ARDS

Timing of ARDS Resolution (TARU): A Pragmatic Clinical Assessment of ARDS Resolution in the ICU

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Abstract

Purpose Lack of a pragmatic outcome measures for acute respiratory distress syndrome (ARDS) resolution is a barrier to meaningful interventional trials of novel treatments. We evaluated a pragmatic, electronic health record (EHR)-based approach toward the clinical assessment of a novel outcome measure: ICU ARDS resolution.

Methods We conducted a retrospective observational cohort study evaluating adult patients with moderate–severe ARDS admitted to the medical intensive care unit (ICU) at Mayo Clinic in Rochester, MN, from January 2001 through December 2010. We compared the association of ICU ARDS resolution vs non-resolution with mortality. ICU ARDS resolution was defined as improvement in $P/F > 200$ for at least 48 h or (if arterial blood gas unavailable) $SpO_2:FiO_2$ (S/F) > 235, or discharge prior to 48 h from first $P/F > 200$ without subsequent decline in P/F, as documented in EHR.

Results Of the 254 patients included, ICU ARDS resolution was achieved in 179 (70%). Hospital mortality was lower in patients who met ICU ARDS resolution criteria as compared to those who did not (23% vs. 41%, $p < 0.01$). After adjusting for age, gender, and illness severity, the patients who met ICU ARDS resolution criteria had lower odds of hospital mortality [odds ratio 0.47, 95% CI 0.25–0.86; $p = 0.015$].

Conclusion The electronic health record-based pragmatic measure of ICU ARDS resolution is associated with patient outcomes and may serve as an intermediate outcome assessing novel mechanistic treatments.

Keywords Respiratory distress syndrome · Critical illness · Critical care · Prognosis · Hypoxia · Oxygen

Introduction

First described by Ashbaugh et al. [1], acute respiratory distress syndrome (ARDS) remains a common intensive care unit (ICU) diagnosis which is associated with substantial morbidity and mortality and tremendous cost [2]. Despite advances in ARDS treatment and supportive measures, the syndrome and its complications still impose a world-wide burden of disease, and its poor prognosis remains similar over more than a decade [3–6]. ARDS commonly occurs in association with critical illness and has been associated with pulmonary (pneumonia, aspiration, lung contusion, toxic inhalation) and extra-pulmonary risk factors (sepsis, shock, trauma, multiple transfusions, pancreatitis, high-risk surgery) [7].

To date, studies have identified multiple sequelae in ARDS survivors, including a reduction in the quality-of-life, declining functional status, and neurocognitive impairment [8–12]. A few studies have evaluated long-term survival of ARDS patients, though the majority of these studies lack a control group of patients at-risk for comparison [8, 13–16]. One study [17] evaluated long-term survival of ARDS patients compared to a control group; however, this study was published before significant changes in the quality of critical care delivery that has occurred over the past two decades [18–22]. This body of literature highlights the need

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for interventional studies that can prevent or effectively treat ARDS.

To date, most interventional trials in patients with ARDS have targeted mortality as the primary outcome [23–29]. Mortality is a late outcome that requires a large study sample size and significant follow-up duration. In addition, mortality in ARDS, similar to COVID or other critical illnesses [30], is often multifactorial and may be due to non-respiratory failure causes and is not the best outcome to measure the effect of trial interventions on the ARDS disease process. Other outcomes have included ventilator-free days (VFD), organ failure-free days, P/F course, and more recently, the ordinal scale utilized by the World Health Organization in clinical trials related to influenza and COVID-19 [23–25, 31–34]. The ordinal scale is highly subjective as the decision to transition from one mode of oxygenation (i.e., ECMO) to another is not standardized and practices vary not only across institutions but also providers. Similarly, VFD may be affected by confounding factors. For instance, in a patient who receives a prolonged course of steroids for treatment of ARDS, while the underlying ARDS process may resolve, the patient may remain on the ventilator for an extended period due to steroid-related myopathy and weakness.

