

Nonintubated Patients With Acute Respiratory Distress Syndrome: A Watchful Evaluation*

Davide Chiumello, MD

Dipartimento di Anestesia, Rianimazione
(Intensiva e Subintensiva) e Terapia del Dolore
Fondazione IRCCS Ca' Granda—Ospedale Maggiore
Policlinico; and
Dipartimento di Fisiopatologia Medico-Chirurgica e dei
Trapianti
Università degli Studi di Milano
Milano, Italy

Silvia Coppola, MD

Dipartimento di Anestesia, Rianimazione (Intensiva e
Subintensiva) e Terapia del Dolore
Fondazione IRCCS Ca' Granda—Ospedale Maggiore
Policlinico
Milano, Italy

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by a diffuse non-cardiogenic pulmonary edema causing severe gas exchange and respiratory mechanics impairment. The management is based on invasive mechanical ventilation with low tidal volume, moderate to high level of positive end-expiratory pressure (PEEP), and oxygen fraction to improve oxygenation and decrease the work of breathing.

The first description of ARDS, almost 50 years ago, did not allow to identify a uniform group of patients, although all patients required mechanical ventilation (1). Thereafter, the subsequent studies on ARDS have mainly included mechanically ventilated patients.

To standardize patients with ARDS for the enrollment in multicenter trials and epidemiological studies, several definitions have been proposed (2, 3). In 1994, the American-European Consensus Conference (AECC) on ARDS defined the syndrome by the following criteria: an acute onset of hypoxemia (i.e., a ratio between partial pressure of oxygen and oxygen fraction [$\text{PaO}_2/\text{FIO}_2$] lower than 200 mm Hg), bilateral infiltrates, and no cardiac failure (2). Over the years, the majority of ARDS studies applied the AECC definition, although it was criticized because it did not explicitly define the time window, did not require a standardized ventilator support to assess the hypoxemia, and underrecognized the subgroup of patients with milder hypoxemia (4–6).

*See also p. 120.

Key Words: acute respiratory distress syndrome; esophageal pressure; hypoxemia; mortality; spontaneous breathing

The authors have disclosed that they do not have any potential conflicts of interest.

Copyright © 2015 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000001438

To achieve a more reliable and feasible description, the “Berlin definition” was developed. It requires in addition to hypoxemia a specific minimum amount of PEEP ($\geq 5 \text{ cm H}_2\text{O}$) for the measurement of $\text{PaO}_2/\text{FIO}_2$ ratio at the time of diagnosis identifying three mutually exclusive categories of increasingly severe ARDS (3). This positive pressure can be delivered noninvasively only in the mild form. When the AECC and the Berlin definition were compared in a cohort of 4,188 patients with ARDS, the new one presented a higher predictive validity for mortality with an area under the receiver operating characteristic curve of 0.57 (95% CI, 0.56–0.59) vs 0.53 (95% CI, 0.52–0.55; $p < 0.001$) (3).

However, the current definition excluding nonventilated hypoxemic patients, and not defining criteria to start positive ventilation, is unable to recognize patients who could deteriorate during the following days requiring endotracheal intubation. It can result in an underestimation of the prevalence of ARDS and in an inadequate treatment of these patients. In fact, in a single retrospective study among 11,465 patients at intensive care admission, 156 patients presented criteria for acute lung injury (ALI)/ARDS, 74 (47%) were mechanically ventilated, and 41 (26%) were not ventilated. Although the mortality rate was significantly higher in ventilated patients (50%) compared with nonventilated patients (22%), the nonventilated patients were at substantial risk of death (7).

To ameliorate the outcome of these patients, similar to the patients with septic shock treated according to the early goal-directed care, ARDS hypoxemic patients should receive adequate therapy before developing mechanical ventilation-dependent respiratory failure. Unfortunately, few studies have evaluated clinical outcomes and prognostic risk factors of ARDS hypoxemic patients not requiring mechanical ventilation support.

In this issue of *Critical Care Medicine*, Kangelaris et al (8) performed a secondary data analysis of a prospective cohort study of patients with ARDS, independent of requirement of positive pressure ventilation, conducted at Vanderbilt University Medical Center between 2006 and 2011. Aim of this study was to explore how many critically ill patients having ARDS criteria were not intubated and to evaluate the clinical outcomes of early, late, and nonintubated patients. Among 475 nontrauma ARDS patients, 23% (106) were not intubated, while 77% (369) were intubated meeting the ARDS criteria the same day. Among the nonintubated patients, 34% (36) required a subsequent intubation (late intubation) mainly at the second day. Nonintubated patients compared with early intubated patients had less severe hypoxemia and lower Acute Physiology and Chronic Health Evaluation II score, while the 60-day mortality rate was similar (36% in each group; $p = 0.91$). Although at admission the late intubation patients presented similar severity of illness compared with never intubated patients, the former had a significantly higher mortality rate (56% vs 26%; $p = 0.02$). Late intubation patients also showed a significantly higher mortality compared with early intubation patients with an adjusted risk of death at 60 days (2.3; 95% CI, 1.32–4.24; $p = 0.004$) (8).

Independently from the major limitations such as a single-center study performed in a long period of time and the absence of clinical factors predicting late intubation and of data regarding the ventilatory management, what can we learn from this study for the clinical practice? First, irrespective of the requirements of intubation, the mortality rate in patients with ARDS remains high, and second, but not less important, patients who were late intubated, although a minority and with similar baseline clinical characteristic to never intubated patients, had a higher mortality compared with patients never or early intubated.

In the present study, Kangelaris et al (8) enrolled patients with an established ARDS, and similar to Cely et al (7), they found that nonintubated represented a quarter of the overall population with a lower severity of illness compared with intubated patients but with a mortality similar to the most severe case of community-acquired pneumonia.

In contrast to very hypoxemic patients in whom invasive mechanical ventilation is almost mandatory, patients with moderate hypoxemia are, paradoxically, more difficult to treat. In fact, they are often managed outside the ICUs and not identified as patients at higher risk of developing respiratory failure requiring positive pressure ventilation within few hours. Levitt et al (9) had found that in patients with acute respiratory failure, the oxygen flow requirement above 6 L/min, maximum respiratory rate (≥ 30 breaths/min), and baseline immune suppression were associated to the development of ARDS requiring positive pressure ventilation with a median time of 20 hours.

After years of studies on lung protective strategy of mechanical ventilation that has been demonstrated as the only disease-specific therapy able to improve survival (10), it is time to focus our interest on the earlier and less severe stages of ARDS because they represent a potentially more treatable phase of ALI.

Thus, the first step should be a careful clinical evaluation of nonintubated hypoxemic ARDS patients to identify the predictors of progression to ARDS requiring a mechanical support. Recently, Sp_{O_2}/F_{iO_2} ratio has been demonstrated a valid tool to stage ARDS patients, as well as the Pa_{O_2}/F_{iO_2} ratio (11). Although Pa_{O_2}/F_{iO_2} at the onset of ARDS is not considered an independent predictor of mortality, a standardization of ventilator setting has greatly improved the risk stratification of ARDS by Pa_{O_2}/F_{iO_2} (12). Thus, a standardized evaluation of hypoxemia should be applied also in spontaneous breathing patients: while patient is receiving 100% oxygen with a flow of at least 15 L/min through a nonbreathing mask (13). Nonbreathing masks have unidirectional valves and a reservoir bag to prevent inspiration of room air. However, due to the possible leaks around the mask, the maximum inspired oxygen fraction is closer to 80%. Knowing this limitation, this method allows to assess very rapidly and also outside intensive care the severity of hypoxemia in ARDS whenever the oxygen fraction is higher than 0.5, because as known Pa_{O_2}/F_{iO_2} is not constant across a range of F_{iO_2} (14). When Sp_{O_2} is below 94–96% corresponding to Pa_{O_2} lower than 100 mm Hg with a pulmonary shunt higher than 30%, patients should be treated with invasive positive ventilation (13). When Sp_{O_2} is between 96% and 98%, patients could be managed by noninvasive ventilation or high-flow oxygen nasal cannulae. However, after few hours if

a patient does not ameliorate gas exchange, endotracheal intubation is required.

