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Low Tidal Volume Ventilation Use in Acute Respiratory Distress Syndrome

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Abstract

Objective—Low tidal volume ventilation (LTVV) lowers mortality in the acute respiratory distress syndrome (ARDS). Previous studies reported poor LTVV implementation. We sought to determine the rate, quality, and predictors of LTVV use.

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Conflicts of Interest:

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

SUPPLEMENTAL DIGITAL CONTENT LEGEND

Supplemental Figure Legend

Figure S1

Table S1

Table S2

Table S3

Table S4

Table S5

Table S6

Table S7

Supplemental Methods

Design—Retrospective cross-sectional study.

Setting—One academic, three community hospitals in the Chicago region.

Patients—362 adults meeting the Berlin Definition of ARDS consecutively admitted between June-December, 2013.

Measurements and Main Results—Seventy patients (19.3%) were treated with LTVV (tidal volume <6.5mL/kg predicted body weight [PBW]) at some time during mechanical ventilation. 22.2% of patients requiring a fraction of inspired oxygen ($F_{I}O_2$) >40% and 37.3% of patients with $F_{I}O_2$ >40% and plateau pressure >30cm H₂O received LTVV. The entire cohort received LTVV 11.4% of the time patients had ARDS. Among patients who received LTVV, the mean (SD) percentage of ARDS time it was used was 59.1% (38.2%), and 34% waited more than 72 hours prior to LTVV initiation. Women were less likely to receive LTVV, whereas sepsis and $F_{I}O_2$ >40% were associated with increased odds of LTVV use. Four attending physicians (6.2%) initiated LTVV within one day of ARDS onset for 50% of their patients, whereas 34 physicians (52.3%) never initiated LTVV within one day of ARDS onset. 54.4% of patients received a tidal volume <8mL/kg PBW, and the mean tidal volume during the first 72 hours after ARDS onset was never less than 8mL/kg PBW.

Conclusions—More than 12 years after publication of the landmark LTVV study, use remains poor. Interventions that improve adoption of LTVV are needed.

Keywords

implementation science; quality improvement; knowledge translation; acute respiratory distress syndrome; critical care; mechanical ventilation

INTRODUCTION

Acute respiratory distress syndrome (ARDS), including the commonly used term acute lung injury, is a clinical syndrome of acute severe hypoxemia due to bilateral non-cardiogenic pulmonary edema.(1) ARDS is commonly diagnosed in critically ill patients and is associated with high mortality and morbidity.(1–3) Low tidal volume ventilation (LTVV) is the most extensively investigated ARDS therapy that improves mortality in patients with ARDS.(4–8) The target of LTVV is a tidal volume of 6 mL/kg predicted body weight (PBW) (some definitions include a target pressure during an end-inspiratory hold maneuver, or plateau pressure [P_{Plat}], less than or equal to 30 cm H₂O).(4, 9)

Despite strong clinical trial evidence of its effectiveness(4–6, 10) and its inclusion in at least one major clinical practice guideline,(11) LTVV remains under-used.(5, 6, 12–18) Many studies reporting low LTVV use come from the same ARDS Network (ARDSNet) institutions that first studied the LTVV intervention;(5, 6, 13, 14) less is known about LTVV adoption in other hospitals. In addition, prior studies have important limitations. Either they were conducted more than eight years ago, used an outdated definition of ARDS, evaluated LTVV utilization only once or twice daily, or did not thoroughly examine predictors of LTVV use.

We conducted this study to analyze the current rate of LTVV use for ARDS in several non-ARDSNet academic and community medical centers using the Berlin Definition of ARDS, continuous ventilator data, and an expanded list of LTVV predictors.(1) We hypothesized that implementation of LTVV would be low despite conducting this study more than one dozen years after the publication of the landmark ARDSNet study.(4)

MATERIALS AND METHODS

Study design

We performed a retrospective cross-sectional study of patients admitted to the intensive care units (ICUs) at one academic (hospital A) and three community hospitals (hospitals B-D) in the Chicago, Illinois region (Table S1 of the Supplemental Digital Content). None of these hospitals used a LTVV protocol or order set at the time of the study. The study was approved by the Institutional Review Boards of Northwestern University and the participating community hospitals.