To date, few truly pragmatic outcome measures have been evaluated in this disease. While P/F is often used clinically to follow disease course, it has not been studied as a measure used to define resolution of ARDS. A pragmatic outcome measure that is easily obtained and assessed at the bedside and extractable from the electronic health record (EHR) is needed to facilitate future interventional studies.

Thus to identify a pragmatic outcome measure that depicts the evolution of the underlying ARDS process, we evaluated the survival of patients with ARDS who met our new proposed definition of ICU ARDS resolution as compared to those without resolution.

Materials and Methods

Study Design

This was an observational cohort study utilizing a convenience sample of a previously described case–control study population spanning 10 years (January 2001–December 2010). In the previous case–control study, short- and long-term outcomes of ARDS cases were compared to matched controls via previously published study methodology [35, 36]. This cohort was obtained from Mayo Clinic Hospital in Rochester, Minnesota, which is a large academic tertiary referral center in Olmstead County and with readily available resources including extracorporeal membrane oxygenation. During the cohort study period, our ICU followed a standardized ventilation protocol for all patients meeting the following criteria: the ratio of partial pressure of oxygen to inspired oxygen concentration (P/F) < 300, bilateral infiltrates on chest imaging, no evidence of heart failure, and clinical picture compatible with ARDS. This was very similar to the Berlin definition of ARDS before its official release and widespread acceptance. The ventilator management protocol consisted of lung-protective ventilation strategies including low tidal volumes (6 ml/kg ideal body weight), table-based FiO_2 and PEEP titration to target SpO_2 88–92%, and plateau pressure goal of < 30 cm H_2O. Volume-targeted assist control was the recommended ventilator mode; however, a pressure-targeted strategy was allowed with the caveat that tidal volumes should not exceed 6 ml/kg of ideal body weight. Daily sedation holiday and standardized weaning protocols were also in place at that time. Our study was approved by the Mayo Clinic Institutional Review Board (IRB # 08-003560). All patients with prior informed consent on file were considered for participation.

Study Population

Eligible patients included all adult residents of Olmsted County, Minnesota, admitted to the ICU with moderate–severe ARDS within 24 h of admission and requiring invasive ventilation. Those patients who did not have ARDS on admission but subsequently developed ARDS were identified using a previously validated electronic surveillance tool [37]: these selected patients were verified by subsequent medical record review. Inclusion criteria were prompted by an electronic alert designed to recognize the following combination of observations: (1) qualifying arterial blood gas analysis: P/F < 200 and (2) qualifying chest radiograph report (free text Boolean query containing trigger words: "bilateral" AND "infiltrate" OR "edema"). Moderate–severe ARDS was defined by the following criteria: P/F < 200 on PEEP ≥ 5 mmHg with bilateral lung infiltrates on chest x-ray and absence of evidence of left atrial hypertension. ICU ARDS resolution was defined as improvement in P/F > 200 for at least 48 h or, if arterial blood gas unavailable, SpO_2:FiO_2 (S/F) > 235, or discharge prior to 48 h from first P/F > 200 without subsequent decline in P/F.

Patients who were admitted for comfort care only, those who died within 24 h of admission or within 48 h of ARDS onset, and those readmitted to the hospital during the study period were excluded. Per Mayo policy, all patients who receive care at our institution receive information regarding the use of their medical records for research purposes. Patients who had previously declined the use of their medical records for research purposes were excluded from this study (approximately 5% of hospitalized Olmsted County residents).

Outcomes Measures

The primary outcome was hospital mortality. All blood gas results (PaO$_2$) and inspired oxygen (FiO$_2$) values were obtained from the database and combined to create *P/F* ratios for each lab draw interval. If PaO$_2$ measurements were not available, corresponding *S/F* ratio was used. Subjects were sorted by medical record numbers and date of onset (earliest to later), such that all results were listed sequentially for each patient. All available *P/F* during patients' index ICU admission were used in the analysis.