The ICU admission of nonintubated ARDS patients and the strict monitoring of Sp_{O_2}/F_{iO_2} are mandatory. Furthermore, a clinical evaluation of respiratory effort should be performed. The clinical scales of dyspnoea can be useful; however, they cannot measure the work of breathing. In fact, we know that high tidal volume under spontaneous ventilation can lead to high transpulmonary pressures with significant stress and strain and work of breathing. Moving from these physiologic concepts, we could consider the monitoring of esophageal pressure to quantify the work of breathing in these patients (15).

Because patients with ARDS not requiring positive pressure ventilation represent a substantial fraction with a higher risk of mortality when subsequently intubated, we should act faster in the correct timeframe by a periodical and watchful evaluation of the hypoxemia and of the work of breathing.

REFERENCES

- Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
- Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
- Ranieri VM, Rubenfeld GD, Thompson BT, et al: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
- 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
- Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693
- Ferguson ND, Frutos-Vivar F, Esteban A, et al: Acute respiratory distress syndrome: Underrecognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit Care Med* 2005; 33:2228–2234
- Cely CM, Rojas JT, Maldonado DA, et al: Use of intensive care, mechanical ventilation, both, or neither by patients with acute lung injury. *Crit Care Med* 2010; 38:1126–1134
- Kangelaris KN, Ware LB, Wang CY, et al: Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; 44:120–129
- Levitt JE, Calfee CS, Goldstein BA, et al: Early acute lung injury: Criteria for identifying lung injury prior to the need for positive pressure ventilation. *Crit Care Med* 2013; 41:1929–1937
- Silversides JA, Ferguson ND: Clinical review: Acute respiratory distress syndrome—Clinical ventilator management and adjunct therapy. *Crit Care* 2013; 17:225
- Chen W, Janz DR, Shaver CM, et al: Clinical Characteristics and Outcomes are Similar in ARDS Diagnosed by Sp_{O_2}/F_{iO_2} Ratio compared with Pa_{O_2}/F_{iO_2} Ratio. *Chest* 2014 Apr 21. [Epub ahead of print]
- Villar J, Blanco J, del Campo R, et al: Spanish Initiative for Epidemiology, Stratification & Therapies for ARDS (SIESTA) Network: Assessment of Pa_{O_2}/F_{iO_2} for stratification of patients with moderate and severe acute respiratory distress syndrome. *BMJ Open* 2015; 5:e006812
- Gattinoni L, Carlesso E, Brazzi L, et al: Friday night ventilation: A safety starting tool kit for mechanically ventilated patients. *Minerva Anestesiol* 2014; 80:1046–1057
- Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1979; 120:1039–1052
- Akoumianaki E, Maggiore SM, Valenza F, et al: PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine): The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014; 189:520–531

Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome*

Kirsten Neudoerffer Kangelaris, MD, MAS¹; Lorraine B. Ware, MD²; Chen Yu Wang, MD, MHA³; David R. Janz, MD, MSc⁴; Hanjing Zhuo, MPH⁵; Michael A. Matthay, MD,^{5,6} Carolyn S. Calfee, MD, MAS^{5,6}

Objective: The prevalence, clinical characteristics, and outcomes of critically ill, nonintubated patients with evidence of the acute respiratory distress syndrome remain inadequately characterized.

Design: Secondary analysis of a prospective observational cohort study.

*See also p. 246.

¹Division of Hospital Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA.

²Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine and Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN.

³Department of Critical Care Medicine, Taichung Veteran General Hospital, Taichung, Taiwan.

⁴Section of Pulmonary and Critical Care Medicine, Department of Medicine, Louisiana State University School of Medicine New Orleans, LA.

⁵Division of Pulmonary and Critical Care, University of California, San Francisco, San Francisco, CA.

⁶Departments Medicine and Anesthesia and the Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA.

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/ccmjournal>).

Dr. Kangelaris was supported by the Society of Hospital Medicine Young Researchers Award, the National Institutes of Health (NIH) National Center for Advancing Translational Sciences through UCSF-CTSI KL2 TR000143, and National Heart, Lung, and Blood Institute (NHLBI) 1K23HL116800-01. Dr. Ware has served on a medical advisory board for Glaxo Smith Kline and as a consultant for Abbot. She was supported by NHLBI HL112656, and HL103836 and received support for article research from the NIH. Her institution received grant support from the NIH and the American Heart Association. Dr. Janz was supported by NIH T32 HL087738. Dr. Zhuo received support for article research from the NIH. Dr. Matthay has served on medical advisory boards for Cerus (ARDS consult - money paid to Dr. Matthay), GlaxoSmithKline (consultant for ARDS and grant for studies of sepsis, grant to UCSF his institution), and Roche Genentec (Chair of DSMB for Asthma trials). He was supported by NHLBI R37 HL51856. He received funding from Quark Pharmaceuticals, received support for article research from the NIH. Dr. Calfee has served on medical advisory boards for Cerus and GlaxoSmithKline. She was supported by HL110969. She received support for travel from Boehringer Ingelheim (travel for meeting related to potential research grant) and for article research from the NIH. Drs. Calfee and Matthay have also received grant support from GlaxoSmithKline. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: kirsten.kangelaris@ucsf.edu

Copyright © 2015 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000001359

Setting: Vanderbilt University Medical Center.

Patients: Among adult patients enrolled in a large, multi-ICU prospective cohort study between the years of 2006 and 2011, we studied intubated and nonintubated patients with acute respiratory distress syndrome as defined by acute hypoxemia ($P_{aO_2}/F_{iO_2} \leq 300$ or $S_{pO_2}/F_{iO_2} \leq 315$) and bilateral radiographic opacities not explained by cardiac failure. We excluded patients not committed to full respiratory support.

Interventions: None.

Measurements and Main Results: Of 457 patients with acute respiratory distress syndrome, 106 (23%) were not intubated at the time of meeting all other acute respiratory distress syndrome criteria. Nonintubated patients had lower morbidity and severity of illness than intubated patients; however, mortality at 60 days was the same (36%) in both groups ($p = 0.91$). Of the 106 nonintubated patients, 36 (34%) required intubation within the subsequent 3 days of follow-up; this late-intubation subgroup had significantly higher 60-day mortality (56%) when compared with the both early intubation group (36%, $P < 0.03$) and patients never requiring intubation (26%; $p = 0.002$). Increased mortality in the late intubation group persisted at 2-year follow-up. Adjustment for baseline clinical and demographic differences did not change the results.

Conclusions: A substantial proportion of critically ill adults with acute respiratory distress syndrome were not intubated in their initial days of intensive care, and many were never intubated. Late intubation was associated with increased mortality. Criteria defining the acute respiratory distress syndrome prior to need for positive pressure ventilation are required so that these patients can be enrolled in clinical studies and to facilitate early recognition and treatment of acute respiratory distress syndrome. (*Crit Care Med* 2016; 44:120–129)

Key Words: acute lung injury; acute respiratory distress syndrome; acute respiratory failure; clinical outcomes; critical care; critical illness; early acute lung injury; intensive care; mechanical ventilation

The acute respiratory distress syndrome (ARDS) was first described almost 50 years ago by Ashbaugh and colleagues in critically ill adults requiring mechanical ventilation (MV) (1). Lacking a formal definition, several subsequent studies similarly described ARDS almost universally in mechanically ventilated patients in the ICU (2–5). The consensus definitions

of ARDS that followed, including the American European Consensus Conference definition of acute lung injury (ALI) and ARDS in 1992 and the Berlin definition for ARDS in 2012, were created with a primary goal of standardizing the diagnosis of ARDS for multicenter treatment trials and epidemiologic studies, rather than to capture the entire spectrum of illness (6, 7). As a result, modern epidemiologic studies and treatment trials of ARDS have continued to focus almost exclusively on intubated, mechanically ventilated patients with ARDS (8–17). In fact, the most recent Berlin definition requires positive pressure ventilation for the diagnosis of ARDS (7).

