OBSERVATIONAL STUDY

OPEN

Hypoxemia Trajectory of Non-COVID-19 Acute Respiratory Distress Syndrome Patients. An Observational Study Focusing on Hypoxemia Resolver Status

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IMPORTANCE: Most studies on acute respiratory distress syndrome (ARDS) group patients by severity based on their initial degree of hypoxemia. However, this grouping has limitations, including inconsistent hypoxemia trajectories and outcomes.

OBJECTIVES: This study explores the benefits of grouping patients by resolver status based on their hypoxemia progression over the first 7 days.

DESIGN, SETTING, AND PARTICIPANTS: This is an observational study from a large single-center database. Medical Information Mart for Intensive Care (MIMIC)-IV and MIMIC Chest X-ray JPEG databases were used. Mechanically ventilated patients that met the Berlin ARDS criteria were included.

MAIN OUTCOMES AND MEASURES: The primary outcome was the proportion of hypoxemia resolvers vs. nonresolvers in non-COVID-19 ARDS patients. Nonresolvers were defined as those whose hypoxemia worsened or remained moderate or severe over the first 7 days. Secondary outcomes included baseline admission characteristics, initial blood gases and ventilation settings, length of invasive mechanical ventilation, length of ICU stay, and ICU survival rates across resolver groups.

RESULTS: A total of 894 ICU admissions were included in the study. Of these, 33.9% were hypoxemia nonresolvers. The resolver groups showed no significant difference in age, body mass index, comorbidities, or Charlson score. There was no significant difference in the percentage of those with initial severe hypoxemia between the two groups (8.1% vs. 9.2%; $p = 0.126$). The initial Pao_2/Fio_2 ratio did not significantly increase the odds ratio (OR) of being a nonresolver (OR, 0.84; 95% CI, 0.65–1.10). Nonresolver mortality was 61.4%, comparable to the survival rates seen in nonresolvers in a previous large COVID-19 ARDS study.

CONCLUSIONS AND RELEVANCE: Our study shows that resolver status is a valuable grouping in ARDS. It has significant advantages over grouping by initial degree of hypoxemia, including better mapping of trajectory and comparable outcomes across other studies. While it may offer insights into disease-specific associations, future studies should include resolver status analysis for more definitive conclusions.

KEYWORDS: acute respiratory distress syndrome; critical care; hypoxemia; intensive care units

The definition, diagnosis, and categorization of acute respiratory distress syndrome (ARDS) has had a long and evolving history and remains a contentious point among experts (1, 2). The Berlin criteria represent the current agreed standard for defining the diagnosis and severity of ARDS (3). Within this, grouping hypoxemia severity into mild, moderate, and severe based on initial

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KEY POINTS

Question: This study explores whether hypoxemia resolver status is a valuable grouping in non-COVID-19 acute respiratory distress syndrome (ARDS) patients.

Findings: Our findings show that hypoxemia resolver status has significant advantages over grouping by initial degree of hypoxemia, used in most other ARDS studies. It shows better mapping of trajectory and comparable outcomes across other studies and may provide insights into disease-specific associations.

Meaning: We recommend that more ARDS studies include resolver status in their research to strengthen conclusions about this grouping.

Pao_2/Fio_2 (P/F) ratios, allows a formal definition group for research and therapeutic comparisons. The grouping has some predictive validity and enables the identification of risk factors associated with the syndrome (3). Despite this, ARDS remains difficult to diagnose, with mild ARDS being missed in 50% and severe ARDS in 20% of cases (4). Some also dispute the value of the initial P/F ratio as the hallmark of defining severity (2, 3). Some studies demonstrate a rapid increase in the P/F ratio over the first 48 hours of intubation (3), suggesting initial P/F values are poor at predicting hypoxemia trajectory. Gattinoni and Marini (1) suggest that new ways of grouping ARDS patients should be investigated to help identify other subgroups in ARDS that could benefit from differentiated treatment. They argue that this will become increasingly important as the rest of the medical field moves toward personalized medicine.

The arrival of COVID-19 ARDS further widened the debate around whether all ARDS should be considered the same or whether subgroups exist and should be managed separately (1, 5–8). Some evidence suggests COVID-19 ARDS patients have similar outcomes to those with non-COVID-19 ARDS (9) and respond similarly to standard ARDS treatments (6, 10). In contrast, other studies argued that COVID-19 ARDS represents a distinct group from non-COVID-19 ARDS (termed ARDS throughout this article) in both its definition and applied management. They suggested that identifying subgroups is vital to direct specific treatments to different ARDS phenotypes (5, 7). One novel method of phenotypic grouping of ARDS divides patients into resolvers or nonresolvers based on their hypoxemia progression over the first 7 days. This was used in a large multicenter COVID-19 ARDS study (11) in the United Kingdom but has not been used in any other ARDS studies. The study identified factors associated with being a nonresolver and the differential trajectories and outcomes based on resolver status.

