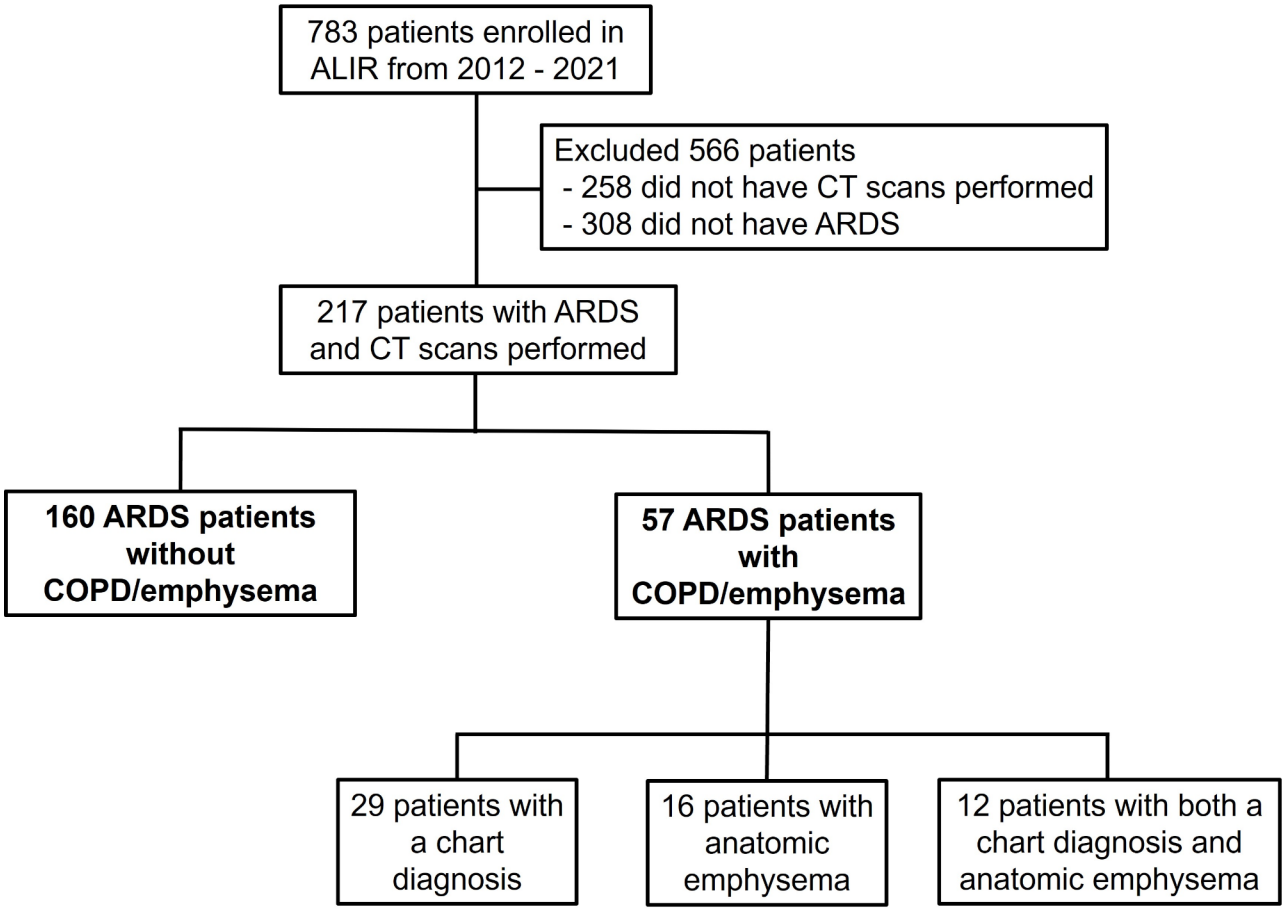

Fig. 1 Study flow chart. Patients previously enrolled in the Acute Lung Injury and Biospecimen Repository (ALIR) at the University of Pittsburgh were included in the current study if and if a diagnosis of acute respiratory distress syndrome (ARDS) by the Berlin criteria had been reached by consensus of at least three board-certified intensivists, and if either a diagnosis of chronic obstructive pulmonary disease (COPD) was present on chart review prior to ARDS diagnosis or if computed tomography (CT) of the chest had been performed within 2 years preceding the incident hospitalization to assess presence or absence of anatomic emphysema. ARDS patients in the current study were classified into two mutually exclusive groups: those with COPD or emphysema (defined by the presence of a chart diagnosis of COPD, radiologic evidence of anatomic emphysema, or both) and those without COPD (no chart diagnosis of COPD or emphysema on CT imaging)

Table 1 Characteristics of the study cohort

Variable	No COPD or emphysema	COPD or emphysema	*p*-value
N	160	57	
Demographics			
Age, years	53 (41–64)	62 (55–69)	< 0.01
Sex, male	99 (61.8%)	25 (43.8%)	0.02
Race, Caucasian	143 (89.3%)	49 (85.9%)	0.63
Body mass index, kg/m^2	31.2 (26.4–36.1)	30.5 (24.9–35.9)	0.29
Tobacco use			
Never	90 (56.3%)	8 (19.5%)	< 0.01
Former	44 (27.5%)	13 (31.7%)	
Current	26 (16.3%)	20 (48.8%)	
Vaping use	6 (3.8%)	6 (10.5%)	0.06
Comorbidities			
Asthma	44 (27.5%)	24 (42.1%)	0.04
Diabetes mellitus	49 (30.6%)	20 (35.0%)	0.53
Chronic renal failure	20 (12.5%)	7.0 (12.8%)	0.97
Congestive heart failure	7.0 (4.3%)	14 (24.5%)	< 0.01
Active neoplasm	8.0 (5.0%)	10 (1.7%)	0.29
Immune suppression	48 (30.0%)	13 (22.8%)	0.30
Pulmonary fibrosis	6.0 (3.7%)	2.0 (3.5%)	0.93