Although this approach has facilitated improvements in ARDS management and reduced mortality, primarily through lung protective ventilation (8, 15), treatment of ARDS remains largely supportive, and disease-specific efforts have failed in multicenter clinical trials (18). The success of early goal-directed care in sepsis offers the possibility that targeted treatments in ARDS may offer greater benefit prior to the onset of MV-dependent respiratory failure, and the recent shift by the National Institutes of Health's ARDS Clinical Trials Network to focus on prevention and early treatment reflects this approach (19). Comprehensive characterization of ARDS in earlier and less severe stages may provide important avenues for improved diagnostic considerations and novel therapies. Nearly one third of children with ARDS are not mechanically ventilated on initial diagnosis (20), and respiratory failure requiring invasive MV likely represents only the most severe subset of a larger clinical syndrome in children (21–25). However, data are limited on the epidemiology and clinical outcomes of nonmechanically ventilated adults with ARDS.

The purpose of the present study was (1) to determine how frequently critically ill patients otherwise meeting the clinical, chest radiographic criteria, and oxygenation criteria are not intubated at the time of meeting all other ARDS criteria and (2) to evaluate the clinical outcomes among these patients when compared with those among patients who were intubated and mechanically ventilated on the first day of ARDS diagnosis.

MATERIALS AND METHODS

Subjects

We conducted a secondary data analysis on patients enrolled between January 2006 and February 2011 in a prospective cohort study entitled the Validation of biomarkers for Acute Lung Injury Diagnosis (VALID) study, a multi-ICU study at Vanderbilt University Medical Center. Details of the VALID study have been described previously (26–28). Briefly, adult patients admitted to the medical, surgical, trauma, or cardiovascular ICUs at Vanderbilt University Medical Center were enrolled on the morning of ICU day 2. Study day 1 was defined as the time between ICU admission and enrollment in the VALID study (~8 AM on ICU day 2). Days 2, 3, and 4 are subsequent 24-hour periods. Exclusions included ICU stay greater than 48 hours prior to Vanderbilt ICU admission, uncomplicated overdose, severe chronic lung disease, plans to transfer out of ICU on ICU day 2, and nonmechanically ventilated or

postsurgical patients in the cardiovascular ICU. Patients were otherwise enrolled independent of their MV requirements.

For the current study, we included patients with ARDS (7), defined as the development of acute, bilateral pulmonary infiltrates (as determined by consensus of two trained physician reviewers), and hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg) not primarily due to heart failure or volume overload. Patients were included independent of need for positive pressure ventilation requirement. Therefore, patients on supplemental oxygen via nasal cannula and facemask were included if they otherwise met the diagnosis of ARDS. We specifically included these patients so that we could focus this study on the clinical outcomes of patients with the clinical phenotype of ARDS who were, at least initially, not requiring intubation. For the ratio of pulse oximetric saturation-to-fraction of inspired oxygen ($\text{SpO}_2/\text{FiO}_2$) less than or equal to 315 was used as a validated surrogate for $\text{PaO}_2/\text{FiO}_2$ for diagnosis of ARDS among patients without an arterial blood gas measurement at the time meeting ARDS criteria (29). The diagnosis of ARDS could be established at any time during the first 4 days in the ICU. Among nonmechanically ventilated patients with supplemental oxygen via nasal cannula, every additional liter of flow of oxygen per minute was estimated as an additional 0.04 FiO_2 over atmospheric FiO_2 of 0.21 (30, 31). For nonmechanically ventilated patients using facemask delivery of oxygen, the recorded supplemental FiO_2 was recorded as the inspired FiO_2 . All ARDS determinations and determinations of intubation and MV status were made independently for each study day.

Patients were excluded for a *do not intubate* order at the time of enrollment or if the primary ARDS risk factor was trauma because the pathogenesis and prognosis of ARDS and the prevalence of intubation differed in trauma-related ARDS (32). Among 2,325 patients enrolled in VALID during the study period, there were 475 nontrauma patients with ARDS. An additional 18 patients were excluded due to an initial *do not intubate* order for a total of 457 patients included in this subcohort study (Fig. 1).

The Institutional Review Board at Vanderbilt University approved the study. Informed consent was obtained from patients or their surrogates whenever possible. For patients who were unable to provide informed consent due to their clinical condition and for whom no surrogates were available, a waiver of informed consent was granted by the institutional review board due to the minimal risk of the observational study.

Primary Measures

The predictor variable was requirement of endotracheal intubation with positive pressure ventilation. We classified patients in the following two groups (1): early intubation: intubated, mechanically ventilated, and meeting ARDS criteria on the same study day and (2) initially nonintubated: not requiring intubation on the day of meeting ARDS criteria. Patients receiving noninvasive positive pressure ventilation (NIPPV) at the time of meeting ARDS criteria were classified as nonintubated in the primary analysis. The initially nonintubated group was further subdivided into two subgroups: never intubated:

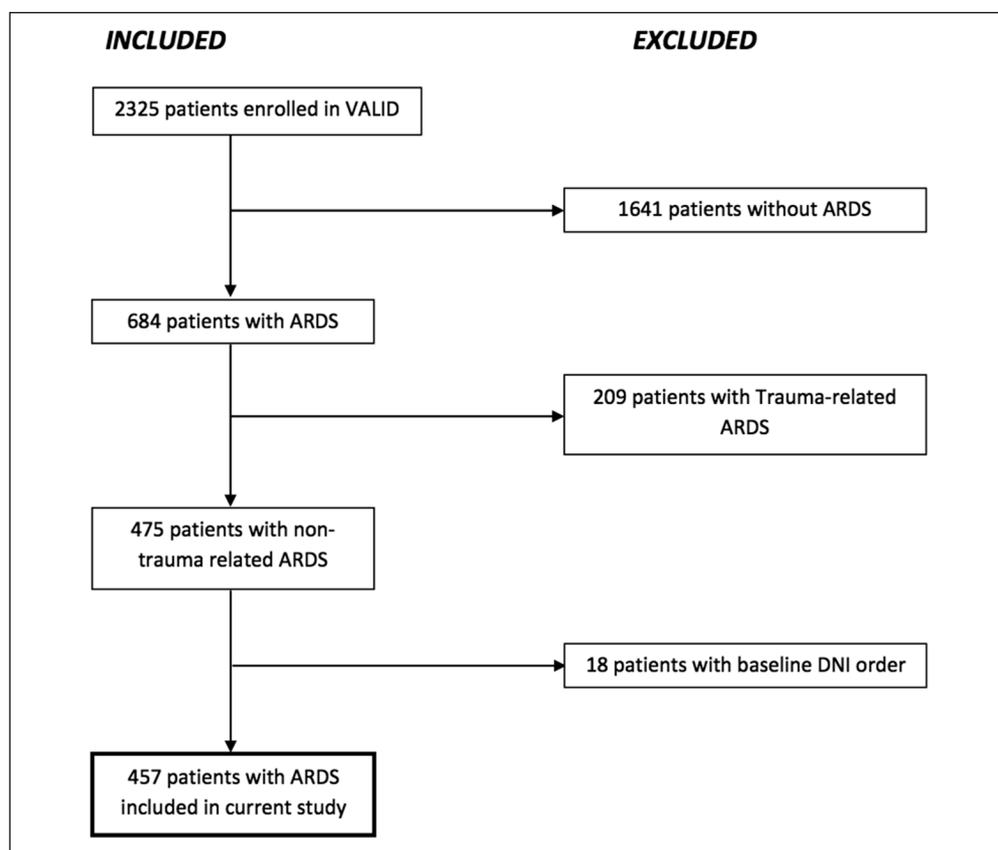


Figure 1. Flow diagram of inclusion and exclusion criteria. This flow diagram illustrates the total number of patients enrolled in the Validation of biomarkers for Acute Lung Injury Diagnosis (VALID) study and the number and reasons for excluding patients based on our predetermined criteria. Following this process, 457 patients with acute respiratory distress syndrome (ARDS) were identified for our study. DNI = do not intubate.

not requiring intubation at admission to ICU or at any time between study days 1 and 4 of follow-up; and late intubation: not intubated on the day of ARDS diagnosis, but intubated on a subsequent study day.