Statistical Analysis

Data were expressed as mean (standard deviation), median (interquartile range), and proportion as appropriate. Baseline characteristics and severity of illness were compared using Wilcoxon's signed rank test for continuous variables and McNemar's chi-square test for categorical variables. The degrees of freedom were set to number of categories − 1 to account for the number of possible outcomes when testing the statistical significance of the difference in outcomes for cases and controls surviving hospitalization. Long-term survival was depicted with Kaplan–Meier survival curves. The *p* value cutoff of ≤ 0.05 was used for statistical significance. Statistical analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC).

Results

During the defined study period, 282 patients met the inclusion criteria of ARDS onset within 24 h of admission to the ICU. Twenty-eight patients died in the first 48 h following ARDS onset and were excluded from the study. Patient characteristics are listed in Table 1. Of the remaining 254 patients, 179 patients met the criteria for ICU ARDS resolution and 75 patients did not. When evaluating by worst *P/F*, 129 were classified as moderate ARDS and 125 were classified as severe ARDS. Between the two groups, there was no difference in median age, gender, or admission APACHE III score. There was a significant difference in worst mean *P/F* during the study period with a lower *P/F* in those with non-resolution [median (IQR) 81 (60–115) vs 138 (81–187); *p* < 0.001]. For those with ICU ARDS resolution as compared to those without, the median age was 68 (inter-quartile range [IQR] = 55–79) and 67 (IQR 60–77; *p* 0.53) years, 99 (55%) and 46 (61%; *p* 0.41) were male, and admission APACHE III score was 46 (IQR 33–59) vs 50 (IQR 38–68; *p* 0.08). Unadjusted hospital mortality was lower in patients who met ICU ARDS resolution compared to those who did not (23% vs. 41%, *p* < 0.01). After adjusting for age, gender, and admission APACHE III, the patients who met ICU

Table 1 Characteristics and outcomes of patients with acute respiratory distress syndrome resolution and those with non-resolution

	ARDS resolution (N=179)	ARDS non-resolution (N=75)	*p*-value
Age in years			
Median (IQR)	68 (52–80)	67 (60–77)	0.53
Gender (male)			
n (%)	99 (55)	46 (61)	0.41
ICU admission APACHE III			
Median (IQR)	46 (33–59)	50 (38–68)	0.08
Worst *P/F*			
Median (IQR)	138 (81–188)	81 (60–115)	< 0.001*
Hospital mortality			
n (%)	41 (23)	31 (41)	< 0.01*
ARDS severity by worst *P/F*			
ARDS severity			
(*n*)	Moderate 129	Severe 125	

*Statistically significant difference between those with and without resolution
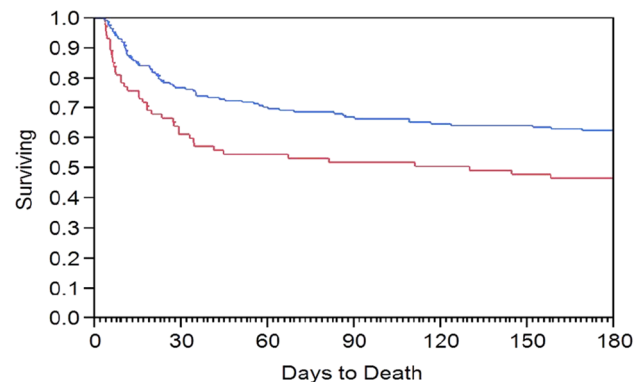

Fig. 1 Survival curve; blue—patients with intensive care unit acute respiratory distress syndrome resolution. Red—patients without intensive care unit acute respiratory distress syndrome resolution