In this study, we explored whether the nonresolver/resolver relationship seen in COVID-19 ARDS is applicable in ARDS. We used the COVID-19 study (11) as the basis of our statistical analysis plan and mirrored the grouping of patients into resolvers and nonresolvers. We aimed to quantify the size of the nonresolver group and identify factors associated with hypoxemia resolver status in ARDS. We predicted that nonresolvers would have distinct associated factors and outcomes compared with resolvers in the ARDS population.

METHODS

Study Design

This was an observational study of granular daily data from invasively mechanically ventilated (IMV) patients with ARDS from a large single-center database.

Data Sources

Two data sources from the Medical Information Mart for Intensive Care (MIMIC) database were used. The core database was MIMIC-IV database (12, 13), which has collated over 30,000 adults' (16 yr old and above) critical care data admitted to ICUs at the Beth Israel Deaconess Medical Centre (BIDMC) Massachusetts (United States) between 2008 and 2019. The second complementary dataset is MIMIC Chest X-ray JPEG (14), a database that contains labeled chest radiographs for MIMIC-IV patients. Labels were derived using the associated free-text radiologist reports and natural language processing with two validated open-source labeling tools, NegBio (National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD) (15) and CheXpert (Department of Computer Science, Stanford University, CA) (16). Access to both datasets was gained through an application via PhysioNet (Margret and H.A. Rey Laboratory for Nonlinear

Dynamics in Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA) (17).

Selection

Criteria for patient inclusion in the study required all of the following conditions:

1) Initiation of IMV.
2) Evidence of hypoxemia on the day of intubation, defined by a P/F ratio of less than 40 kPa (300 mm Hg) (3).
3) Evidence of bilateral infiltrates on chest radiograph: Labeled as "bilateral" AND "infiltrates" by the NegBio and CheXpert tools (18) within the previous week (day 7) or the subsequent 2 days (day 2) from the time of intubation.

The start time of mechanical ventilation (intubation) was identified by the first instance of any mechanical ventilation code (e.g., positive end-expiratory pressure [PEEP], pressure support, inspiratory pressure, ventilator mode, minute volume, etc.). Patients were excluded if these ventilation codes included noninvasive mechanical ventilation methods, including high-flow nasal cannula, bilevel positive airway pressure, or continuous positive airway pressure. Extubation was identified by codes for either a specific extubation event, noninvasive oxygen therapy, or noninvasive ventilation (18).

Criteria that excluded patients from the study included:

1) Intubation length of less than 24 hours.
2) *International Classification of Diseases*, 10th Revision diagnostic code for concurrent acute heart failure, to exclude bilateral infiltration attributable to hydrostatic edema, as per the Berlin criteria (3).
3) Those who received extracorporeal membrane oxygenation (ECMO) during their ICU stay. This aligned with their exclusion from the COVID-19 U.K. study (11).

Variables

Patients were analyzed based on both their initial hypoxemia status at intubation and their progression of hypoxemia over the first 7 days of intubation. Initial hypoxemia status was categorized as per the Berlin definition criteria (3): mild hypoxemia (P/F ratio: 26.7–40.0 kPa or 200–300 mm Hg); moderate hypoxemia (P/F ratio: 26.7–13.3 kPa or 100–200 mm Hg); and severe hypoxemia (P/F ratio < 13.3 kPa or < 100 mm Hg). For progression, we categorized the evolution of hypoxemia over the first 7 days into either "resolvers" or "nonresolvers" as was done in the COVID-19 study (11). Patients who moved to a less severe hypoxemia category (e.g., from severe to moderate), remained mild or were discharged from ICU were categorized as "resolvers." Patients who moved to a more severe hypoxemia category, remained moderate or severe, or died were categorized as "non-resolvers." Non-COVID-19 ARDS is shortened to ARDS for simplicity throughout this study. All-cause ARDS is used to describe both non-COVID-19 and COVID-19 ARDS inclusively.

Primary Outcome

The primary outcome was the proportion of hypoxemia nonresolvers in the ARDS population.

Secondary Outcomes

Secondary outcomes included baseline characteristics (gender, age, body mass index [BMI]), admission characteristics (admission type [emergency or elective] and time from admission to intubation), comorbidities (including Charlson score), ICU type (medical, surgical, or cardiac), initial blood gas results and ventilator measurements on day 0 of intubation, outcomes (length of IMV, length of ICU stay [LOS], and ICU survival rates), and discharge destination across resolver status groups. Analysis was also performed across initial P/F ratio groups (mild, moderate, and severe). Progression of P/F ratio, blood gas parameters, and ventilator settings were also analyzed over time.