The primary outcome variable was mortality at 60 days. Secondary outcomes were mortality at 1 and 2 years, 28-day ventilator-free days (VFD), defined as the number of days alive and free of MV to day 28, with VFD equals 0 for patients who died in the first 28 days (33), and the total number of ICU days in survivors to hospital discharge.

Covariates Affecting Intubation Timing and Status

We considered several baseline characteristics, comorbidities, clinical variables, severity of illness measures, and initial process of care measures as possible factors influencing likelihood of and timing of intubation in ARDS as outlined in **Tables 1** and **2**. Organ failure was classified according to Brussels criteria: coagulation failure defined as platelet count less than or equal to $80 \times 10^3/\text{mm}^3$; renal failure defined as creatinine greater than or equal to 2 mg/dL; circulatory failure defined as systolic blood pressure less than or equal to 90 mm Hg and unresponsive to fluid; and hepatic failure-bilirubin greater than or equal to 2 mg/dL (34). The Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated using data from the 24 hours prior to enrollment (35). The presence of consensus-defined

sepsis was assessed daily for the first 4 study days (36). Process of care measures included time from admission to ICU in days, fluid balance on day of ARDS diagnosis, and the use of NIPPV at any point on the day meeting ARDS criteria.

Statistical Analysis

For bivariate analysis, the Wilcoxon signed rank test and *t* test were used for continuous variables as appropriate, and the chi-square test was used for categorical variables. Kaplan-Meier survival plots demonstrate the time from admission to 60 days and 2 years of follow-up and the log-rank test was used for these survival analyses.

Two multivariate models were used to evaluate the effect of potential confounders on the association between intubation status and mortality at 60 days, 1 year, and 2 years of follow-up. Both regression models incorporated baseline demographic, comorbidities, and severity of illness mea-

asures (Tables 1 and 2), which varied according to intubation status with a *p* value of less than 0.20. Variables included in the models were sex, source of admission, alcohol abuse by history, current smoker, established diagnosis of chronic obstructive pulmonary disease, HIV, cirrhosis, leukemia or stem cell transplant, any cancer diagnosis, ARDS risk factor, respiratory rate, severity of hypoxemia (according to $\text{PaO}_2/\text{FiO}_2$ or $\text{SpO}_2/\text{FiO}_2$), presence of shock, hepatic failure, APACHE II, NIPPV use, and fluid balance. First, a Cox proportional hazards backward selection model approach was used. Second, a propensity score was generated to estimate the causal effects of late endotracheal intubation on mortality within the initially nonventilated group. Propensity score quintiles were then included in a Cox proportional hazards regression model with likelihood of late intubation as the dependent variable. Goodness of fit and discrimination of the model were assessed using the Hosmer-Lemeshow test and C-statistic, respectively.

A sensitivity analysis was performed reclassifying patients receiving NIPPV on the day of ARDS diagnosis into the early intubation group because NIPPV is included in the current Berlin definition of mild ARDS and has been included in some other epidemiologic studies of ARDS to date (7, 15, 37–43).

The analyses were performed using STATA version 12 (STATA, College Station, TX). Statistical significance was defined as a two-tailed *p* value of less than 0.05 for all analyses.

TABLE 1. Baseline Demographics and Comorbidities According to Intubation Status Among 457 Patients With Acute Respiratory Distress Syndrome

| | All Acute Respiratory Distress Syndrome (n = 457) | | | Initially Nonintubated (n = 106) | | p |
|---|---|----------------------------------|---------|----------------------------------|-------------------------|------|
| | Early Intubation (n = 351) | Initially Nonintubated (n = 106) | | Never Intubated (n = 70) | Late Intubated (n = 36) | |
| Baseline demographics | | | | | | |
| Age (yr), mean ± sd | 55 ± 16 | 54 ± 15 | 0.76 | 54 ± 16 | 56 ± 13 | 0.56 |
| Men | 174 (50) | 63 (59) | 0.08 | 46 (66) | 17 (47) | 0.07 |
| Race | | | 0.73 | | | 0.74 |
| White | 298 (85) | 92 (87) | | 60 (86) | 32 (89) | |
| Black | 45 (13) | 13 (12) | | 9 (13) | 4 (11) | |
| Other | 8 (2) | 1 (1) | | 1 (1) | 0 (0) | |
| Source of admission | | | < 0.001 | | | 0.66 |
| Emergency department | 80 (23) | 38 (36) | | 26 (37) | 12 (33) | |
| Transfer from floor | 122 (35) | 48 (45) | | 30 (43) | 18 (50) | |
| Outside hospital | 94 (27) | 12 (11) | | 7 (10) | 5 (14) | |
| Operating room | 52 (15) | 7 (7) | | 6 (9) | 1 (3) | |
| Other | 3 (1) | 1 (1) | | 1 (1) | 0 (0) | |
| Current smoker | 115 (33) | 31 (29) | 0.50 | 17 (24) | 14 (39) | 0.12 |
| Alcohol abuse | 57 (16) | 6 (6) | 0.006 | 3 (4) | 3 (8) | 0.39 |
| Illicit drug use | 27 (8) | 6 (6) | 0.48 | 4 (6) | 2 (6) | 0.97 |
| Comorbidities | | | | | | |
| Chronic obstructive pulmonary diseases | 54 (15) | 9 (9) | 0.07 | 6 (9) | 3 (8) | 0.97 |
| HIV | 12 (3) | 8 (8) | 0.07 | 6 (9) | 2 (6) | 0.58 |
| Diabetes | 107 (30) | 24 (23) | 0.12 | 16 (23) | 8 (22) | 0.94 |
| Cirrhosis | 32 (9) | 5 (5) | 0.15 | 1 (1) | 4 (11) | 0.03 |
| Congestive heart failure | 44 (13) | 10 (9) | 0.39 | 6 (9) | 4 (11) | 0.67 |
| Chronic kidney disease | 53 (15) | 18 (17) | 0.64 | 11 (16) | 7 (19) | 0.63 |
| Solid tumor (metastatic and nonmetastatic) | 72 (21) | 16 (15) | 0.22 | 13 (19) | 3 (8) | 0.16 |
| Leukemia (chronic or acute) or stem cell transplant | 26 (7) | 25 (24) | < 0.001 | 18 (26) | 7 (19) | 0.47 |
| Any cancer (solid or liquid tumor) | 93 (27) | 37 (35) | 0.09 | 27 (39) | 10 (28) | 0.27 |

Presented as n (%) unless otherwise specified. There was no statistically significant difference ($P > 0.20$) across groups for stroke (ischemic or hemorrhagic), solid organ transplant, history of coronary artery disease, or acute coronary syndrome.