We screened all patients 18 years old consecutively admitted to a participating hospital's ICU between June 24, 2013 and December 31, 2013 who received mechanical ventilation via an endotracheal tube or tracheostomy. We included patients if they met the Berlin Definition of ARDS.(1) We addressed some limitations in Berlin Definition specificity in the following ways: 1) we required qualifying P_aO_2/F_iO_2 ratios and infiltrates to occur within 48 hours of each other (ARDSNet trials generally required enrollment within 36–48 hours after ARDS onset);(14) 2) we developed criteria to identify bilateral infiltrates based on radiologists' reports, and ARDS risk factors and cardiac failure based on attending physician notes; and 3) we developed criteria for the objective assessment of cardiac failure based on echocardiographic findings and β -natriuretic peptide measurement (see Supplemental Methods in the Supplemental Digital Content for cohort development).

We excluded patients receiving non-invasive ventilation due to concerns regarding the accuracy of tidal volume measurements. ARDS onset was defined as the later time of P_aO_2/F_iO_2 300mm Hg or bilateral infiltrates on chest imaging.

Measurements

Data were collected from the electronic health records at participating hospitals. We recorded continuous ventilator settings during mechanical ventilation. The primary outcome was the percentage of patients with ARDS with at least one LTVV ventilator setting between ARDS onset and the earliest of extubation, ICU discharge, or death. LTVV was defined as $V_T < 6.5$ mL/kg PBW, consistent with the cutoff chosen by ARDSNet when evaluating LTVV adherence.(14) LTVV without consideration of P_{Plat} was chosen as the primary outcome because P_{Plat} was not recorded at hospitals C and D.

Secondary ventilator outcomes included: the percentage of time patients received LTVV from ARDS onset to the earliest of extubation, ICU discharge, or death; among patients treated with LTVV, the time from ARDS onset to initial LTVV; the percentage of patients who had P_{Plat} 30 cm H₂O at all times after LTVV initiation; and the percentage of time after LTVV initiation that patients had P_{Plat} 30 cm H₂O. We determined the percentage of

patients who received $V_T < 8\text{mL/kg PBW}$, a more lenient definition of LTVV that includes the upper 95% confidence interval (CI) for the low tidal volume arm of the ARDSNet study. (19)

Clinical characteristics included patient demographic and clinical characteristics, ICU type (for hospital A), ARDS severity (per Berlin Definition), (1) ARDS risk factor, and the attending physician on each day a patient had ARDS. We constructed univariate and multivariate models to determine whether clinical, demographic, or severity of illness variables were associated with the delivery of LTVV. (20–22)

Subgroup analyses were conducted for the primary and secondary outcomes for two subgroups of ARDS patients: 1) patients requiring $F_{I}O_2 > 40\%$ at least once after ARDS onset and 2) patients with both $F_{I}O_2 > 40\%$ and $P_{\text{plat}} > 30\text{ cm H}_2\text{O}$ at least once after ARDS onset. For these two subgroups, the relevant timeframe for analysis was the time a patient received $F_{I}O_2 > 40\%$ between ARDS onset and the earliest of extubation, ICU discharge, or death. Also, we conducted a sensitivity analysis to identify whether ARDS duration < 12 hours or whether P:F ratio/infiltrates interval ≤ 24 hours affected the primary outcome.

Statistical analysis

Data are presented as mean (standard deviation, SD), median [interquartile range, IQR] for non-normal data, or frequency (%). We used Fisher's exact test to compare categorical variables and Student's *t* test or Kruskal-Wallis test to compare continuous variables, as appropriate. The relationship between time to LTVV and ARDS severity was analyzed by Spearman's rank correlation coefficient. Logistic regression results are expressed as odds ratios (OR) with 95% CI.