Data Processing and Analysis

The final daily blood gas and ventilator setting parameter was taken for each patient for analysis from the beginning of intubation until extubation, discharge, or death. For the initial (day 0 of IMV) value analysis, continuous variables were analyzed with Mann-Whitney *U* or Kruskal-Wallis tests, as appropriate. Categorical variables were compared using the Fisher exact test or the chi-square test for equal proportion, as appropriate. A p value of less than or equal to 0.05 was considered statistically significant, and all statistical tests were two-sided. Missing data was imputed using the Last Observation Carried Forward method, with the limit of carrying forward being 1 day previous. Time series plots used the mean daily values from day 0 to 20 of IMV with 95% CIs. Hypoxemia trajectories were analyzed as the change in hypoxemia status over time, from intubation to ICU discharge or death. Univariable

odds ratios (ORs) were calculated for odds of being a nonresolver vs. resolver, with all continuous variables being transformed into categorical variables based on quartiles to enable interpretable and comparable ORs. ORs were calculated from the initial values at the time of intubation (e.g., day 0). Multivariable logistic regression models were applied (with screening univariable; $p < 0.1$) to resolver status to test associations with independent variables. Kaplan-Meier curves were analyzed, and the curves between groups were compared for statistical significance using the log-rank test. Length of IMV, LOS, and percentages for specific discharge destinations were only calculated for survivors to reduce bias. Data was extracted from crude data tables using PostgreSQL (PostgreSQL Global Development Group, Santa Barbara, CA). Analysis was completed using R Studio (Boston, MA, R Version 1.2.5033).

Ethics Approval

The Multiparameter Intelligent Monitoring in Intensive Care-IV database was approved by the Institutional Review Board (IRB No. 0403000206) of the BIDMC (IRB Protocol No. 2001P001699). It was granted a waiver of informed consent (13). Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements. As a purely observational study, no procedures were performed.

RESULTS

Baseline Demographics, Comorbidities, and Admission Details

A total of 894 patients with ARDS were included in the study, which represented 2.7% of all ICU admissions (**Supplementary Fig. 1**, http://links.lww.com/CCX/B257). Of all included patients, 33.9% were hypoxemia nonresolvers (**Supplementary Table 1**, http://links.lww.com/CCX/B257). There was no significant difference in age, BMI, comorbidities, or Charlson score between the resolver groups (Supplementary Table 1, http://links.lww.com/CCX/B257; and **Fig. 1**). There was no significant difference in the admission type, ICU type, or time to intubation between the resolver groups (Supplementary Table 1, http://links.lww.com/CCX/B257).

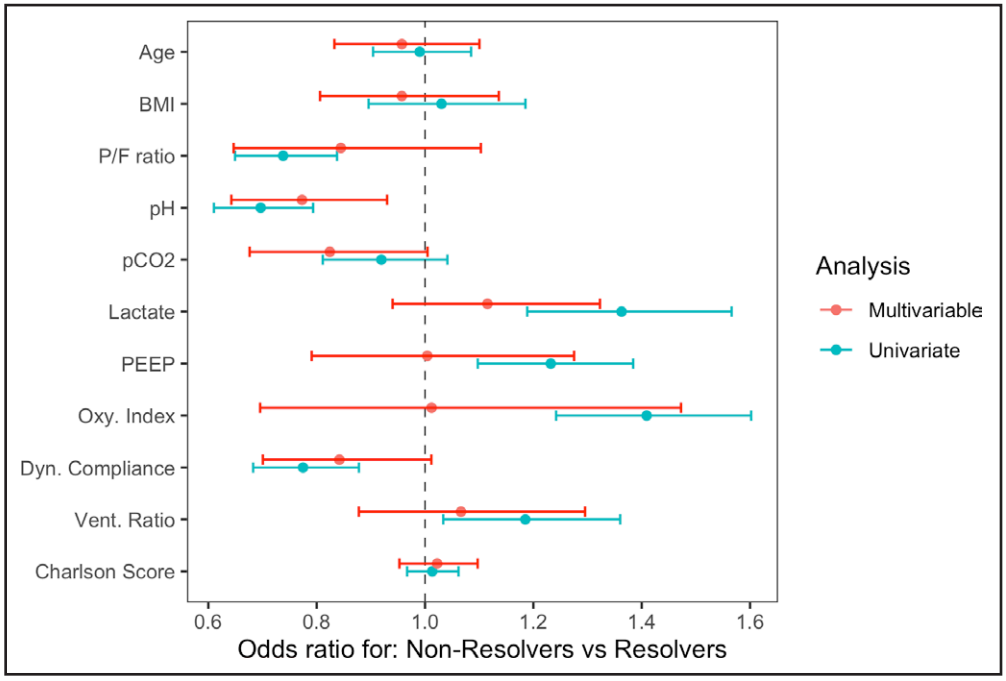

Figure 1. Odds ratios of being a nonresolver vs. resolver for baseline characteristics, blood gases, and ventilator settings. Univariant analysis in *blue*. Multivariable analysis in *red*. The odds ratios for these continuous variables depicted the risk increase per quartile increase in measurement. Odds ratios for age are presented per decade increase, Charlson score depicted an increase per unit increase in score, and binary variables depicted the odds ratios of being positive (e.g., male or the presence of a specific comorbidity). BMI = body mass index, dyn. compliance = dynamic compliance, oxy. index = oxygenation index, P/F = Pao_2/Fio_2 ratio, PEEP = positive end-expiratory pressure, vent. ratio = ventilatory ratio.

