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Risk Factors for Acute Respiratory Distress Syndrome in Patients Mechanically Ventilated for Greater Than 48 Hours

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Abstract

Background—Low tidal volume ventilation for Acute Respiratory Distress Syndrome (ARDS) is a well accepted concept. However, controversy persists regarding the optimal ventilator settings for ventilated patients without ARDS. This study tested the hypothesis that ventilator settings influence the development of new ARDS.

Methods—Retrospective analysis of patients from the MIMIC-II database who were mechanically ventilated for ≥ 48 hours between 2001 and 2005.

Results—2583 patients required greater than 48 hrs of ventilation. Of 789 patients who did not have ARDS at admission, 152 (19%) went on to develop ARDS. Univariate analysis revealed high peak inspiratory pressure (PIP) (OR 1.53 per standard deviation, 95% confidence interval 1.28 – 1.84), increasing PEEP (OR 1.35 per SD, 95%CI 1.15 – 1.58) and tidal volume (OR 1.36 per SD, 95%CI 1.12 – 1.64) to be significant risk factors. Major non-ventilator risk factors for ARDS included sepsis, low pH, elevated lactate, low albumin, transfusion of packed red blood cells, transfusion of plasma, high net fluid balance, and low respiratory compliance. Multivariable logistic regression showed that peak pressure (OR 1.31 per SD, 95%CI 1.08 – 1.59), high net fluid balance (OR 1.3 per SD, 95%CI 1.09 – 1.56), transfusion of plasma (OR 1.26 per SD, 95%CI 1.07 – 1.49), sepsis (OR 1.57, 95%CI 1.00 – 2.45) and tidal volume (OR 1.29 per SD, 95%CI 1.02 – 1.52) were significantly associated with the development of ARDS.

Conclusions—The associations between the development of ARDS and clinical interventions, including high airway pressures, high tidal volume, positive fluid balance and transfusion of blood products, suggests that ARDS may be a preventable complication in some cases.

Keywords

lung injury; ventilator; ARDS; tidal volume; plateau pressure; transfusion

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Introduction

Patients in the intensive care unit are commonly supported using mechanical ventilation for days to weeks. Recent studies suggest that initial ventilator settings may affect patient outcome^{1–4}. In particular, patients with Acute Respiratory Distress Syndrome (ARDS) have lower mortality rates when ventilated at lower tidal volumes⁴. The idea that mechanical ventilator settings may greatly influence respiratory health and mortality, has prompted clinicians to find protective measures for minimizing iatrogenic lung injuries. However, there have been few studies and no firm recommendations on the optimal settings for patients who require this intervention for reasons apart from respiratory failure. In fact, patients without respiratory failure make up a significant portion (20 – 30%) of all who are mechanically ventilated in the ICU^{1,3}.

There is increasing evidence that mechanical ventilation can trigger inflammatory pulmonary edema in both animal models⁵ and human patients^{6,7}. Both short-term endotracheal intubation and long term mechanical ventilation are known to increase the risk for nosocomial pneumonia⁸. Some studies have shown that higher tidal volumes are associated with more cases of ARDS and ALI in patients without the disease at the outset^{9,10}. Others show that ventilation with high pressures increases mortality rates in patients with ARDS¹¹. PEEP is hypothesized to have protective effects on the lungs during mechanical ventilation^{12,13}, although randomized trials are equivocal in this area.

Due to the multitude and complexity of risk factors associated with ventilator-induced ARDS, it is necessary to analyze the disorder in large patient populations. In this study, we examined a large ICU database to find physiological and ventilator-associated risk factors for ARDS. We hypothesized that initial ventilator settings as well as other, potentially preventable, risk factors may be associated with the development of ARDS in patients mechanically ventilated for greater than 48 hours but who did not have ARDS at the outset.