We anticipated *a priori* that 42.3% of patients with ARDS would receive LTVV based on prior studies. (13, 14, 23) Inclusion of 353 patients would be sufficient to determine this utilization rate $\pm 5\%$ with 95% confidence. All tests are two-tailed, and a *P* value < 0.05 was considered significant. Analyses were performed with SAS. (24)

RESULTS

A total of 1,628 adult intubated patients were screened for inclusion, and 362 met inclusion criteria (Figure 1). Demographic and clinical characteristics are shown in Table 1 and Table S2; 20.7% of the cohort had severe ARDS. The most common ARDS risk factors were sepsis (49.5%) and pneumonia (48.9%); 84.2% of patients had at least one risk factor, and 16.8% had cardiac failure in addition to ARDS. Compared to hospital A (the academic urban hospital), patients from the three community hospitals were older, were more likely to be Hispanic (specifically hospital D), had a shorter time from intubation to ARDS onset, were less likely to have sepsis and shock, and were more likely to have pneumonia, aspiration, or $F_{I}O_2 > 40\%$ at any time after ARDS onset.

Seventy patients (19.3%) were treated with low tidal volume ventilation at any point after ARDS onset (Table 2). LTVV use was 22.2% for patients who had at least one $F_{I}O_2 > 40\%$ after ARDS onset, and 37.3% for those who had at least one $F_{I}O_2 > 40\%$ and one $P_{\text{plat}} > 30\text{cm}$

H₂O after ARDS onset. LTVV utilization did not differ significantly between the academic hospital and the three community hospitals. More patients with severe ARDS were treated with LTVV (26.7%) than moderate or mild ARDS (18.1% and 16.8%, respectively), although this difference was not statistically significant ($P=0.21$) (Table 2). In none of the subgroups analyzed (e.g., sepsis, pneumonia, individual hospital) did more than half of patients receive LTVV (Tables S3 and S4). Results were similar when we included only patients whose P:F ratio/infiltrates interval was less than or equal to 24 hours (19.6% overall utilization, 22.6% in the $F_{I}O_2>40\%$ subgroup), or when we excluded patients who had ARDS for less than 12 hours.

The entire 362 patient cohort received LTVV 11.4% of the time patients had ARDS, which increased to 20.7% for those who had at least one $F_{I}O_2>40\%$ and one $P_{plat}>30\text{cm H}_2\text{O}$ after ARDS onset. Among the seventy patients who received LTVV, the mean (SD) percentage of time that they received LTVV was 59.1% (38.2%). This percentage was similar in the $F_{I}O_2>40\%$ and $F_{I}O_2>40\%$ plus $P_{plat}>30\text{cm H}_2\text{O}$ subgroups (Table S5). The median proportion of time that patients received LTVV that was daytime (7:00am-6:59pm) was 0.50 [0.48–0.53].

The mean (SD) tidal volume (mL/PBW) in patients who received LTVV was not $<6.5\text{mL/kg PBW}$ but was lower than those who did not receive LTVV (6.62mL/kg PBW [0.68mL/kg PBW] vs. 8.84mL/kg PBW [1.50mL/kg PBW], $P<0.001$). The distribution of tidal volumes for the first three days after ARDS onset is illustrated in Figure S1. The weighted mean (SD) tidal volumes (mL/kg PBW) were: 8.44 (1.66) mL/kg PBW zero to 24 hours after ARDS onset, 8.35 (1.61) mL/kg PBW 24–48 hours after ARDS onset, and 8.36 (1.58) mL/kg PBW 48–72 hours after ARDS onset.