Initial Blood Gases and Ventilation Settings

Nonresolvers did have a slightly lower P/F ratio (22.7 kPa [170 mm Hg] vs. 26.4 kPa [198 mm Hg]; $p < 0.001$; Supplementary Table 1, http://links.lww.com/CCX/B257). However, the mean initial degree of hypoxemia for both resolver groups was within the moderate hypoxemia category (26.7–13.3 kPa or 100–200 mm Hg). Furthermore, in our multivariable OR analysis, a decrease in the P/F ratio did not significantly increase the odds of being a nonresolver (OR, 0.84; 95% CI,

0.65–1.10; Fig. 1). A higher proportion of those with initial moderate hypoxemia progressed to become nonresolvers (40.3%; **Supplementary Table 2**, http://links.lww.com/CCX/B257) compared with those with severe hypoxemia (36.8%). There was no significant difference in the percentage of those with initial severe hypoxemia between the two resolver groups (8.1% vs. 9.2%; $p = 0.126$; Supplementary Table 1, http://links.lww.com/CCX/B257).

Of the other initial blood gas parameters, pH was significantly lower in nonresolvers (**Table 1**) and showed a reduced OR for nonresolvers (OR, 0.77; 95% CI, 0.64–0.92; Fig. 1). Pco_2 was not significantly different between the groups. Although lactate was higher in the nonresolver group (1.9 vs. 1.5 mmol/L; $p < 0.001$), it did not display a significantly higher OR in our multivariable analysis (Fig. 1). Nonresolvers required higher intensity of ventilatory support on the first day of ventilation, as seen by higher PEEP (7.0 vs. 9.0 cm H_2O; $p < 0.001$; Supplementary Table 1, http://links.lww.com/CCX/B257) and peak inspiratory pressure (22.0 vs. 24.0 cm H_2O; $p < 0.001$). Nonresolvers also displayed greater severity of organ failure as seen by significantly higher oxygenation index (7.3 vs. 5.6; $p < 0.001$), higher ventilatory ratio (1.7 vs. 1.6; $p < 0.017$), and lower dynamic compliance (28.5 vs. 33.3 mLs/cm H_2O; $p < 0.001$; Supplementary Table 1, http://links.lww.com/CCX/B257).

Initial Hypoxemia and Hypoxemia Trajectories

The proportion of patients with initial mild, moderate, and severe hypoxemia was 44.3%, 47.2% and 8.5%, respectively (Supplementary Table 2, http://links.lww.com/CCX/B257). Hypoxemia improved for 33.6%, remained constant for 45.9% and worsened for 20.5% (Table 1 and **Fig. 2**) over the first 7 days.

Resolvers had a rapid improvement in their P/F ratio over the first 5 days (**Supplementary Fig. 2**, http://links.lww.com/CCX/B257), whereas there was minimal improvement in the P/F ratio of nonresolvers over this time. However, time series grouped by initial hypoxemia severity showed that patients with moderate and severe initial hypoxemia showed rapid improvement of hypoxemia within the first week of intubation (**Supplementary Fig. 3**, http://links.lww.com/CCX/B257). This pattern was reflected in the progression of patients with moderate and severe hypoxemia displayed in the alluvial plot (Fig. 2).

Outcomes

Overall survival across all patients was 70.2%. Nonresolvers had a higher mortality than resolvers (61.4 % vs. 14.2%, respectively; $p < 0.001$; Supplementary Table 1, http://links.lww.com/CCX/B257; and **Fig. 3**). Nonresolvers had an increased length of mechanical ventilation compared with resolvers (4.0 vs. 5.7 d, respectively; $p = 0.001$; Supplementary Table 1, http://links.lww.com/CCX/B257). ICU LOS was similar between resolvers and nonresolvers.

Group analysis by initial hypoxemia category showed a mortality gradient associated with severe hypoxemia (mortality 39.5 %) when compared with moderate (30.3%) and mild (28.3) (Supplementary Table 2, http://links.lww.com/CCX/B257; **Supplementary Fig. 4**, http://links.lww.com/CCX/B257). Length of IMV was lowest in those with initial mild hypoxemia (3.7 d

TABLE 1.

Percentages of Patients Changing Between Mild, Moderate, and Severe Hypoxemia Categories From Day 1 to Day 7 of Invasive Mechanical Ventilation

		P/F Day 7 Medical Information Mart for Intensive Care			
		> 26.7	13.3–26.6	< 13.3	Total
P/F Day 0	> 26.7	73.4%	11.3%	15.1%	20.5%
	13.3–26.6	59.7%	21.6%	18.7%	
	< 13.3	34.2%	28.9%	36.8%	
	Total	33.6%			45.9%

P/F = Pao_2/Fio_2 ratio.

Percentages in red, orange, or blue reflect those who have worsened, remained static, or improved hypoxemia status, respectively, over the 7 d.