Outpatient medication use			
Long acting beta agonists	45 (28.1%)	32 (56.1%)	< 0.01
Long acting antimuscarinics	7 (4.4%)	15 (26.3%)	< 0.01
Inhaled glucocorticoids	19 (11.9%)	15 (26.3%)	< 0.01
Severity of illness			
Pulmonary injury	132 (82.5%)	47 (82.5%)	0.99
COVID-19 infection	58 (36.2%)	13 (22.8%)	0.06
Modified SOFA score	8 (5–10)	7 (5–8)	0.08
Laboratory results			
White blood cell count, 10^9/L	12.1 (8.7–17.6)	11.2 (9.0-15.1)	0.30
Hemoglobin g/dL	10.3 (8.7–12.1)	9.9 (8.7–11.4)	0.22
Platelets, 10^9/L	187 (119–259)	213 (134–272)	0.63
Creatinine, mg/dL	1.1 (0.8–2.1)	1.5 (0.8–2.5)	0.34
Bicarbonate, mEq/L	25 (22–29)	24 (20–28)	0.26
Blood urea nitrogen mg/dL	31 (21–43)	35 (17–49)	0.83
Blood glucose mg/dL	143 (114–183)	143 (122–171)	0.95

Data are presented as median (interquartile range) or n (%) as appropriate. Participants in the "COPD" group have a preexisting diagnosis of chronic obstructive pulmonary disease (COPD), presence of anatomic emphysema on computational tomography (CT) imaging of the chest, or both. Participants in the "No COPD" group have neither a chart diagnosis of COPD and have an absence of anatomic emphysema on CT imaging. Pulmonary insult indicates presence of at least one direct risk factor for acute respiratory distress syndrome determined by consensus and includes pneumonia, aspiration, and inhalational injury. SOFA score is modified to exclude the neurologic component as Glasgow Coma Scale were not routinely collected on patients in our study. p-values represent differences between groups compared by Mann-Whitney U test or by chi-squared analysis as appropriate. *Abbreviations*: COPD- chronic obstructive pulmonary disease; COVID-19- Coronavirus Disease-19; SOFA- Sequential Organ Failure Assessment