Thirty-eight patients (54%) who received LTVV were already receiving LTVV at ARDS onset. In patients for whom LTVV was initiated after ARDS onset, the median time from ARDS onset to LTVV was 22.1 [IQR 5.4–125.2] hours (Table S6). In the $F_{I}O_2>40\%$ subgroup, a lower percentage of patients (43%) were receiving LTVV at ARDS onset; for those who weren't, median time to LTVV was 26.1 [IQR 9.5–155.1] hours (Table S6). In the $F_{I}O_2>40\%$ subgroup (but not the overall cohort), patients with more severe ARDS had a shorter median time to LTVV initiation (severe ARDS: 7.0 [IQR 3.2–11.8] hours, moderate ARDS: 41.3 [IQR 20.4–166.0] hours, mild ARDS: 72.6 [IQR 21.4–249.2] hours, Spearman's $\rho=0.41$, $P=0.019$). Of 56 patients who received LTVV who had P_{plat} recorded after ARDS onset, 14 (25%) had at least one $P_{plat}>30\text{cm H}_2\text{O}$ during LTVV administration; the mean percentage of time $P_{plat}>30\text{cm H}_2\text{O}$ was 44.4% (SD 29.9%).

In multivariable regression modeling (Table 3), women were less likely to receive LTVV (adjusted OR 0.31, 95% CI 0.17–0.56, $P<0.001$). Sepsis and $F_{I}O_2>40\%$ were both associated with increased odds of LTVV (adjusted OR 1.85, 95% CI 1.07–3.20, $P=0.028$; and adjusted OR 2.21, 95% CI 1.15–4.24, $P=0.017$, respectively). Mean (SD) height was lower for women than men (63.4 ± 3.2 inches vs. 69.2 ± 3.7 inches, $P<0.001$).

Sixty-five attending physicians cared for a median of 5 [IQR 2–10] patients within one day of ARDS onset and who were eligible but not already receiving LTVV. Four physicians

(6.2%) initiated LTVV within one day of ARDS onset for 50% or more of their eligible patients, whereas 34 physicians (52.3%) never initiated LTVV within one day of ARDS onset (including 15 physicians who cared for five or more eligible patients) (Table S7).

One hundred ninety-seven patients (54.4%) received $V_T < 8 \text{ mL/kg PBW}$ at least once after ARDS onset, of whom 156 (79.2%) were already receiving $V_T < 8 \text{ mL/kg PBW}$ at ARDS onset. The percentage was no different in the $F_{I\text{O}_2} > 40\%$ subgroup (54.8%).

The mean (SD) percentage of time that the entire 362 patient cohort received $V_T < 8 \text{ mL/kg PBW}$ was 44.6% (46.7%), which was similar for the $F_{I\text{O}_2} > 40\%$ subgroup (46.7% [47.2%]). Among the 197 patients who received $V_T < 8 \text{ mL/kg PBW}$, the mean percentage of time that they received it was 81.9% (SD 30.8%). This percentage was similar in the $F_{I\text{O}_2} > 40\%$ subgroup (85.3% [27.8]).

DISCUSSION

Although low tidal volume ventilation improves outcomes in patients with ARDS and has been recommended in practice guidelines, we found that adoption of LTVV remains poor: LTVV was administered to less than 20% of 362 ARDS patients admitted to four hospitals. Even for the most severe cases of ARDS, LTVV was administered to no more than 40% of patients at some time while on mechanical ventilation. For those who did receive LTVV, LTVV was used less than 60% of the time patients were eligible and was often started after significant delay. While a majority were initiated on LTVV within 24 hours of ARDS onset, 34% waited more than 72 hours. Furthermore, many of the patients who received LTVV had plateau pressures above 30cm H₂O.

Women had lower odds of receiving LTVV, consistent with previous studies.(5, 6) A possible explanation is that if patients are treated with a default tidal volume that is not gender-based (e.g., 450ml or 500ml), women who are on average shorter than men (also demonstrated in our cohort) would have required a greater tidal volume change from this default range than men.

LTVV utilization rates in our study are similar to those reported in studies from the time of the original ARDSNet study more than a dozen years prior (Figure 2). While the criteria used to define LTVV differ among these studies, the low rate of LTVV use is remarkably consistent. The exception is Needham *et al.*, who demonstrated LTVV use between 63–70%.(5, 6) These studies are the exception to the overall trend of LTVV utilization and may be due to unique characteristics of the providers and institutions where they were conducted.