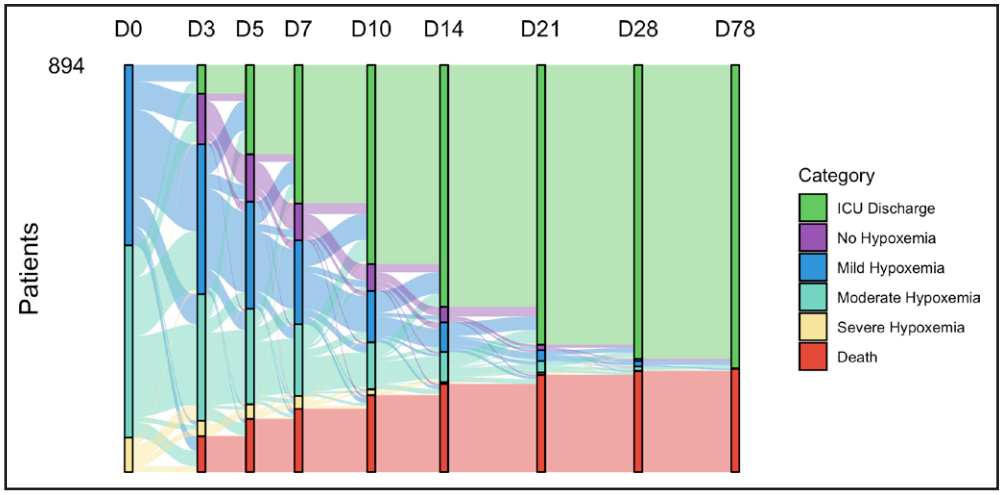

Figure 2. Alluvial plot showing the initial hypoxemia status (no hypoxemia, mild, moderate, and severe, *left side* of the plot) and progression to either ICU discharge or death (*right side* of the plot) in acute respiratory distress syndrome patients. Day 0 represents the initiation of invasive mechanical ventilation.

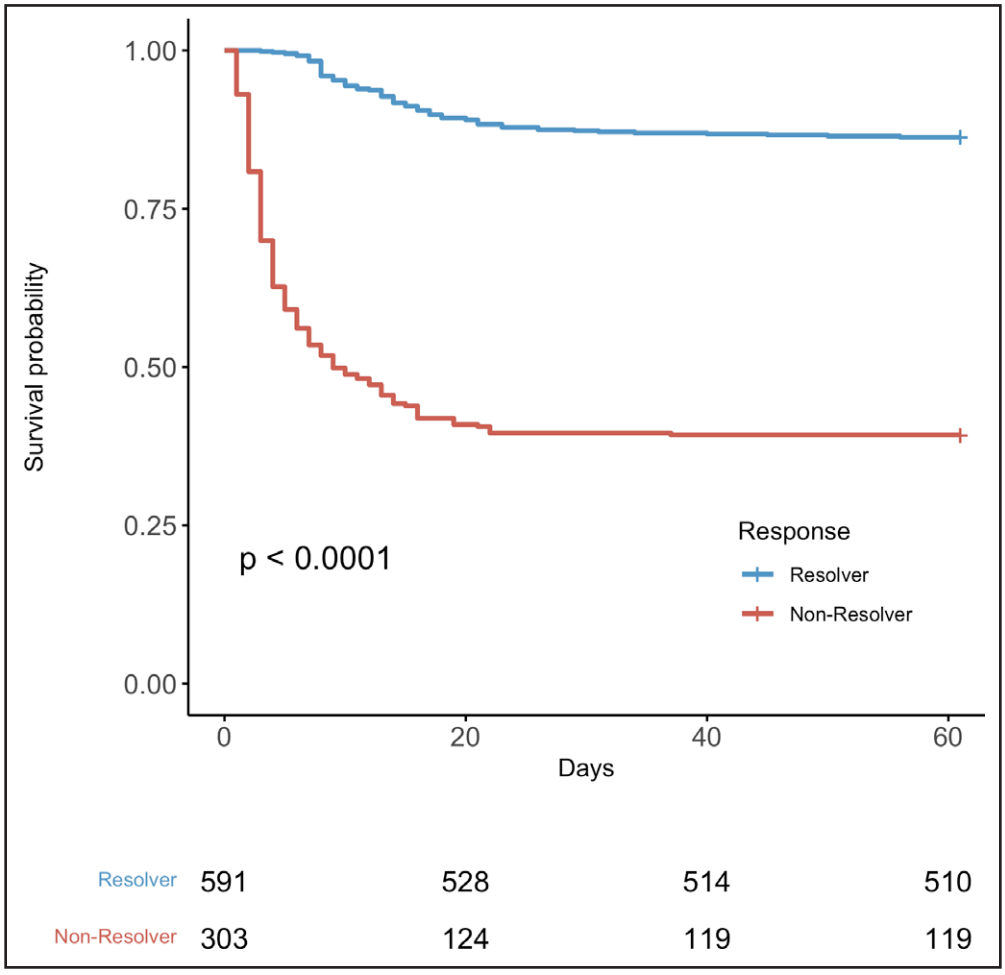

Figure 3. Survival plot showing the probability of hospital survival in days from the first day of invasive mechanical ventilation grouped by resolver/nonresolver status in acute respiratory distress syndrome.