ARDS resolution criterion were less likely to die (odds ratio [OR] 0.47, 95% confidence interval = 0.25–0.86, *p* = 0.015). This difference in survival persisted when these patients were followed for 6 months which is illustrated in the survival curve (Fig. 1). A sensitivity analysis was completed evaluating only those with sustained *P/F* < 200 (*P/F* < 200 for at least the first 24 h). The trend of hospital mortality for sustained moderate–severe ARDS was 41% (*p* = 0.025). In addition, we observed the trend in *P/F* (Fig. 2). During their ICU stay, while initial mean *P/F* were similar between the two groups, patients with ICU ARDS resolution demonstrated an increasing trend in mean *P/F* and an increase
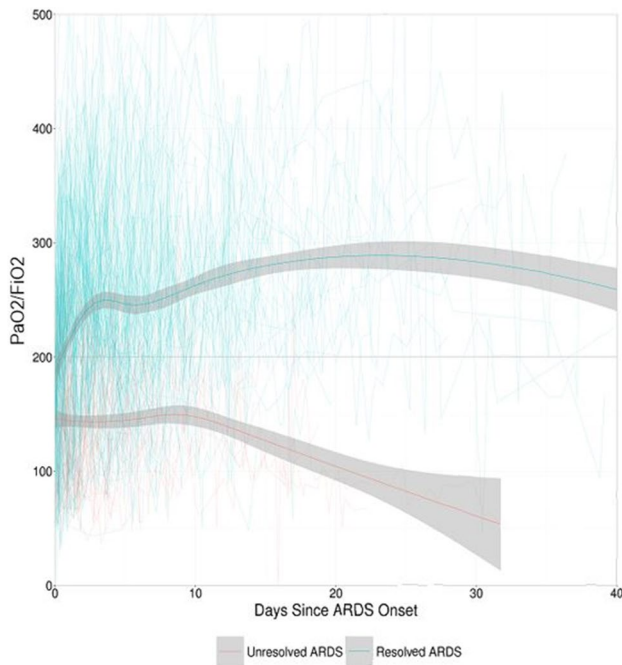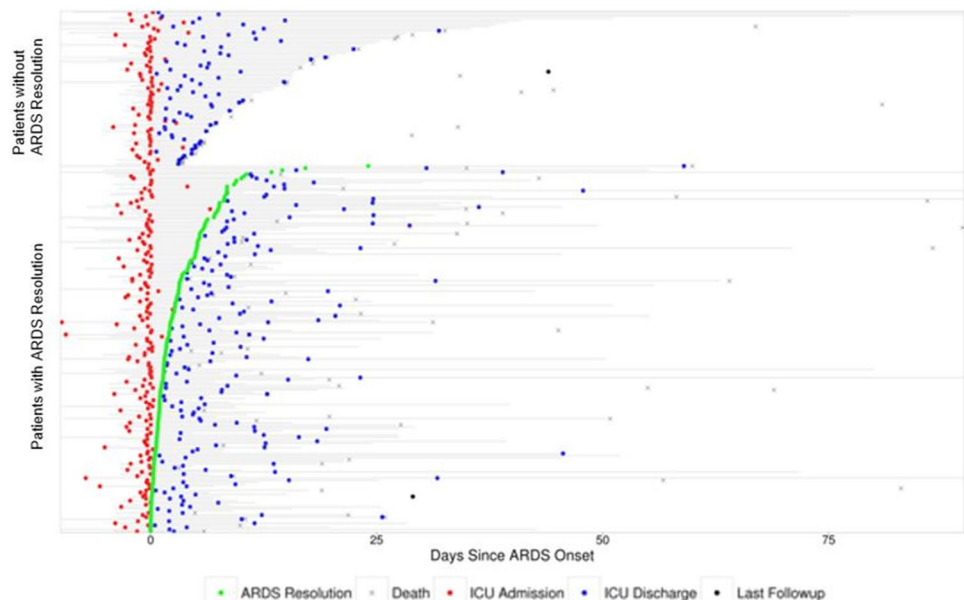
Fig. 2 Temporal PaO$_2$/FiO$_2$ trends during ICU stay

Discussion

In our study, adult patients who were admitted to the ICU with moderate–severe ARDS requiring mechanical ventilation and who met our suggested ICU ARDS resolution criteria had a lower risk of hospital mortality. This suggests that our proposed ICU ARDS resolution definition can be used as an intermediate marker to predict the patient outcome of mortality and can be used for future studies. In addition, while the initial mean *P/F* was similar between the two groups, patients with ICU ARDS resolution had a temporal increase in *P/F* as compared to the non-resolution group. This further differentiates these two populations and highlights the predictive nature of the *P/F*, the physiologic variable in our resolution definition that illustrates the change in the underlying disease process. Interestingly, this pre-COVID cohort demonstrated a relatively rapid median time to resolution. This is in line with previously published data demonstrating an increasing prevalence of rapidly resolving ARDS [38].