of COPD. Emphysema severity was assessed in ARDS patients with COPD who had images available for independent review ($n=43$) and revealed most patients had no anatomic emphysema ($n=15$, 35%) or mild emphysema ($n=14$, 33%). Fewer ARDS patients with COPD had moderate emphysema ($n=10$, 23%) or severe emphysema ($n=4$, 9%) on review of CT imaging. The agreement between the radiology report and independent review for the visual assessment of emphysema was excellent, with a κ coefficient for interrater reliability of 0.93.

Baseline clinical characteristics

In our cohort, ARDS patients with COPD/emphysema were older (median age 62 [interquartile range: 55–69] versus 53 [41–64] years, $p<0.01$) and were more likely to be male (62% versus 44%, $p=0.02$) compared to ARDS patients without COPD (Table 1). BMI did not differ significantly between ARDS patients with or without COPD/emphysema (30.5 [24.9–35.9] versus 31.2 [26.4–36.1], $p=0.29$). ARDS patients with COPD/emphysema had a higher prevalence of asthma (42% versus 28%, $p=0.04$) and congestive heart failure (25% versus 4%, $p<0.01$), but otherwise, comorbid conditions were similar between COPD and no COPD groups. Current and former tobacco use, as well as the use of outpatient inhaler therapies for COPD, were higher in the ARDS patients with COPD/emphysema. The cause of ARDS was similar as 59% of ARDS patients with COPD/emphysema had direct pulmonary injury (primary insult caused by pneumonia, aspiration event, or inhalation injury) compared to 56% without COPD ($p=0.32$). In our cohort, 23% of ARDS patients with COPD/emphysema had COVID-19 infection compared to 36% in patients without COPD, though this difference did not reach statistical significance ($p=0.06$). As determined by the modified SOFA score, the severity of illness was also similar in both groups ($p=0.29$) (Table 1).

Ventilator characteristics on the day of study enrollment

We compared baseline ventilator parameters between groups on the day of study enrollment. Several parameters did not differ significantly, including minute ventilation, positive end-expiratory pressure (PEEP), tidal volume, peak inspiratory pressures, plateau pressure, driving pressures, and static compliance (Fig. 2). The ventilatory ratio was higher in ARDS patients with COPD/emphysema compared to ARDS patients without COPD/emphysema (2.1 [1.7–2.8] vs. 1.9 [1.5–2.4], $p=0.02$), potentially reflecting higher dead space in the COPD/emphysema group. ARDS severity, as determined by the P/F ratio, did not differ significantly between groups (120 [84–174] in the ARDS with COPD/emphysema group versus 126 [83–203] in the ARDS without COPD/emphysema group, $p=0.56$).