Several characteristics of our study are unique compared to previous studies. First, patients in our study were admitted in 2013, eight years after the most recent comparably large studies.(5, 6) Second, we employed the Berlin Definition of ARDS, which addresses several limitations of the American-European Consensus Conference on ARDS definition used in previous studies, and has better predictive validity.(1, 25) Third, our study was conducted in non-ARDSNet settings. Fourth, we analyzed physician-specific utilization and found LTVV use to be consistently poor. Finally, by obtaining continuous ventilator settings instead of

once- or twice-daily settings, we were able to examine the degree to which actual LTVV use corresponded to recommended parameters.

The reasons why LTVV remains poorly implemented are unclear. LTVV is part of one of few convincingly proven therapies in critical care medicine shown to reduce mortality in randomized controlled trials and subsequent observational studies. It is part of at least one clinical practice guideline.(11) Some perceived barriers to implementation of LTVV include poor physician recognition of ARDS, unwillingness of physicians to use a protocol, and perceptions of contraindications to LTVV.(26) In our study, the consistently poor use of LTVV among physicians in the study may be due to difficulty with ARDS recognition (only 12.4% of the cohort were identified by attending physicians as having ARDS) or other system barriers that may be impeding implementation. Negative attitudes are also possible: a clinician survey in this study is ongoing to explore these issues. If barriers can be identified, interventions should be designed to provide real-time diagnostic information to improve the recognition of ARDS(27, 28) and the sustained delivery of LTVV, and to address perceptions of providers reluctant to adopt LTVV. On a policy level, operationalizing LTVV use in ARDS as a performance measure could greatly assist in its implementation.

This study has several potential limitations. First, as stated in the Methods, the Berlin Definition criteria lack some clarity, especially regarding the identification of and temporal relationship among ARDS diagnostic criteria and the objective criteria for assessing cardiac failure. These raise the possibility of misclassification bias, leading to the concern that our ARDS cohort is not truly representative of the ARDS phenotype. We addressed these limitations by adapting the ARDSNet trials' enrollment criteria and previous literature,(14, 28) and through expert opinion. Also, the validity of our diagnostic process should have been increased through the use of highly conservative inclusion criteria (especially concerning the objective assessment of cardiac failure). Second, our algorithm for identifying qualifying radiographic infiltrates, ARDS risk factors, and cardiac failure has not been validated. Third, we relied on attending physician identification of ARDS risk factors. While misclassification could have occurred because these are subjective data, we believe it was important to reflect whether practicing physicians were themselves identifying ARDS risk factors, and therefore identifying their patients who would be eligible for LTVV. Fourth, our results from only four sites in a single metropolitan area may not be generalizable to the United States at large or other countries' experience with LTVV implementation. However, our study was conducted in a large academic medical center and three community hospitals in geographically and socioeconomically diverse communities, and in ICUs with varying high- and low-intensity critical care structures; these factors potentially enhance the generalizability of our results.

Fifth, some controversy exists as to what constitutes lung protective ventilation, specifically whether achieving a plateau pressure ≤ 30 cm H₂O is at least as important as achieving a low tidal volume,(11, 18, 29, 30) although other evidence suggests that low tidal volumes improve outcomes regardless of whether P_{plat} is above or below this threshold.(9) In any case, the ARDSNet ventilator protocol clearly requires the initial stepwise reduction of tidal volume to a goal of 6 mL/kg PBW;(4) only after this target tidal volume is achieved can tidal volume potentially be increased based on P_{plat} or patient dyspnea. Even using a generous

definition of LTVV as **any one** tidal volume $< 6.5\text{mL/kg PBW}$, LTVV was still used in a minority of patients in our cohort with at least one $P_{\text{plat}} > 30\text{cm H}_2\text{O}$.