[2.0–8.3 d]; Supplementary Table 2, http://links.lww.com/CCX/B257) and was significantly higher in those with initial severe hypoxemia (6.3 d [2.5–11.8 d]; $p = 0.011$).

DISCUSSION

Findings

Of all included patients, 33.9% were hypoxemia nonresolvers. Nonresolvers had a higher mortality than resolvers (61.4 % vs. 14.2%, respectively; $p < 0.001$). Age, BMI, and comorbidities, including Charlson score, did not appear to be associated with resolver status. Interestingly, the correlation between the initial degree of hypoxemia and resolver status was weaker than expected despite severe initial hypoxemia being a part of the definition of nonresolver status. There was a small absolute difference in the initial P/F ratios between resolver groups. However, the P/F ratio did not significantly affect the odds of being a nonresolver, and hypoxemia categories did not map consistently to a particular resolver status.

Findings in Context

We performed this study to identify whether the resolver status grouping seen in previous COVID-19 populations (11) was generalizable to ARDS.

Comparing the two populations, there was a lower proportion of nonresolvers in ARDS (33.9% vs. 57.9% in COVID-19 ARDS). The overall mortality of ARDS patients was significantly lower than COVID-19 ARDS patients (29.8% vs. 57.7%, respectively).

Interestingly, nonresolvers' mortality was similar in the two populations (61.4% in our study vs. 60.4% COVID-19 ARDS). Mortality of resolvers was also comparable (14.2% vs. 17.6%). Nonresolvers had similar survival rates despite all the differences in the study cohorts, explored further in our limitations, including that the COVID-19 cohort was early in the pandemic before many treatments were available. This suggests that resolvers may offer a phenotypic grouping applicable across all causes of ARDS.

In the COVID-19 cohort, certain risk factors were associated with nonresolvers, including age and presence of hypertension, congestive heart failure, and previous myocardial infarction (11). These factors were not found in our study, highlighting that analysis of resolver groups can identify disease-specific associations. This is particularly useful as ARDS is often diagnosed and managed as one large group without an appreciation of such cause-related factors.

Our finding that the initial degree of hypoxemia did not correlate strongly with resolver status was also reflected in the COVID-19 ARDS study. This was displayed first by moderate hypoxemia being the most prevalent initial hypoxemia severity of nonresolvers in both studies. Second, there was no significant difference in the proportion of patients with initial severe hypoxemia between resolver groups in both our results and the COVID-19 study (11). There is also evidence from our results and others (19) that there is a rapid improvement in the P/F ratio within the first 48 hours after intubation, which is also not captured by the stratification of groups based on only their initial P/F ratio.

Furthermore, there was a large variation in mortality of the initial hypoxemia categories between the two studies, with lower mortality in the severe (39.5% vs. 51.8%) and moderate (30.3% vs. 44.4%) hypoxemia groups in our study compared with the COVID-19 study. Significant variation in the outcomes of initial hypoxemia groups has been widely reported in many other ARDS studies (11, 20–22). There are also inconsistent patterns when comparing the first and second waves of COVID-19. Some studies showed an improvement in mortality within these hypoxemia groups (23), whereas others showed no improvement (24) or a worsening (25). Such significant variations in outcomes highlight the limitations in using the initial degree of hypoxemia to define groups that are robust and consistent enough to allow meaningful comparisons to be identified.

Our study suggests that hypoxemia progression, as denoted by resolver status, should be considered alongside the initial degree of hypoxemia to define severity in ARDS. In research, it could be used to define phenotypic subgroups of patients that have reproducible outcomes across all causes of ARDS. This would enable more reliable conclusions to be made from comparing risk factors, response to interventions and outcomes between these resolver groups. This could be applied to both specific causes of ARDS and all-cause ARDS. In a clinical setting, the trajectory of hypoxemia over the first 7 days appears strongly indicative of risk stratification of the patient. It is closely tied to the patient's probability of survival. This highlights the importance of timely and well-targeted interventions within the first week to increase the proportion of resolvers. After 1 week, resolver status appears to have prognostic value, with such a stark difference in survival between the resolver status groups. Further studies should confirm this predictive validity so clinicians can use it reliably to support resource allocation, care planning, clinical decision-making, and prognostication. Further work could also aim to identify how particular ARDS interventions influence the prevalence and outcomes of nonresolvers to build on evidence-based practice.

Strengths and Limitations

Our study used granular longitudinal data collected over several years to perform a comprehensive analysis and visualization of routine clinical measurements throughout the entire ICU time course of ARDS patients. This enabled us to highlight temporal evolution and trajectories, a key strength of our analysis. The inclusion criteria used to identify ARDS patients in our study was based on the same method recommended by the curators of the MIMIC-IV database (18) and included a sizeable overall population.