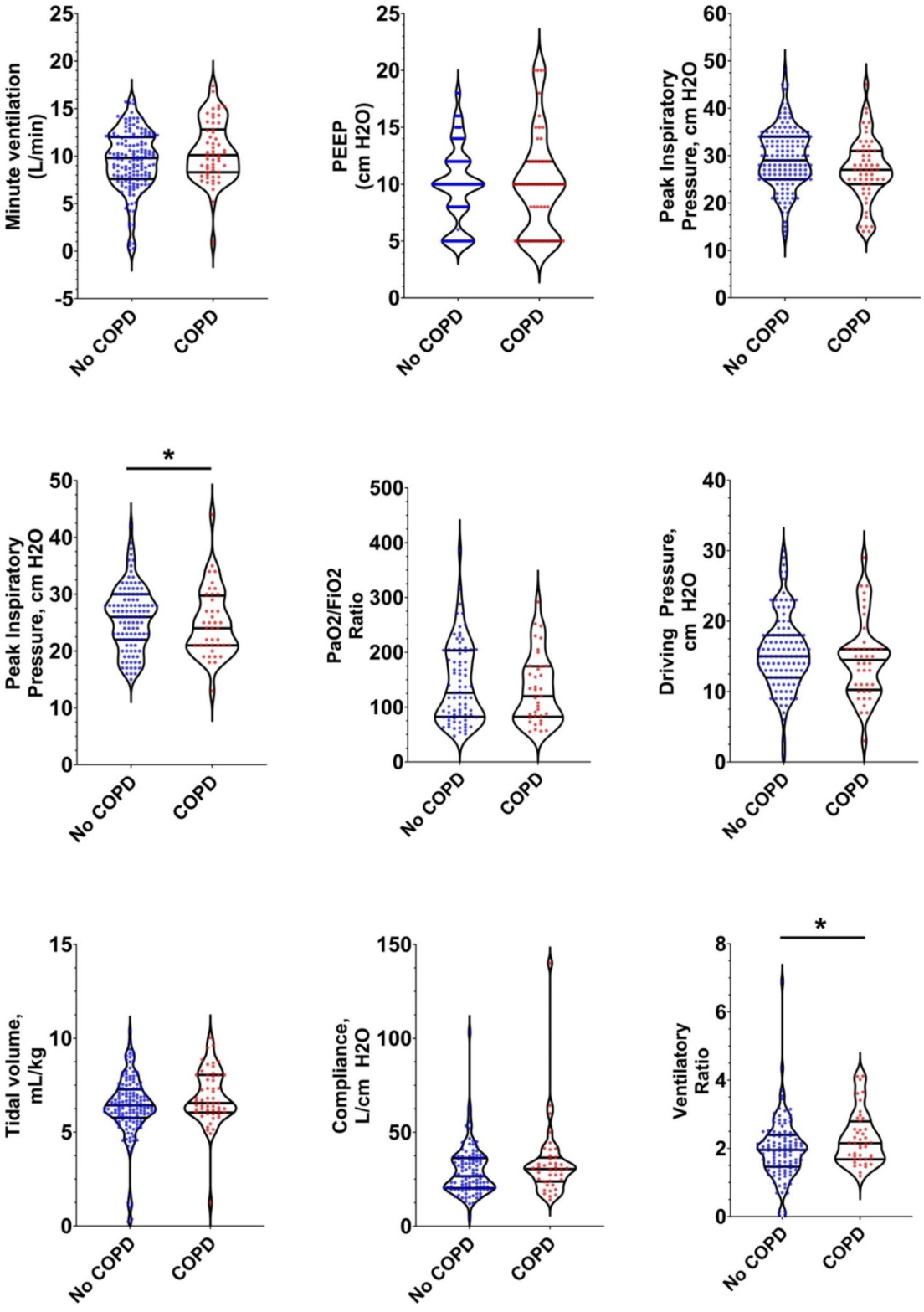

Fig. 2 Ventilatory parameters compared in ARDS patients by presence or absence of COPD or emphysema. COPD in figures denotes the COPD or emphysema group. Data are presented as violin plots with medians and 25th and 75th percentiles demarcated. Each dot represents an individual patient. * denotes significance at $p < 0.05$ by Kruskal-Wallis test. Abbreviations: COPD = chronic obstructive lung disease; PEEP = positive end-expiratory pressure

Table 2 Plasma host response biomarkers measured on study enrollment compared between ARDS patients with and without COPD or emphysema

Variable	No COPD or emphysema	COPD or emphysema	*p*-value
Angiopoetin-2 (pg/mL)	6883 [3761–13735]	8935 [4153–19008]	0.22
Interleukin-8 (pg/mL)	24 [14–40]	27 [14–54]	0.40
Interleukin-6 (pg/mL)	118 [30–413]	111 [37–198]	0.43
Interleukin-10 (pg/mL)	1.7 [1.0-8.6]	3.4 [1.3–11.8]	0.17
Procalcitonin (pg/mL)	670 [305–2885]	853 (193–4510)	0.42
Suppressor of tumorigenicity-2 (pg/mL)	161,171 [809997 – 350891]	189,618 [90955–422669]	0.77
Fractalkine (pg/mL)	2302 [1198–4024]	2133 [1179–3815]	0.48
Pentraxin-3 (pg/mL)	7833 [3669–20785]	8076 [3604–15562]	0.74
Soluble receptor for advanced glycation endproducts (pg/mL)	5212 [2760–9811]	5275 [2260–7866]	0.66
Beta-D-glucan (pg/mL)	24 [14–35]	28 [15–41]	0.35