RESULTS

Among 457 patients with evidence of ARDS, 23% ($n = 106$) were not intubated and mechanically ventilated (initially nonintubated) on day 1 and 77% were intubated and mechanically ventilated (early intubation) on day 1 (Fig. 2). Of the 106 initially nonintubated patients, only 36 (34% of initially

nonintubated) progressed to require intubation (late intubation) in the subsequent follow-up period, whereas 70 patients (66% of initially nonintubated) did not require intubation (never intubated) during the follow-up period.

Initially nonintubated patients differed significantly from the early intubation group (Tables 1 and 2, columns 2–4).

TABLE 2. Severity of Illness, Process of Care Measures, and Clinical Outcomes According to Intubation Status among 457 Patients With Acute Respiratory Distress Syndrome

| | All ARDS (n = 457) | | | Initially Nonintubated (n = 106) | | |
|---|----------------------------|----------------------------------|---------|----------------------------------|-------------------------|---------|
| | Early Intubation (n = 351) | Initially Nonintubated (n = 106) | p | Never Intubated (n = 70) | Late Intubated (n = 36) | p |
| Severity of illness | | | | | | |
| Primary ARDS risk factor | | | 0.03 | | | 0.65 |
| Sepsis | 147 (42) | 43 (41) | | 27 (39) | 16 (44) | |
| Pneumonia | 95 (27) | 34 (32) | | 23 (33) | 11 (31) | |
| Aspiration | 74 (21) | 11 (10) | | 9 (13) | 2 (6) | |
| Other | 35 (10) | 18 (17) | | 11 (16) | 7 (19) | |
| Respiratory rate (breaths/min) | 31±9 | 33±8 | 0.01 | 32±8 | 34±7 | 0.27 |
| Pao ₂ /Fio ₂ ^a , mean ± SD | 146±84 | 181±86 | 0.006 | 180±87 | 182±87 | 0.93 |
| Spo ₂ /Fio ₂ ^b , mean ± SD | 160±62 | 211±76 | < 0.001 | 212±79 | 212±71 | 0.99 |
| Shock (circulatory failure) | 261 (74) | 50 (47) | < 0.001 | 34 (49) | 16 (44) | 0.69 |
| Coagulation failure | 74 (21) | 30 (28) | 0.12 | 20 (29) | 10 (28) | 0.93 |
| Renal failure | 111 (32) | 30 (28) | 0.52 | 20 (29) | 10 (28) | 0.93 |
| Hepatic failure | 74 (21) | 14 (13) | 0.07 | 8 (11) | 6 (17) | 0.45 |
| Acute Physiology and Chronic Health Evaluation II, mean ± SD | 31±7 | 22±6 | < 0.001 | 22±6 | 23±7 | 0.57 |
| Process measures | | | | | | |
| Time from admission to ICU (d), median (IQR) | 0 (0–3) | 1 (0–4) | 0.45 | 1 (0–4) | 1 (0–2.5) | 0.89 |
| Noninvasive positive pressure ventilation on initial day of ARDS | 2 (1) | 20 (19) | < 0.001 | 13 (19) | 7 (19) | 0.91 |
| Fluid balance on enrollment (L), median (IQR) | 2.8 (1.0 to 5.6) | 1.2 (–0.4 to 2.7) | < 0.001 | 1.2 (–0.2 to 3.2) | 1.0 (–0.6 to 2.3) | 0.66 |
| Clinical outcomes | | | | | | |
| Death at 60 d | 128 (36) | 38 (36) | 0.91 | 18 (26) | 20 (56) | 0.002 |
| Died in the hospital | 104 (30) | 28 (26) | 0.52 | 10 (14) | 18 (50) | < 0.001 |
| Ventilator-free days, median (IQR) | 16 (0 to 23) | 24 (8 to 28) | < 0.001 | 28 (23 to 23) | 7 (1 to 20) | < 0.001 |
| ICU days in hospital survivors, median (IQR) ^c | 9 (6 to 16) | 6 (3 to 10) | < 0.001 | 4 (3 to 7) | 11.5 (9 to 17) | < 0.001 |
| Days of mechanical ventilation in hospital survivors, median (IQR) ^c | 6 (3 to 12) | 0 (0 to 4) | < 0.001 | 0 (0 to 0) | 8 (4 to 15) | < 0.001 |

ARDS = acute respiratory distress syndrome, IQR, interquartile range.

^aAvailable in 339 patients, 283 early intubation, and 56 initially nonintubated.

^bAvailable in 420 patients, 327 early intubation, and 93 initially nonintubated.

^c247 Early intubation and 78 initially nonintubated patients survived to discharge; of initially nonintubated patients, 60 were never intubated and 18 were late intubation.

Presented as n (%) unless otherwise indicated.

When compared with the early intubation group, patients who were initially nonintubated at the time of ARDS diagnosis were more likely to be admitted from the emergency department and transferred from the floor ($p \leq 0.001$). Initially nonintubated patients were less likely to have a known history of

alcohol abuse (6% vs 16%; $p = 0.006$) but were more likely to have an underlying hematologic malignancy (24% vs 7%; $P < 0.001$). The severity of illness was lower in initially nonintubated patients than in early intubation patients (Table 2) with lower mean APACHE II score (22 ± 6 vs 31 ± 7; $p < 0.001$),

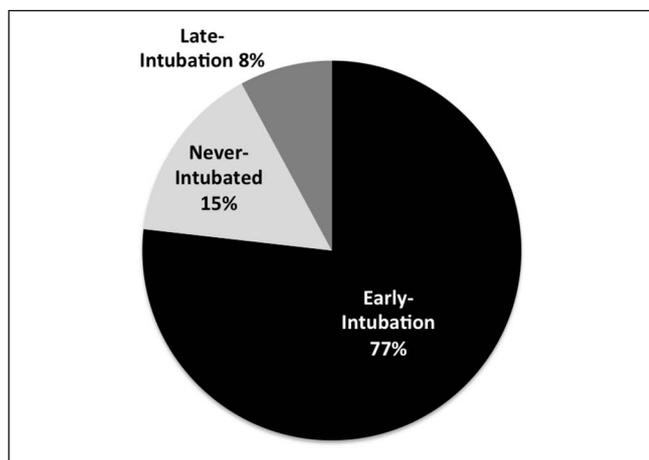


Figure 2. Intubation group (early intubation, never intubated, late intubation) among 457 patients with acute respiratory distress syndrome.

less severe hypoxemia ($\text{PaO}_2:\text{FiO}_2$, 181 ± 86 vs 146 ± 84 mm Hg; $p = 0.006$ and $\text{SpO}_2:\text{FiO}_2$, 211 ± 76 vs 160 ± 62 ; $p < 0.001$), and lower rates of shock (47% vs 74%; $p < 0.001$). Initially nonintubated patients were more likely to be treated with NIPPV (9% vs 1%; $p < 0.001$) on the day of meeting ARDS criteria, and respiratory rates were increased in initially nonintubated patients when compared with those in early intubation ($p = 0.01$). Fluid balance in both groups was positive measured from the 24 hours prior to enrollment but was lower in the initially nonintubated group than in the early intubation group ($+1.2$ vs 2.8 L; $p < 0.001$).

Among the 106 initially nonintubated patients, there were few demographic or initial clinical differences between the minority who progressed to require intubation (late intubation) and the majority who did not (never intubated) (Tables 1 and 2, columns 5–7). There was no difference between the groups in the proportion of patients treated with NIPPV (19% in both never-intubated [$n = 13$ of 70] and late intubation [$n = 7$ of 36] groups; $p = 0.91$). The late-intubation group was more likely to have a history of cirrhosis (11% vs 1%, $p = 0.03$) than patients who did not progress to require endotracheal

intubation for lung injury. However, other demographic and presenting clinical characteristics including age, sex, race, source of admission, serious comorbidities, and severity of illness measures were similar between groups.