Finally, it is possible that $V_T < 8\text{mL/kg PBW}$ may be more realistic for provider adherence, and sufficiently less than the 12mL/kg PBW in the ARMA study control group to be considered lung protective.(4) Our finding that 54% of patients received $V_T < 8\text{mL/kg PBW}$ at least once could suggest some clinician movement in the direction of lower tidal volumes for ARDS, or it could represent the evolution of the standard for tidal volumes for intubated patients. However, the mean tidal volume during the first 72 hours after ARDS onset was never less than 8mL/kg PBW . The sensitivity analyses we conducted address concerns with plateau pressure and the tidal volume threshold, demonstrating poor LTVV use even when plateau pressure was above $30\text{cm H}_2\text{O}$ and under the most lenient definition of low tidal volume.

CONCLUSIONS

In summary, we demonstrate that low tidal volume ventilation, a well-supported therapy that reduces mortality in patients with ARDS, remains poorly implemented. Researchers, individual providers, hospitals, and policymakers should work to design and evaluate interventions and develop systems and standards that address both the complexity and importance of LTVV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Flow diagram for patient inclusion

Figure 2. LTVV utilization since ARDSNet study

Studies are listed according to last name of first author and placed along the X-axis according to the mid-point between the first and last patient enrollment (from published articles and publicly available information). Each study had slightly different LTVV criteria. Needham 1 and Needham 2 were separate analyses and published articles from the same cohort.(5, 6, 12–14, 16, 17)

Table 1

Characteristics of acute respiratory distress syndrome cohort.

Characteristic	Overall (N=362)	Hospital A ^a (N=282)	Hospitals B-D ^a (N=80)
Age (years), mean (SD)	60.8 (16.4)	59.1 (16.2)	66.7 (16.0)
Female, no. (%)	154 (42.5)	112 (39.7)	42 (52.5)
Race, no. (%)			
White	197 (54.4)	150 (53.2)	47 (58.8)
Black	93 (25.7)	80 (28.4)	13 (16.3)
Hispanic	37 (10.2)	23 (8.2)	14 (17.5)
Asian	12 (3.3)	10 (3.6)	2 (2.5)
Other, declined or unable to answer	23 (6.4)	19 (6.7)	4 (5.0)
Ethnicity, no. (%)			
Hispanic	32 (9.8)	20 (7.1)	12 (26.1) ^b
Non-Hispanic	265 (80.8)	231 (81.9)	34 (73.9) ^b
Unable or declined to answer	31 (9.5)	31 (11.0)	0 ^b
ARDS severity, no. (%)			
Severe ($P_aO_2:F_iO_2$ 100)	75 (20.7)	55 (19.5)	20 (25.0)
Moderate ($100 < P_aO_2:F_iO_2$ 200)	144 (39.8)	116 (41.1)	28 (35.0)
Mild ($200 < P_aO_2:F_iO_2$ 300)	143 (39.5)	111 (39.4)	32 (40.0)
ARDS risk factor, no. (%) ^c			
Sepsis	179 (49.5)	151 (53.6)	28 (35.0)
Pneumonia	177 (48.9)	126 (44.7)	51 (63.8)
Aspiration	58 (16.0)	37 (13.1)	21 (26.3)
Shock	134 (37.0)	119 (42.2)	15 (18.8)
Drug overdose	2 (0.6)	1 (0.4)	1 (1.3)
Trauma	5 (1.4)	4 (1.4)	1 (1.3)
Pancreatitis	6 (1.7)	6 (2.1)	0
Burn	0	0	0
Transfusion-related acute lung injury (TRALI)	1 (0.3)	1 (0.4)	0
Any one risk factor (N=360)	303 (84.2)	230 (82.1)	73 (91.3)
Cardiac failure, no. (%) ^d	60 (16.8)	42 (15.1)	18 (22.5)
Time from intubation to ARDS onset (days), median [IQR]	0.7 [0.3–1.5]	0.8 [0.5–1.7]	0.2 [0.05–1.0]
Patients with $F_iO_2 > 40\%$ at any time during ARDS, no. (%)	252 (69.6)	187 (66.3)	65 (81.3)
Patients with $P_{plat} > 30$ cm H ₂ O at any time during ARDS, no. (%) (N=304)	74 (24.3)	69 (24.5)	5 (22.7) ^e
P_{plat} (cm H ₂ O) from ARDS onset to earlier of extubation, death, or ICU discharge, mean (SD)	21.1 (4.9)	21.1 (5.0)	21.0 (3.4) ^e