Data are presented as median [interquartile range]. Biomarker data at baseline was available for a subset of participants ($n=207$ total; no COPD: $n=154$; COPD: $n=53$). p-values represent differences between groups compared by Mann-Whitney U test

Serum and lower respiratory tract host-response biomarker profiles

We compared host-response biomarkers at study enrollment between ARDS patients with and without COPD/emphysema. Most had biomarker data available (eTable 1). Serum biomarkers assessing systemic inflammation, endothelial injury, epithelial injury, and host response to bacterial infection did not significantly differ between groups (Table 2). Membership to a hyperinflammatory host response subphenotype did not differ between ARDS patients with (28%) or without COPD/emphysema (24%, $p=0.65$). In exploratory analyses, we investigated host response biomarkers in lower respiratory tract samples in a subset of patients (ARDS without COPD/emphysema $n=48$; ARDS with COPD/emphysema $n=9$) and similarly did not detect significant differences (eTable 2).

Clinical outcomes

Median duration of mechanical ventilation (7 [4–16] versus 12 [6–20] days, $p=0.04$) and ICU length of stay (10 [7–18] versus 17 [9–28] days, $p=0.01$) were shorter in ARDS patients with COPD/emphysema versus ARDS patients without COPD/emphysema. We hypothesized this may be due to differences in the prevalence of COVID-19 between groups. In the subgroup of patients without COVID, the duration of mechanical ventilation was 5 [3–9] and 6 [3–13] days in the ARDS patients with and without COPD/emphysema respectively ($p=0.29$), and ICU length of stay was 8 [5–12] and 10 [6–18] days respectively ($p=0.09$). In the subgroup of patients with COVID, the duration of mechanical ventilation was 11 [7–18] and 19 [10–29] days with and without COPD/emphysema respectively ($p=0.73$), and ICU length of stay was 10 [8–19] and 27 [13–38] days respectively ($p=0.28$). Kaplan-Meier curves of unadjusted time to liberation from mechanical ventilation (eFigure 1 A) demonstrate an initial separation between both groups between 3 and 14 days, but the overall number liberated appears equivalent by 30 days.

Early glucocorticoid use did not differ significantly between ARDS patients with and without COPD/emphysema (61% versus 74%, $p=0.06$) (Table 3). Dexamethasone regimens were most common in ARDS patients with COPD/emphysema (37% of those receiving glucocorticoids), and hydrocortisone regimens were most common in those without COPD/emphysema (37%). Many advanced therapies for ARDS were less commonly used in ARDS patients with COPD/emphysema, including prone positioning (23% versus 44%, $p<0.01$), ECMO

Table 3 Receipt of therapeutic interventions compared between ARDS patients with and without COPD/emphysema

Treatment	No COPD/emphysema	COPD/emphysema	*p*-value
Early glucocorticoids, any	119 (74.4%)	35 (61.4%)	0.06
Type of glucocorticoid received			
Dexamethasone	44 (37.0%)	8 (22.9%)	0.74
Hydrocortisone	39 (32.8%)	13 (37.1%)	
Methylprednisolone	15 (12.6%)	5 (14.3%)	
Prednisolone	2 (1.7%)	1 (2.9%)	
Prednisone	5 (4.2%)	2 (5.7%)	
Mixed regimens	14 (11.8%)	6 (17.1%)	
Prone positioning	70 (43.8%)	13 (23.2%)	< 0.01
Neuromuscular blockade	89 (55.6%)	23 (41.1%)	0.06
Inhaled pulmonary vasodilators	21 (13.1%)	6 (10.7%)	0.64
ECMO	25 (15.6%)	3 (5.3%)	0.05
Tracheostomy	50 (31.3%)	9 (15.8%)	0.02

Data are presented as n (%) or median [interquartile range]. p-values represent differences between groups compared by chi-squared analysis or Mann-Whitney U test as appropriate

(5% versus 16%, $p=0.05$), and tracheostomy (16% versus 31%).