Intubation Status and Clinical Outcomes

Mortality at 60 days was the same in initially nonintubated patients than in early intubation patients (Table 2, 36% in each group; $p = 0.91$). Patients in the early intubation group had increased overall respiratory failure as measured by fewer VFD, increased number of ICU days, and increased days of MV ($p < 0.001$ for all comparisons; Table 2) when compared with the initially nonintubated group.

After classifying patients according to intubation status over the 4-day follow-up period, patients in the late-intubation subgroup had significantly increased mortality at 60 days when compared with both the never-intubated (56% vs 26%; $p = 0.002$) and the early intubation (56% vs 36%; $p = 0.03$) groups (Table 3). The majority ($n = 27$) of the late-intubation group underwent intubation on day 2 of follow-up (Fig. 3). An additional nine patients underwent intubation on days 3 and 4 after meeting ARDS criteria. Mortality at 60 days was similarly elevated in the day 2 and day 3 to 4 late-intubation subgroups (Fig. 3). Differences in mortality across intubation groups persisted at 60 days ($p = 0.004$) and at both 1-year ($p = 0.01$) and 2-year ($p = 0.02$) follow-up (Fig. 4, A and B).

The late-intubation subgroup also had significantly fewer VFDs, more days requiring MV, and increased ICU days in survivors to hospital discharge than the never-intubated group (Table 3; all $p < 0.05$). Although there was a trend toward lower VFD and increased ICU and MV days in the late-intubation group than in the early intubation patients, these differences were not statistically significant (Table 3).

Multivariate Analyses

Using a Cox proportional hazards, backward selection model (final variables selected for 60-day follow-up are specified in Table 4), the adjusted risk of death at 60 days was 2.37 times higher in the late-intubation group than in the early intubation

TABLE 3. Clinical Outcomes in Three Intubation Groups

| | Early Intubation | Never Intubated | Late Intubation |
|---------------------------------------|------------------|-------------------------|--------------------------|
| <i>n</i> | 351 | 70 | 36 |
| Death at 60 d, <i>n</i> (%) | 128 (36) | 18 (26) | 20 (56) ^{ab} |
| Died in the hospital, <i>n</i> (%) | 104 (30) | 10 (14) ^a | 18 (50) ^{ab} |
| Ventilator-free days, median (IQR) | 16 (0–23) | 28 (23–28) ^a | 7 (1–20) ^b |
| ICU days, median (IQR) ^c | 9 (6–16) | 4 (3–7) ^a | 11.5 (9–17) ^b |
| Days of MV, median (IQR) ^c | 6 (3–12) | 0 (0–0) ^a | 8 (4–15) ^b |

IQR = interquartile range, MV = mechanical ventilation.

^a $p < 0.05$ vs early intubation.

^b $p < 0.05$ vs never intubated.

^cAmong survivors to hospital discharge: 247 early intubation and 78 initially nonintubated patients. Of initially nonintubated patients, 60 were never intubated and 18 underwent late intubation.

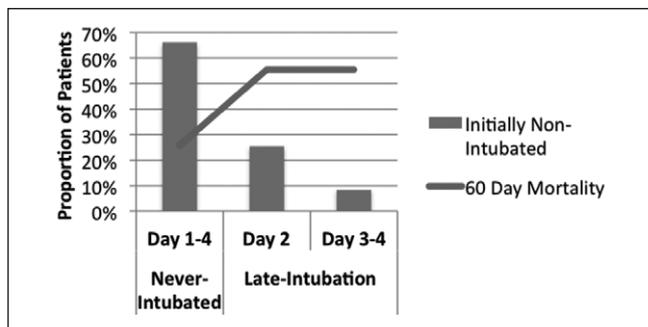


Figure 3. Timing of intubation in 106 initially nonintubated patients with acute respiratory distress syndrome.

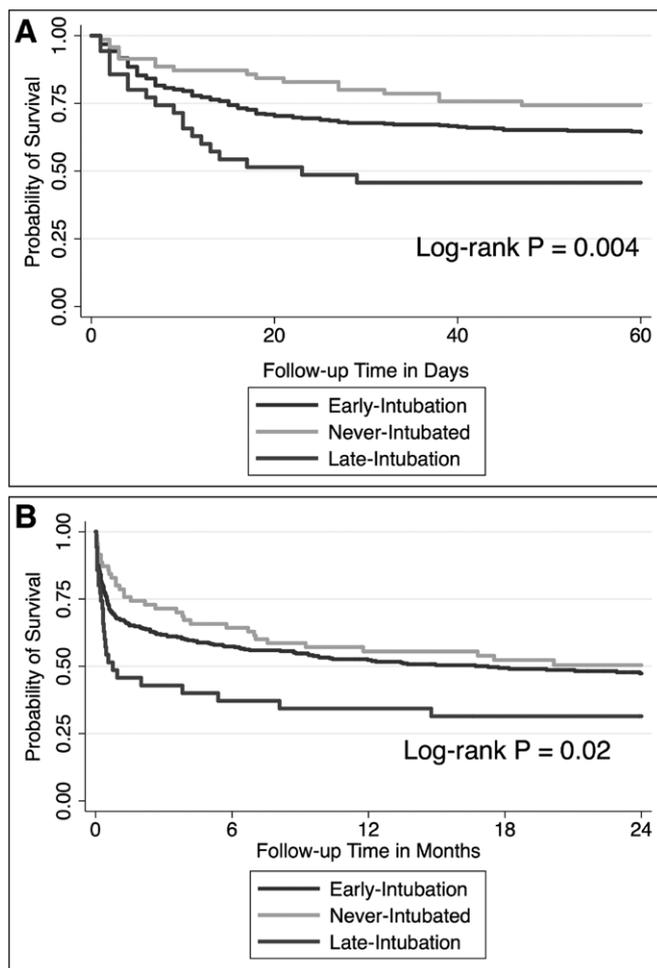


Figure 4. Kaplan-Meier curve showing probability of survival at follow-up. **A**, At 60-d and **(B)**, At 2-yr follow-up.

(95% CI, 1.32–4.24; $p = 0.004$). In contrast, there was no significant difference in mortality in the never-intubated and early intubation groups at 60 days in adjusted analysis. Results were similar at both 1- and 2-year follow-up (data not shown).

A propensity score to account for baseline covariates that differed according to intubation status was limited to 106 initially nonintubated patients. Model fit of the Cox-proportional hazards regression model adjusting for propensity quintile was adequate (goodness-of-fit, $p = 0.81$),

and the c -statistic was 0.77. The distribution of propensity scores was similar in the never-intubated and late-intubation groups. After adjustment for propensity quintile, late intubation was associated with a 3.53-fold increased risk of death at 60 days when compared with never-intubated patients (95% CI, 1.70–7.34; $p = 0.001$; **Table 5**). At 1 and 2 years of follow-up, the late-intubation group remained at 2.5-fold increased risk of death when compared with patients who did not require intubation.

Reclassifying Patients Treated With NIPPV as Intubated

Among patients who were nonintubated on the day of meeting ARDS criteria, NIPPV was used for an equal proportion of the never-intubated and late-intubated groups (19% in each group; **Table 2**). Mortality at 60 days among patients treated with NIPPV was high at 55%. However, there was no evidence that NIPPV modified the association between intubation and mortality (test of interaction $p = 0.40$). In a sensitivity analysis reclassifying NIPPV as part of the early intubation group (because NIPPV is included in the Berlin definition for ARDS), the differences in mortality between intubation groups remained similar (**Supplementary Fig. 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B461>, which illustrates Kaplan-Meier curve showing probability of survival at 60 d after reclassifying patients undergoing NIPPV with the early intubation group).

