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

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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.
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 ($Pao_2/Fio_2 \leq 300$ or $Spo_2/Fio_2 \leq 315$) 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

***See also p. 246.**

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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 ($Pao_2/Fio_2 \leq 300$ 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 (Spo_2/Fio_2) less than or equal to 315 was used as a validated surrogate for Pao_2/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:

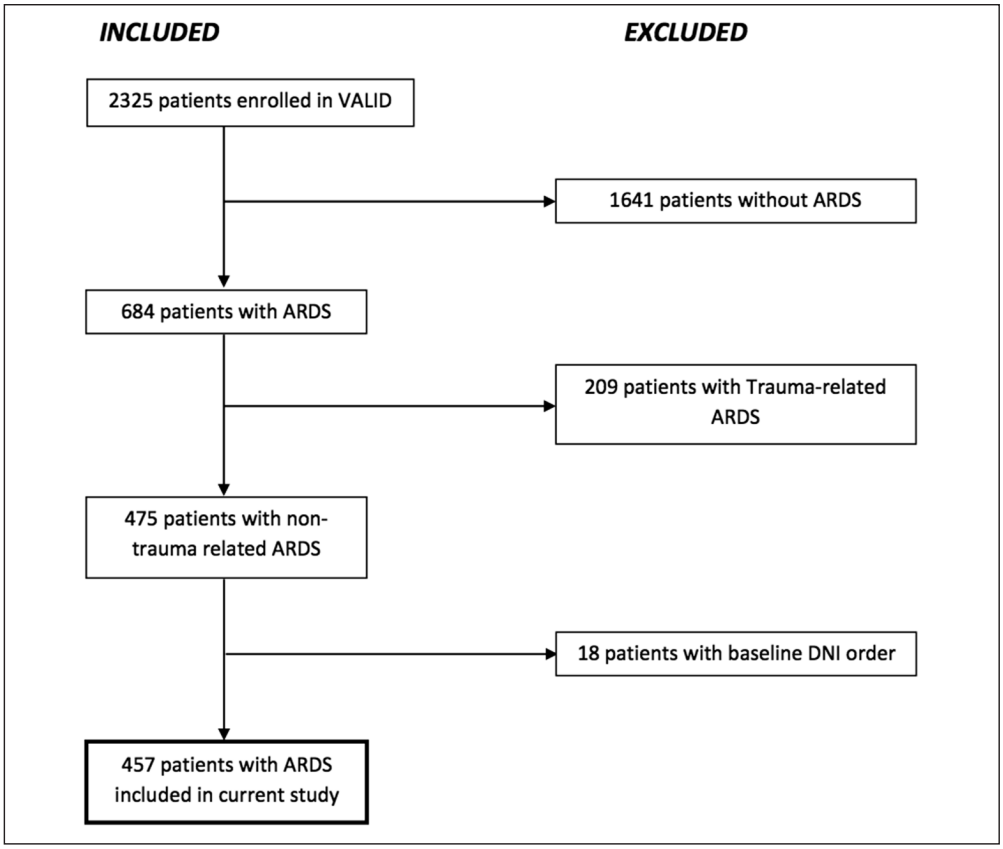

Figure 1. Flow diagram of inclusion and exclusion criteria. This flow diagram illustrates the total number of patients enrolled in the Validation of biomarkers for Acute Lung Injury Diagnosis (VALID) study and the number and reasons for excluding patients based on our predetermined criteria. Following 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 $80 \times 10^3/mm^3$; 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 measures (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 Pao_2/Fio_2 or Spo_2/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 ($n = 106$)		
	Early Intubation ($n = 351$)	Initially Nonintubated ($n = 106$)	p	Never Intubated ($n = 70$)	Late Intubated ($n = 36$)	p
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.

[a]Available in 339 patients, 283 early intubation, and 56 initially nonintubated.

[b]Available in 420 patients, 327 early intubation, and 93 initially nonintubated.