Mortality did not differ significantly between ARDS patients with or without COPD/emphysema (90-day mortality 40% with COPD/emphysema and 37% without COPD/emphysema, $p=0.64$). Mortality at 90 days did not differ between groups in unadjusted analyses (odds ratio [OR] 1.16, 95% CI 0.62–2.15, $p=0.64$) or in analyses adjusted for age, history of congestive heart failure, and COVID-19 status (OR 0.87, 95% CI 0.43–1.76, $p=0.69$).

Sensitivity analyses

First, when the subgroup of ARDS patients was restricted only to patients with a documented history of COPD in the electronic medical record ($n=41$), differences between groups in baseline demographics, comorbidities, and laboratory values were consistent with the primary analyses, as were the lack of significant differences in mechanical ventilation parameters, host response biomarkers, and mortality (eTables 3–6). Second, when the subgroup of ARDS patients was restricted to only patients with anatomic emphysema on CT imaging ($n=28$), differences in age, race, and history of congestive heart failure were no longer significantly different. Body mass index was lower in ARDS patients with emphysema compared to those without COPD (median 31.2 [IQR 26.4–36.1] versus 26.7 [23.7–33.9], $p=0.01$). Other comorbidities, laboratory values, host response biomarkers, and mortality were otherwise similar in ARDS patients with emphysema compared to those without COPD (eTables 7–10). Third, some differences in ARDS treatments emerged in sensitivity analyses focused on ARDS with a chart diagnosis of COPD or on ARDS with anatomic emphysema but trends remained similar with numerically lower use of glucocorticoids or advanced ARDS therapies in the ARDS group without COPD/emphysema.

Discussion

We performed a detailed assessment of the differences in baseline demographics, comorbid conditions, mechanical ventilation parameters, systemic and pulmonary host responses, and clinical outcomes in ARDS patients with and without COPD or emphysema. We found that, generally, pre-existing COPD or emphysema did not impact ARDS pathogenesis. ARDS patients with COPD or emphysema were older, more likely to be male, and had a higher prevalence of heart failure compared to ARDS patients without COPD or emphysema, but other comorbidities and severity of illness were similar. The ventilatory ratio was higher on study enrollment in ARDS patients with COPD or emphysema, suggesting a higher fraction of dead space, but otherwise, ventilator parameters were comparable. Host response biomarker profiles did not differ between groups in serum or in lower respiratory tract samples. Median duration of mechanical ventilation and ICU length of stay were slightly shorter in ARDS patients with COPD or emphysema, but overall mortality at 90 days did not differ between groups. Use of advanced therapies for ARDS was lower in ARDS patients with COPD or emphysema, and early glucocorticoid use was similar or slightly less frequent.

COPD is a common comorbidity in critically ill patients, and the prevalence of COPD or emphysema in our ARDS cohort was ~26%. While our prevalence is slightly higher than the ~20% reported in LUNG-SAFE, prior studies investigating COPD in ARDS relied on a review of the medical record for diagnosis. By performing a systematic investigation into radiologic evidence of anatomic emphysema, our study likely grouped more ARDS patients into the COPD or emphysema group and less into the no COPD or emphysema group. Notably, diagnosing ARDS may be more challenging in the setting of COPD or emphysema. First, anatomic emphysema may obfuscate the detection of bilateral airspace opacities. Second, the threshold for hypoxia criteria may be reached more easily in COPD or emphysema patients, resulting in uncertainty on the etiology of respiratory failure as secondary to ARDS, COPD, or a combination of both. Our study managed these challenges by consensus of at least three board-certified intensivists for ARDS classification.