^aHospital A is an academic hospital and Hospitals B-D are community hospitals.^bEthnicity was not reported separately at hospital C.

^cPatients may have had more than one risk factor.

^dMissing four patients.

^eP_{Plat} not recorded at hospitals C-D.

ARDS: acute respiratory distress syndrome. SD: standard deviation. IQR: interquartile range. F_IO₂: fraction of inspired oxygen. P_{Plat}: plateau pressure. ICU: intensive care unit.

Table 2

Low tidal volume ventilation use for acute respiratory distress syndrome patients.

Proportion of patients who received LTVV ^a	All patients		F _I O ₂ >40%		F _I O ₂ and P _a lat>30cm H ₂ O ^d	
	No. (%) ^b	P value ^c	No. (%) ^d	P value ^c	No. (%) ^d	P value ^c
Overall	70 (19.3)		56 (22.2)		22 (37.3)	
Academic (hospital A)	59 (20.9)		47 (25.1)		22 (40.0)	
Community (hospitals B-D)	11 (13.8)	0.20	9 (13.8)	0.08	0	0.29
ARDS severity ^e						
Severe	20 (26.7)		18 (25.7)		8 (40.0)	
Moderate	26 (18.1)	0.21	24 (19.7)	0.58	10 (37.0)	0.99
Mild	24 (16.8)		14 (23.3)		4 (33.3)	

^a Pplat not recorded at hospitals C and D.

^b Between ARDS onset and the earlier of extubation, death, or ICU discharge.

^c Fisher's exact test.

^d Between ARDS onset and the earlier of extubation, death, or ICU discharge and during which F_IO₂>40%.

^e Severe: P_aO₂:F_IO₂ 100, moderate: 100<P_aO₂:F_IO₂ 200, mild: 200<P_aO₂:F_IO₂ 300.

F_IO₂: fraction of inspired oxygen. Pplat: plateau pressure. LTVV: low tidal volume ventilation. ARDS: acute respiratory distress syndrome.

Table 3Predictors of low tidal volume ventilation.^a

	Crude OR (95% CI)	Univariate <i>P</i> value^b	Adjusted OR (95% CI)	Multivariate <i>P</i> value^b
Female gender	0.33 (0.18–0.61)	<0.001	0.31 (0.17–0.56)	<0.001
F _I O ₂ >40% during ARDS	1.96 (1.04–3.70)	0.038	2.21 (1.15–4.24)	0.017
Sepsis	1.70 (1.00–2.88)	0.051	1.85 (1.07–3.20)	0.028

^aThe following variables were not predictors of LTVV: age, race, ethnicity, hospital, ARDS severity, mean F_IO₂, time from intubation to ARDS onset, P_{plat} during ARDS, Acute Physiology Score on day of ARDS onset, APACHE IV predicted mortality, SOFA score on day of ARDS onset, ARDS risk factors (other than sepsis), pH<7.30, and pH<7.15. The highest P_{plat} on the day of ARDS onset was associated with LTVV at hospitals A and B (adjusted OR [95% CI]: 1.10 [1.03–1.17], *P*=0.002).

^bWald chi square test.

LTVV: low tidal volume ventilation. OR: odds ratio. CI: confidence interval. F_IO₂: fraction of inspired oxygen. ARDS: acute respiratory distress syndrome. P_{plat}: plateau pressure. APACHE IV: Acute Physiology and Chronic Health Evaluation IV.(20, 21) SOFA: Sequential Organ Failure Assessment.(22)