[c]247 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; $p < 0.001$),

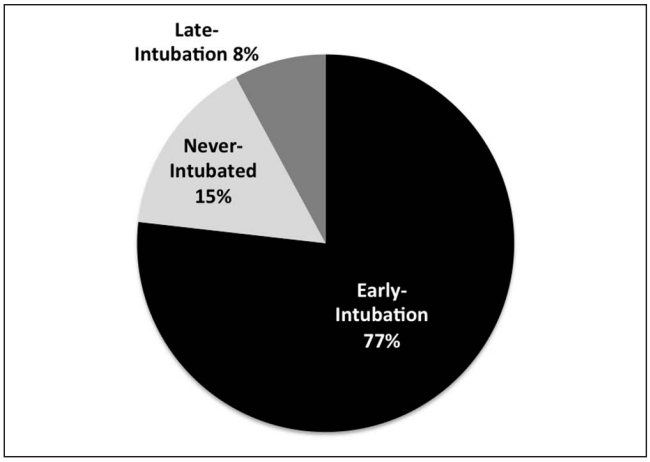

Figure 2. Intubation group (early intubation, never intubated, late intubation) among 457 patients with acute respiratory distress syndrome.

less severe hypoxemia (Pao_2:FIO_2, 181 ± 86 vs 146 ± 84 mm Hg; $p = 0.006$ and Spo_2: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
n	351	70	36
Death at 60 d, *n* (%)	128 (36)	18 (26)	20 (56)[a,b]
Died in the hospital, *n* (%)	104 (30)	10 (14)[a]	18 (50)[a,b]
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.

[c]Among 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.

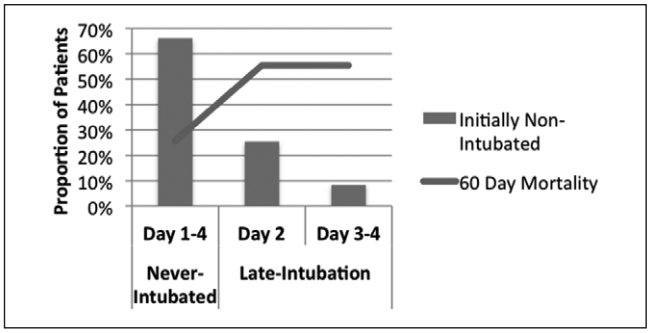

Figure 3. Timing of intubation in 106 initially nonintubated patients with acute respiratory distress syndrome.

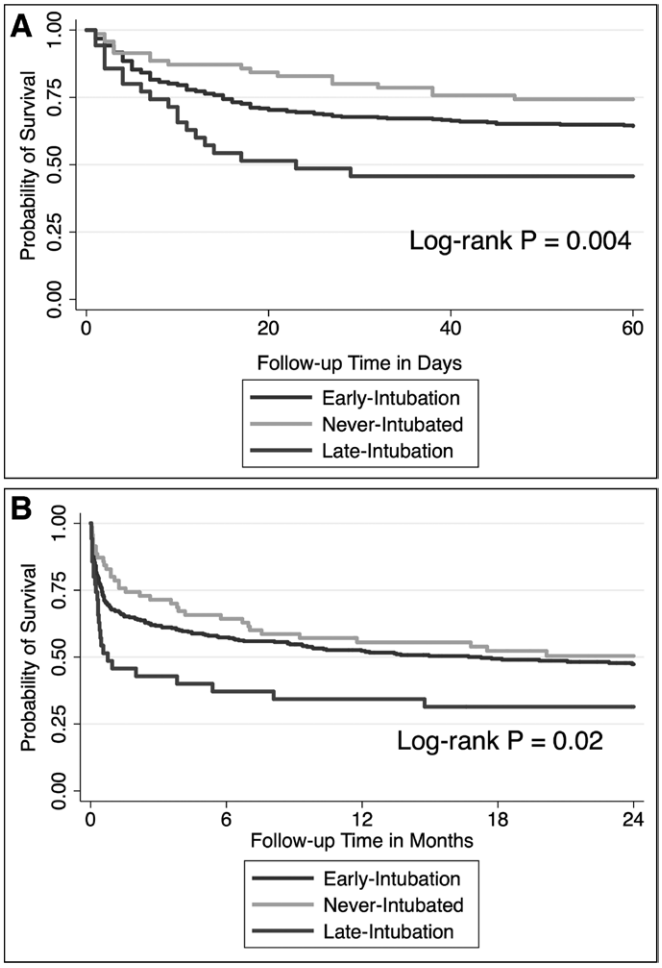

Figure 4. Kaplan-Meier curve showing probability of survival at follow-up. **A**, At 60-d and (**B**). At 2-yr follow-up.

(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	*p*	HR	95% CI	*p*
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.

[a]Results at 1 and 2 years similar. Follow-up 90% (411/457) at 1 year and 81% (369/457) at 2 years.

[b]Backward section 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	*p*	HR	95% CI	*p*
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 preformed 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 Pa_{O_2}/F_{IO_2} (and likely the Sp_{O_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.

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