However, our study is limited by its retrospective and observational design from a single center. For patient selection, we excluded patients with acute heart failure codes. However, we could not ensure objective

assessment to exclude hydrostatic edema for all patients as per the Berlin criteria (3). Furthermore, the MIMIC database lacks a comprehensive fluid status assessment, hindering the exclusion of those with fluid overload. Despite these limitations, our methods improved on some previous applications of the Berlin criteria, which do not exclude cardiac failure (26), and our ARDS prevalence was comparable to previous studies (27). Unfortunately, the MIMIC-IV cohort did not allow us to identify specific ARDS causes reliably. We could not be certain that a particular condition, such as pneumonia, was the direct cause of ARDS or a concurrent condition due to the limitations in the datasets' coding.

Our study focused on predisposing and initial factors that affect resolver status and trajectory rather than specific ARDS interventions such as PEEP titration, medication administration, or proning. We assumed that gold standard treatment was provided to all patients in our study. It is challenging to assess all intervention parameters from the MIMIC-IV database due to a lack of coding and variable accuracy in recording when interventions were initiated. Proning, in particular, was poorly coded in the MIMIC-IV dataset. Patients who had ECMO were removed from our study to mirror the COVID-19 study, which may introduce bias. However, studies suggest (28) that there is no significant difference in survival of patients who received ECMO in COVID-19 ARDS vs. ARDS, highlighting that this should not have significantly changed our overall conclusions. The study period between 2008 and 2019 is extensive. It involves significant changes in the management of ARDS over this time, including the introduction of proning (Prone Positioning in Severe Acute Respiratory Distress Syndrome, June 2013 [29]), more widespread use of steroids (30) and muscle relaxants (31), which have improved overall survival in ARDS. We could not analyze, from our results, what effect their introduction had on hypoxemia trajectories and how this may have affected the prevalence or outcomes of nonresolvers.

Another limitation of the resolver status grouping is that changes in PEEP or ventilatory settings could influence P/F ratios and thus categorization into resolver/nonresolver status. However, this is not unique to this stratification; it would be a similar case for the severity of hypoxemia being defined by the P/F ratio in the Berlin criteria. Furthermore, if a patient were to improve with PEEP, it could reflect a response to recruitment and, thus an improvement in lung prognosis and mechanics. However, there is growing support for measurements to be standardized for PEEP (19), which would be useful to explore in future work.

Comparison of our results is limited to the COVID-19 ARDS study, which is the only other study to use resolver status. However, a comparison of the two groups is challenging for several reasons. There are large differences in study design, including single vs. multicenter, era differences, different nationalities, and different resource pressures amidst the pandemic. As discussed, the long study period of our trial included the introduction of new treatments for ARDS. Furthermore, the COVID-19 U.K. study was early in the pandemic (March 2020 to August 2020), which was before landmark studies introduced dexamethasone (Randomised Evaluation of COVID-19 Therapy, February 2021 [32]) and tocilizumab (Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia, April 2021 [33]) into the routine management of severe COVID-19 ARDS. The introduction of such treatments either within the study period or soon after may reduce the generalizability of the results to other COVID-19 ARDS populations later in the pandemic. However, using an early COVID-19 cohort allowed a comparison between prior ARDS and new COVID-19 ARDS. Furthermore, despite these large differences, it was notable that the survival of the resolver groups was similar across the two populations. This reinforces our recommendation that more ARDS studies should include resolver status in their research to strengthen conclusions about this grouping.

CONCLUSIONS

Our study shows that resolver status is a valuable grouping in ARDS. It has significant advantages over grouping by initial degree of hypoxemia, used in most other ARDS studies, including better mapping of trajectory and comparable outcomes across other studies. It may provide insights into disease-specific associations, but future studies must incorporate resolver status analysis for more definitive conclusions to be drawn.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Drs. Toal, Fowler, and Prowle were involved in data curation, formal analysis, investigation, software, and visualization. Drs. Puthucheary and Prowle were involved in funding acquisition and project administration. Drs. Patel, Puthucheary, and Prowle were involved in methodology. Drs. Toal and Prowle were involved in resources. Dr. Prowle was involved in supervision. Drs. Toal, Fowler, Puthucheary, and Prowle were involved in validation. Dr. Toal was involved in writing–original draft. All authors were involved in conceptualization and writing–review and editing.