DISCUSSION

The primary findings of this study can be summarized as follows. First, in a multi-ICU tertiary care center prospective cohort, 23% of patients otherwise meeting criteria for ARDS, as defined as acute onset of hypoxemia and noncardiogenic pulmonary edema, did not require intubation and MV on the day of meeting ARDS criteria. Second, only a minority of these patients (34% of initially nonintubated) later progressed to require endotracheal intubation and MV, most within the subsequent 1–2 days. This subset of patients who underwent late intubation had markedly higher mortality rates than both patients who were intubated early and patients who never progressed to require intubation. This observation withstood adjustment for comorbidities and severity of illness on the day of ARDS diagnosis. These findings support and extend the findings of a prior pediatric study (20) and adult studies (21–25), indicating that it is feasible and important to identify nonintubated patients with ARDS, in part, to facilitate earlier treatment and hopefully improve outcomes (19).

This study enriches the understanding of the epidemiology of ARDS and complements the few existing studies of nonintubated patients with ARDS (21, 24, 25). Cely et al (21) found that only 57% of patients meeting American European Consensus Conference criteria for ALI/ARDS in a Veteran Affairs Medical Center were initially invasively mechanically ventilated in the ICU. Of the remaining 43%, there were 26% who were non-mechanically ventilated in the ICU and 17% who were never mechanically ventilated or admitted to the ICU. Similarly, Quartin et al (24) and Ferguson et al (25) identified ALI among

TABLE 4. Risk of Death at 60 Days When Compared With Early Intubation Referent^a

| | Unadjusted | | | Multivariate Adjusted ^b | | |
|-----------------|------------|-----------|----------|------------------------------------|-----------|----------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Death at 60 d | | | | | | |
| Never intubated | 0.64 | 0.39–1.05 | 0.08 | 0.76 | 0.42–1.38 | 0.37 |
| Late intubation | 1.81 | 1.13–2.90 | 0.01 | 2.37 | 1.32–4.24 | 0.004 |

HR = hazard ratio.

^aResults at 1 and 2 years similar. Follow-up 90% (411/457) at 1 year and 81% (369/457) at 2 years.

^bBackward selection including variables associated with intubation status, *p* < 0.20. Final selected variables: alcohol abuse by history, admission from the operating room, cirrhosis, leukemia or stem cell transplant, any cancer, hepatic failure, Acute Physiology and Chronic Health Evaluation II, noninvasive positive pressure ventilation use, acute respiratory distress syndrome risk factor, and fluid balance at time of enrollment.

TABLE 5. Risk of Death in the Late-Intubation Group When Compared With Never-Intubated Referent

| | Unadjusted | | | Propensity Adjusted | | |
|---------------|------------|-----------|----------|---------------------|-----------|----------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| Death at 60 d | 2.86 | 1.51–5.43 | 0.001 | 3.53 | 1.70–7.34 | 0.001 |
| Death at 1 yr | 2.15 | 1.26–3.67 | 0.005 | 2.54 | 1.37–4.69 | 0.003 |
| Death at 2 yr | 2.06 | 1.22–3.46 | 0.006 | 2.50 | 1.36–4.60 | 0.003 |

HR = hazard ratio.

nonintubated patients in non-ICU wards. Our study demonstrates that ARDS is prevalent among ICU patients prior to developing respiratory failure severe enough for intubation and in patients never requiring intubation.

Our research group has previously studied patients presenting to the emergency department with bilateral opacities on chest radiograph prior to the need for endotracheal intubation to establish a definition of early ALI (22, 23). The goal of these studies was to identify clinical predictors of progression to ARDS requiring positive pressure ventilation (via endotracheal tube or face mask). Although these prior studies focused on less acutely ill patients, the majority of whom were admitted to non-ICU beds and excluded all patients meeting consensus criteria for ARDS receiving positive pressure MV on presentation, they identified a similar proportion of patients with ARDS without fulminant respiratory failure who went on to require intubation as in the current study (25–33% vs 34%).

In the current study, we identified increased mortality in the late-intubation subgroup that was not explained by demographics, comorbidities, initial severity of illness, or propensity to receive endotracheal intubation. No clinical or demographic factor clearly predicted the clinical deterioration for these patients. In contrast, patients with early intubation were markedly sicker at the time of ARDS diagnosis with increased organ dysfunction, shock, and higher APACHE II scores when compared with nonintubated patients, including the late-intubation subgroup. Furthermore, the increased risk of death for the late-intubation group persisted at both 1 and 2 years of follow-up and withstood reclassification of

patients receiving NIPPV to the early intubation group; thus, there was no evidence that delay of endotracheal intubation through the use of NIPPV mediated the increased mortality observed in late-intubation subgroup. One possible explanation for increased risk of death in the late-intubation subgroup includes the higher proportion of patients with malignancy in the initially nonintubated group than the early intubation patients; however, the proportion of these patients did not significantly differ between the never-intubated and late-intubation subgroups, and, in fact, there was a trend to higher prevalence of malignancy among the never-intubated group, suggesting that delay in intubation due to malignancy was not a likely explanation.

These results have implications for clinical practice in terms of providing new epidemiologic data on the clinical manifestations and outcomes in ARDS and also for timing of patient selection in future studies. Because current definitions of ARDS exclude patients not requiring positive pressure respiratory support, both researchers and clinicians may miss opportunities to diagnose and treat patients with high morbidity and mortality earlier in the course of illness. Furthermore, with the growing data supporting the therapeutic value of high-flow nasal oxygen over NIPPV in acute hypoxemic respiratory failure (44), the proportion of ARDS patients who never require intubation or require intubation and MV later in the course of illness is likely to grow. Yet there are no clear clinical classifications for these patients—only after they were treated with NIPPV or intubated did these patients meet the classical definition of Berlin ARDS (7).

Further study in larger cohorts is warranted to confirm the increased mortality observed particularly in the late-intubation group. The current study cannot assess causality, and clinical factors predicting late intubation were not identified. One possible contributor to worse outcomes in the late-intubation group may have been delayed intubation. However, at the time of diagnosis of ARDS, these patients did not appear to be significantly different from the never-intubated group; therefore, this study cannot provide insight as to what early signs may have predicted decline in these patients. More work must be done to identify patients likely to decline before they require intubation to eventually test the hypothesis that early intubation in a higher risk groups could improve outcomes. In addition, future studies must incorporate alternative therapies such as high-flow nasal oxygen, which are likely to reduce the need for positive pressure ventilation and potentially reduce ARDS mortality (44, 45).

Strengths of the current study include its prospective design, large study sample, detailed phenotyping of clinical characteristics and severity of illness, and long-term follow-up. Importantly, patients with a 'do not intubate' order were excluded so that differences in goals of care would not bias the results. However, some limitations warrant discussion. First, it was performed at a single, tertiary care site. However, the study included a large, multidisciplinary medical and surgical subcohort of patients with ARDS derived from a broad range of critically ill patients, which is likely to improve generalizability overall. Furthermore, this study is unique in that it included patients who were nonintubated at the time of ARDS diagnosis. Second, although several recent studies have reported that nonintubated patients represent a substantial fraction of the ARDS population in both adults and children (21, 24, 25), there are challenges in defining the severity of hypoxemia in this population. The F_{IO_2} is more difficult to measure accurately, and thus the P_{aO_2}/F_{IO_2} (and likely the S_{pO_2}/F_{IO_2}) is less reliable at low F_{IO_2} due to shunting (46). Furthermore, positive end-expiratory pressure ≥ 10 cm H_2O has been associated with improved consistency in the measurement of hypoxemia (47), and half of the mechanically ventilated patients and all of the nonmechanically ventilated patients in our study had either lower PEEP levels or no supplemental PEEP, potentially leading to an overestimation of the severity of hypoxemia in these patients. However, the purpose of this study was to study the epidemiology and clinical outcomes in patients with clinical and radiographic evidence of ARDS and some degree of arterial hypoxemia prior to the need for intubation and MV. This approach enabled us to identify differences in clinical outcomes according to the timing of intubation. Third, we do not have detailed data on indications for intubation, exact timing of intubation, or detailed data on ventilator management in this cohort. These are details that will be critical to obtain in future studies to better understand the epidemiology of ARDS in initially nonintubated patients. Finally, this study does not include non-ICU patients, and further study of clinical outcomes in this population is necessary.