Consistent with prior reports, our study demonstrates that the mechanical ventilation delivered to ARDS patients with COPD or emphysema is similar to patients without COPD [26]. We hypothesized that the respiratory mechanics and gas exchange characteristics in ARDS patients with COPD or emphysema at baseline would be characterized by lower elastance (or higher compliance), worse gas exchange, and dynamic hyperinflation [27]. We found both groups had similar static compliance of the respiratory system and similar gas exchange, which is noteworthy given prior studies demonstrating differences in ventilation practices and outcomes for patients with COPD exacerbations and ARDS patients [11]. Since both groups of ARDS patients had severe acute hypoxemic respiratory failure, baseline differences in groups may have been overcome by the severity of illness and lung injury. Our findings are consistent with findings from the PRoVENT-COVID study (a multicenter, observational cohort study done in patients with COPD and COVID ARDS in the Netherlands) and do not support the theoretical notion that ARDS with COPD is a separate clinical phenotype distinct with a "low-elastance" ARDS phenotype [26]. Several questions remain unanswered. Recent studies have highlighted heterogeneity within ARDS and within COPD [28–31], and delivery of mechanical ventilation may require consideration of individual variations

in risk of dynamic intrinsic PEEP, tendency toward hypercapnia and respiratory acidosis, severe flow limitations, altered lung compliance, and gas exchange deficits. Notably, many landmark ARDS trials excluded patients with severe chronic lung disease, but future studies with larger sample sizes may be able to answer unanswered questions in personalizing ventilation in ARDS with COPD or emphysema in specified subgroups [4].

To the best of our knowledge, our study is the first to investigate differences in host response biomarkers in the plasma and lower respiratory tract samples of patients with ARDS with and without COPD or emphysema. In the outpatient setting, COPD patients exhibit higher circulating levels of IL-6 and IL-8 and lower levels of sRAGE than healthy controls [32]. However, ARDS is characterized by a much more severe and acute inflammatory lung response [33]. Our finding of the similarity in plasma and lower respiratory tract biomarker profiles could potentially be attributed to the fact that both groups experienced an acute insult leading to ARDS, had similar rates of pulmonary insults, and exhibited comparable severity of illness, overwhelming any differences in baseline local or systemic host responses. We acknowledge two caveats in the interpretation of the host response. First, we recognize that most patients in our ARDS with COPD or emphysema group had no or minimal anatomic emphysema. Higher severity of anatomic emphysema may alter lung and systemic host responses, but the low prevalence of severe emphysema in our cohort prevented an in-depth study. Second, we did not have spirometry data available for participants in our study and recognize that both that currently spirometry and not emphysema is required for diagnosis of COPD and that differences in biologic responses may emerge based on the severity of obstruction.

We noted that ARDS patients with COPD or emphysema in our study had shorter ICU stay and shorter duration of mechanical ventilation compared to ARDS patients without COPD but similar 90-day mortality. Our findings contrast the results of prior studies in COVID patients with ARDS, which showed higher 28-day and 90-day mortality in patients with COPD [26, 34, 35], but are consistent with a single-center cohort study that showed COPD did not increase rates of ICU admission, mechanical ventilation, or in-hospital mortality in COVID-19 when adjusting for other comorbid conditions [36]. We hypothesize the shorter duration of mechanical ventilation and ICU length of stay in ARDS patients without COPD or emphysema is attributable to the differences observed in ARDS therapies. Glucocorticoid use did not differ significantly between groups in our study and may even have been lower in the ARDS with COPD or emphysema group but may have been more efficacious in liberation from mechanical ventilation, particularly given the higher prevalence of asthma and if a concomitant COPD exacerbation had been present. Furthermore, the higher use of prone positioning, ECMO, and tracheostomy in our cohort suggests that the extent of lung injury may have been more severe in ARDS patients without COPD or emphysema despite similar severity of illness scores. Our cohort may also have a lower prevalence of participants with rapidly improving ARDS (a clinical phenotype of ARDS characterized by rapid resolution of lung injury) compared to prior observational studies such as LUNG-SAFE as such patients may improve before recruitment efforts are successful [1, 37, 38].