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REFERENCES

1. Gattinoni L, Marini JJ: Isn't it time to abandon ARDS? The COVID-19 lesson. *Crit Care* 2021; 25:326
2. Vincent JL, Slutsky AS: We've never seen a patient with ARDS!. *Intensive Care Med* 2020; 46:2133–2135
3. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
4. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
5. Chiumello D, Busana M, Coppola S, et al: Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: A matched cohort study. *Intensive Care Med* 2020; 46:2187–2196
6. Goligher EC, Ranieri VM, Slutsky AS: Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter? *Intensive Care Med* 2021; 47:83–85
7. Gattinoni L, Chiumello D, Caironi P, et al: COVID-19 pneumonia: Different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; 46:1099–1102
8. Lascarrou JB, Gaultier A, Soumagne T, et al; COVADIS study group: Identifying clinical phenotypes in moderate to severe acute respiratory distress syndrome related to COVID-19: The COVADIS Study. *Front Med* 2021; 8:632933
9. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al; COVID-19 Spanish ICU Network: Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med* 2020; 46:2200–2211
10. Griffiths M, Meade S, Summers C, et al: RAND appropriateness panel to determine the applicability of UK guidelines on the management of acute respiratory distress syndrome (ARDS) and other strategies in the context of the COVID-19 pandemic. *Thorax* 2022; 77:129–135
11. Patel BV, Haar S, Handslip R, et al; United Kingdom COVID-ICU National Service Evaluation: Natural history, trajectory, and management of mechanically ventilated COVID-19 patients in the United Kingdom. *Intensive Care Med* 2021; 47:549–565
12. Johnson A, Bulgarelli L, Pollard T, et al: MIMIC-IV (version 1.0). *PhysioNet* 2021. doi: 10.13026/s6n6-xd98
13. Johnson AEW, Pollard TJ, Shen L, et al: MIMIC-III, a freely accessible critical care database. *Sci Data* 2016; 3:1–9
14. Johnson AEW, Pollard TJ, Greenbaum NR, et al: MIMIC-CXR-JPG, a large publicly available database of labeled chest radiographs. *arXiv* Preprint posted online November 14, 2019. doi: 10.48550/arXiv.1901.07042
15. Peng Y, Wang X, Lu L, et al: NegBio: A high-performance tool for negation and uncertainty detection in radiology reports. *AMIA Jt Summits Transl Sci Proc* 2018; 2017:188–196
16. Irvin J, Rajpurkar P, Ko M, et al: CheXpert: A large chest radiograph dataset with uncertainty labels and expert comparison. 33rd AAAI Conference on Artificial Intelligence, AAAI 2019, 31st Innovative Applications of Artificial Intelligence Conference, IAAI 2019 and the 9th AAAI Symposium on Educational Advances in Artificial Intelligence, EAAI 2019. Vol. 33. Hilton Hawaiian Village, Hawaii, USA, AAAI Press, 2019, pp 590–597
17. Goldberger AL, Amaral LA, Glass L, et al: PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. *Circulation* 2000; 101:E215–E220
18. Serpa Neto A, Deliberato RO, Johnson AEW, et al; PROVE Network Investigators: Mechanical power of ventilation is associated with mortality in critically ill patients: An analysis of patients in two observational cohorts. *Intensive Care Med* 2018; 44:1914–1922
19. Ranieri VM, Rubenfeld G, Slutsky AS: Rethinking acute respiratory distress syndrome after COVID-19: If a "better" definition is the answer, what is the question? *Am J Respir Crit Care Med* 2023; 207:255–260
20. Hernu R, Wallet F, Thiollière F, et al: An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med* 2013; 39:2161–2170
21. Caser EB, Zandonade E, Pereira E, et al: Impact of distinct definitions of acute lung injury on its incidence and outcomes in Brazilian ICUs: Prospective evaluation of 7,133 patients*. *Crit Care Med* 2014; 42:574–582
22. Villar J, Mora-Ordoñez JM, Soler JA, et al: The PANDORA study: Prevalence and outcome of acute hypoxemic respiratory

failure in the Pre-COVID-19 era. *Crit Care Explor* 2022; 4:e0684

23. Portacci A, Carpagnano GE, Tummolo MG, et al: COVID-19 clinical phenotypes and short-term outcomes: Differences between the first and the second wave of pandemic in Italy. *Expert Rev Respir Med* 2021; 15:1619–1625
24. Contou D, Fraissé M, Pajot O, et al: Comparison between first and second wave among critically ill COVID-19 patients admitted to a French ICU: No prognostic improvement during the second wave? *Crit Care* 2021; 25:3
25. Ritchie AI, Kadwani O, Saleh D, et al: Clinical and survival differences during separate COVID-19 surges: Investigating the impact of the SARS-CoV-2 alpha variant in critical care patients. *PLoS One* 2022; 17:e0269244
26. Neto AS, Barbas CSV, Simonis FD, et al: Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): An international, multicentre, prospective study. *Lancet Respir Med* 2016; 4:882–893
27. Webster NR, Cohen AT, Nunn JF: Adult respiratory distress syndrome—how many cases in the UK? *Anaesthesia* 1988; 43:923–926
28. Golicnik A, Zivanovic I, Gorjup V, et al: Same but different—ECMO in COVID-19 and ARDS of other etiologies. Comparison of survival outcomes and management in different ARDS groups. *J Intensive Care Med* 2023; 38:635–642
29. Guérin C, Reignier J, Richard J-C, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
30. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
31. Papazian L, Forel J-M, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
32. Hornby P, Wei Shen L, Emberson J, et al: Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384:693–704
33. Gordon AC, Mouncey PR, Al-Beidh F, et al; REMAP-CAP Investigators: Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; 384:1491–1502