CONCLUSIONS

The results of this study demonstrate that a large subset of patients with ARDS are never intubated and those who are intubated later in the course of illness have poor clinical outcomes. Current definitions of ARDS do not include most of these nonintubated patients with ARDS, and both researchers and clinicians may miss opportunities to diagnose and treat these patients earlier in the course of illness. Consensus definitions and further prospective epidemiologic, treatment, and biology studies are necessary to identify high-risk nonintubated patients with ARDS. These patients may represent an ideal target for novel therapies.

ACKNOWLEDGMENTS

We thank all the patients who participated in the study and the research staff who assisted with the study. None of the supporting funding sources had any role in the collection of data, interpretation of results, or preparation of this article.

REFERENCES

- Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
- Bell RC, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med* 1983; 99:293–298
- Fowler AA, Hamman RF, Good JT, et al: Adult respiratory distress syndrome: Risk with common predispositions. *Ann Intern Med* 1983; 98:593–597
- Pepe PE, Potkin RT, Reus DH, et al: Clinical predictors of the adult respiratory distress syndrome. *Am J Surg* 1982; 144:124–130
- Sloane PJ, Gee MH, Gottlieb JE, et al: A multicenter registry of patients with acute respiratory distress syndrome. Physiology and outcome. *Am Rev Respir Dis* 1992; 146:419–426
- Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
- Ranieri VM, Rubenfeld GD, Thompson BT, et al: Acute respiratory distress syndrome: The Berlin Definition. *JAMA* 2012;307:2526–2533
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
- Bersten AD, Edibam C, Hunt T, et al; Australian and New Zealand Intensive Care Society Clinical Trials Group: Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med* 2002; 165:443–448
- Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
- Goss CH, Brower RG, Hudson LD, et al; ARDS Network: Incidence of acute lung injury in the United States. *Crit Care Med* 2003; 31:1607–1611
- Luhr OR, Antonsen K, Karlsson M, et al: Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. *Am J Respir Crit Care Med* 1999; 159:1849–1861
- Matthay MA, Brower RG, Carson S, et al. Randomized, Placebo-Controlled Clinical Trial of an Aerosolized Beta-2 Agonist for Treatment of Acute Lung Injury. *Am J Respir Crit Care Med* 2011.
- Roupie E, Lepage E, Wysocki M, et al: Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. SRLF Collaborative Group on Mechanical

- Ventilation. Société de Réanimation de Langue Française. *Intensive Care Med* 1999; 25:920–929
15. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693
 16. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006;354(21):2213–2224.
 17. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575
 18. Levitt JE, Matthay MA: The utility of clinical predictors of acute lung injury: Towards prevention and earlier recognition. *Expert Rev Respir Med* 2010; 4:785–797
 19. NHLBI Clinical Trials Research Network for the Prevention and Treatment of Acute Lung Injury (PETAL Network). 2014 [cited August 21 2014]. Available at:<http://petalnet.org>. Accessed September 8, 2015
 20. Flori HR, Glidden DV, Rutherford GW, et al: Pediatric acute lung injury: Prospective evaluation of risk factors associated with mortality. *Am J Respir Crit Care Med* 2005; 171:995–1001
 21. Cely CM, Rojas JT, Maldonado DA, et al: Use of intensive care, mechanical ventilation, both, or neither by patients with acute lung injury. *Crit Care Med* 2010; 38:1126–1134
 22. Levitt JE, Bedi H, Calfee CS, et al: Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest* 2009; 135:936–943
 23. Levitt JE, Calfee CS, Goldstein BA, et al: Early acute lung injury: Criteria for identifying lung injury prior to the need for positive pressure ventilation*. *Crit Care Med* 2013; 41:1929–1937
 24. Quartin AA, Campos MA, Maldonado DA, et al: Acute lung injury outside of the ICU: Incidence in respiratory isolation on a general ward. *Chest* 2009; 135:261–268
 25. Ferguson ND, Frutos-Vivar F, Esteban A, et al: Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: A prospective observational study. *Crit Care* 2007; 11:R96
 26. Siew ED, Ware LB, Gebretsadik T, et al: Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. *J Am Soc Nephrol* 2009; 20:1823–1832
 27. Kangelaris KN, Calfee CS, May AK, et al: Is there still a role for the lung injury score in the era of the Berlin definition ARDS? *Ann Intensive Care* 2014; 4:4
 28. Wang CY, Calfee CS, Paul DW, et al: One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014; 40:388–396
 29. Rice TW, Wheeler AP, Bernard GR, et al; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network: Comparison of the SpO₂/FIO₂ ratio and the PaO₂/FIO₂ ratio in patients with acute lung injury or ARDS. *Chest* 2007; 132:410–417
 30. Bazuaye EA, Stone TN, Corris PA, et al: Variability of inspired oxygen concentration with nasal cannulas. *Thorax* 1992; 47:609–611
 31. Wettstein RB, Shelledy DC, Peters JI: Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care* 2005; 50:604–609
 32. Calfee CS, Eisner MD, Ware LB, et al; Acute Respiratory Distress Syndrome Network, National Heart, Lung, and Blood Institute: Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. *Crit Care Med* 2007; 35:2243–2250
 33. Schoenfeld DA, Bernard GR; ARDS Network: Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; 30:1772–1777
 34. Bernard GR, Wheeler AP, Arons MM, et al: A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group. *Chest* 1997; 112:164–172
 35. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
 36. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
 37. Rocker GM, Mackenzie MG, Williams B, et al: Noninvasive positive pressure ventilation: Successful outcome in patients with acute lung injury/ARDS. *Chest* 1999; 115:173–177
 38. Auriant I, Jallot A, Hervé P, et al: Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med* 2001; 164:1231–1235
 39. Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001; 344:481–487
 40. Rana S, Jenad H, Gay PC, et al: Failure of non-invasive ventilation in patients with acute lung injury: Observational cohort study. *Crit Care* 2006; 10:R79
 41. Schettino G, Altobelli N, Kacmarek RM: Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: Experience at the Massachusetts General Hospital. *Crit Care Med* 2008; 36:441–447
 42. Agarwal R, Aggarwal AN, Gupta D: Role of noninvasive ventilation in acute lung injury/acute respiratory distress syndrome: A proportion meta-analysis. *Respir Care* 2010; 55:1653–1660
 43. Thille AW, Contou D, Fragnoli C, et al: Non-invasive ventilation for acute hypoxemic respiratory failure: Intubation rate and risk factors. *Crit Care* 2013; 17:R269
 44. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group: REVA Network: High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372:2185–2196
 45. Matthay MA: Saving lives with high-flow nasal oxygen. *N Engl J Med* 2015; 372:2225–2226
 46. Gowda MS, Klocke RA: Variability of indices of hypoxemia in adult respiratory distress syndrome. *Crit Care Med* 1997; 25:41–45
 47. Villar J, Pérez-Méndez L, López J, et al; HELP Network: An early PEEP/FIO₂ trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 176:795–804