Our study does have several additional limitations to acknowledge. First, our study included primarily ARDS patients requiring mechanical ventilation. Newer definitions of ARDS may include patients on high-flow nasal cannula oxygen but not on mechanical ventilation. We hypothesize that such modalities may be preferred for ARDS patients with chronic lung diseases such as COPD when possible and may have been missed in our cohort. Second, we did not have detailed information on the severity of baseline hypoxia in our COPD patients. We hypothesize that the need for home oxygen may impact gas exchange in COPD patients with ARDS. Third, we investigated host response biomarkers and mechanical ventilation parameters on study enrollment but acknowledge that the time from hospitalization to time of study enrollment, as the use of other modalities such as high flow oxygen or non-invasive ventilation, may have differed between groups and will be a focus of future studies. Fourth, our study design required the presence of a CT chest in patients without a chart diagnosis of COPD to assess anatomic emphysema to increase confidence in our comparison groups but this inclusion criteria may have introduced a selection bias in our study.

Conclusion

In conclusion, our findings suggest that ARDS patients with COPD or emphysema are similar to ARDS patients without COPD or emphysema in several key clinical, physiologic, and biologic parameters, but further study is warranted. Personalization of ARDS care is a research priority, and consideration should be given to the impact of chronic conditions alongside strategies guided by biologic responses or clinical signatures on presentation [13, 39, 40]. The clinical and biological heterogeneity within COPD underscores the importance of larger studies to understand the difference in pathogenesis, recovery, and effect on quality of life in patients with COPD who develop ARDS.

Abbreviations

ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease

COVID-19	Coronavairus-19
ALIR	Acute Lung Injury and Biospecimen Repository
IL	Interleukin
sTNFR-1	Soluble tumor necrosis factor receptor-1
ST-2	Suppressor of tumorigenicity-2
RAGE	Receptor of advanced glycation end-products
Ang-2	Angiopoietin-2
SOFA	Sequential organ failure assessment
ΔP	Driving pressure
PEEP	Positive end-expiratory pressure
Pplat	Plateau pressure
Pmax	Maximum airway pressure
VR	Ventilatory ratio
PaCO2	Partial pressure of carbon dioxide in arterial blood
CRS	Respiratory system compliance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-024-03027-2.

Supplementary Material 1

Acknowledgements
None.

Author contributions
SN, JB, JE, and FAS conceived and designed the study. SN, HQ, HA, and FAS performed the acquisition of data, performed statistical analyses, and drafted the initial manuscript. FAS, GDK, WB, and BJM provided resources for the completion of the study. SN, HQ, HA, GDK, WB, TS, NP, MH, CS, YZ, JB, BJM, JE and FAS contributed to the interpretation of data, reviewed the manuscript, provided significant contributions to the writing and editing of the manuscript, and agreed to the submission of the final version.

Funding
This manuscript is supported by grants from the National Institutes of Health: K23GM122069 (FAS); P01HL114453 (BJM).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All research was conducted consistent with standards set in the Declaration of Helsinki. All participants in this study were enrolled in the Acute Lung Injury Registry and Biospecimen Repository (ALIR) at the University of Pittsburgh after obtaining informed consent from patients or legally authorized representatives. ALIR protocols have been approved by the Human Research Office at the University of Pittsburgh under protocol number STUDY19050099.

Consent to publish from the patient
Not Applicable. No identifying images or other personal or clinical details of participants are presented that compromise anonymity.

Consent for publication
All authors reviewed the final version of the manuscript and consented to submission and publication.

Competing interests
GDK has received research funding from Karius, Inc., Pfizer, Inc., and Genentech, Inc, unrelated to this work. BJM has received grant funding from Genentech and consulting fees from BioAegis, Beohringer Ingelheim, and Synairgen Research.

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Received: 25 July 2024 / Accepted: 25 October 2024
Published online: 08 November 2024

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