This study identifies our newly proposed definition of ICU ARDS resolution as an early and pragmatic outcome measures that is easily obtained from standard lab measures obtained in most ICU patients with ARDS. In addition, if PaO$_2$ measures are not available, *S/F* ratio, which is easily obtained at the bedside or from the EHR, can be substituted. This has important implications for future clinical trials as an early and pragmatic marker occurs earlier in the disease

over time, while those without resolution demonstrated a progressive decline. Events in the first 90 days (death, ARDS resolution, ICU discharge, and last follow-up) occurring from ARDS onset in patients with and without ICU ARDS resolution are seen in Fig. 3.

Fig. 3 Events since acute respiratory distress syndrome onset in patients with and without acute respiratory distress syndrome resolution

process allowing for shorter trial duration and hence lower trial cost.

Our study does have limitations. In our definition of ICU ARDS resolution, we chose to define resolution as $P/F > 200$, despite Berlin criteria which defines the presence of ARDS by $P/F < 300$. The cut-off point of $P/F > 200$ was chosen based on conventional weaning guidelines that recommend using a P/F of $> 150–200$ as oxygenation criteria as part of the evaluation for consideration of extubation [39]. Our inclusion criteria utilized the Berlin definition which was published after the end date of this cohort collection. Although this population may have been classified differently at the time of their illness (ARDS per American European Consensus Conference definition), the Berlin definition showed minimal improvement in prognostication over the AECC criteria and certainly, it is advisable to use the most current definition on a retrospective cohort. Use of the worst P/F ratio as our daily assessment of resolution has limitations as a single measurement may not reflect the overall picture of the patient on any given day. However, we chose this measurement in an attempt to limit overestimation and for pragmatic use in further clinical and research applications. Our study also did not assess the contribution of the intensity of mechanical ventilation such as would be done if the oxygenation index was used. As noted above, the purpose of this study was to evaluate a pragmatic marker of ARDS resolution and ventilator measurements such as mean airway pressure cannot be reliably extracted from the EHR. In addition, as discussed above, our ventilator protocol at that time did consist of lung protective strategies and best practices for the care of critically ill patients with ARDS (including sedation holidays and spontaneous awakening trials). Therefore, this variation in classification is of little to no significance. Several studies have described subtypes of ARDS such as pulmonary and extra-pulmonary types. We did not differentiate these groups in our study; however, while several characteristics (i.e., lung mechanics) differ between these two groups, mortality does not differ and therefore, differentiating these groups would not affect our study outcome [40–42]. This single-center experience in a discrete population of southern Minnesota residents may not be generalizable to a broader population and would require larger studies for external validation. In addition, the retrospective nature of our study does not allow for consideration of potential physician variation in evaluation and management of the patients and we are limited by the data available which did not allow us to adjust for other confounding variables such as adjunctive therapies. However, as previously mentioned, well-established protocolized ventilator management practices were in place during the study period and evaluation of the impact of treatment methods is beyond the scope of this study whose aim was to evaluate the intermediate outcome measure, ICU ARDS resolution. In addition, other than lung-protective ventilation and prone positioning, adjunctive interventions and therapies have not definitively demonstrated reduction in mortality. Our cohort was completed prior to completion of guidelines recommending use of prone positioning. Further studies will be needed for external validation of this marker.

Conclusion

In our cohort study, the proposed definition of ICU ARDS resolution was associated with the patient outcomes and may serve as an intermediate surrogate outcome in future quality improvement projects, cohort studies, and clinical trials.

Declarations

Conflict of interest The authors have no financial or non-financial disclosures. The authors do not have conflict/competing interests related to this manuscript.

Ethical Approval Our study was approved by the Mayo Clinic Institutional Review Board (IRB # 08-003560).

Consent to Participate Per Mayo Clinic policy, patients who had previously declined the use of their medical record data were excluded from this study.

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