Methods

The MIMIC-II database

The Multi Parameter Intelligent Monitoring of Intensive Care (MIMIC-II) project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (BIDMC) and granted a waiver of informed consent. The MIMIC-II database includes physiologic information from bedside monitors in the adult ICU's of BIDMC. These data (heart rate, blood pressures, etc.) were validated by ICU nurses on an hourly basis. The database also contains records of arterial blood gases and lab values, nursing progress notes, IV medications, fluid I/O, and other clinical variables. Ventilator settings were documented by respiratory therapists at intubation and as ventilator settings were adjusted. Radiological films were evaluated by specialists at the time of patient care, and written evaluations were recorded into the database. ICD-9 codes were documented for specific diseases as required by hospital staff upon patient discharge. Currently, the database includes more than 17,000 medical records collected between 2001 and 2005¹⁴. The distribution of patients from the MIMIC-II database is shown in Figure 1.

Patient selection

We examined medical records of patients who were mechanically ventilated for longer than 48 hours and who did not have ARDS at the outset of ventilation. To rule out cardiogenic causes of pulmonary edema, we excluded patients with evidence of congestive heart failure during their hospital stay.

Definitions

The length of mechanical ventilation was defined as the duration of the first continuous ventilation period according to recorded ventilator settings. ARDS was diagnosed using the American European consensus conference criteria¹⁵ (acute onset, $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg, bilateral infiltrates on chest x-ray, and not congestive heart failure). $\text{PaO}_2/\text{FiO}_2$ values were calculated by finding the ratio of each PaO_2 measurement to the nearest FiO_2 value available before the corresponding blood gas value (this difference was approximately 2 ± 1.9 hrs apart). Due to the absence of pulmonary wedge pressure in the majority of records (86%), patients with congestive heart failure were identified using ICD-9 code 428 and were excluded from the study. To be considered as without ARDS at the outset, patients must have had two $\text{PaO}_2/\text{FiO}_2$ values above 200 mmHg in the first 12 hrs of mechanical ventilation. Development of ARDS was identified as having an acute drop in $\text{PaO}_2/\text{FiO}_2$ to below 200 mmHg for at least 24 hours with evidence of bilateral infiltrates and/or consolidations in the chest x-ray report. Reports from 24 hrs before to 72 hours after the drop in $\text{PaO}_2/\text{FiO}_2$ ratio were independently evaluated by two expert intensivists for the presence of bilateral disease. A random sample of 25% of x-ray films were reviewed and in all cases confirmed findings from the report and were consistent with a diagnosis of ARDS. Discrepancies were settled by a joint evaluation of the overall data available but blinded to the exposure variables (e.g. baseline mechanical ventilator settings etc.).

Physiologic information and ventilator settings were collected from the first 24 hours of mechanical ventilation *and* prior to any new lung injury, as defined by $\text{PaO}_2/\text{FiO}_2$ dropping below 200 for more than 24 hours. Potential risk factors for development of new ARDS (predictor variables) included:

1. Demographic information: sex, age, weight, height.
2. Underlying illness/indicators of organ health: pneumonia, sepsis, SAPS, creatinine, albumin, ALT.
3. Ventilator settings: tidal volume (V_T), plateau pressure (P_{plat}), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), inspired oxygen fraction (FiO_2), and total respiratory rate.
4. Indicators of gas exchange and metabolism: arterial pH, PaO_2 , PaCO_2 , bicarbonate and lactate.
5. Transfusion of blood products: packed red blood cells (PRBC), plasma, and platelets.

When patient height information was available (60% of records), predicted body weight was calculated using the following formulae⁹:

Predicted male weight in kg = $50 + 0.91 \times (\text{height in centimeters} - 152.4)$

Predicted female weight in kg = $45.5 + 0.91 \times (\text{height in centimeters} - 152.4)$

Tidal volume per ideal body weight was then calculated using predicted weight. Static respiratory compliance (C_{rs}) was calculated as $V_T/(P_{\text{plat}} - \text{PEEP})$. When more than one ventilator setting was present on a given day, the “worst” values (highest tidal volume, highest ventilator pressures) were selected. For all laboratory values and blood gases, the first value after the outset of ventilation was collected for analysis. Presence of pneumonia and sepsis as an underlying illness was identified by ICD-9 codes (480 – 486 for pneumonia, 038 for sepsis). Transfusion of blood products was recorded as the number of 375 mL units (or volume equivalent) administered on the first day of mechanical ventilation. If the patient developed ARDS on day one, fluids administered before the onset of ARDS were used. The net fluid balance was calculated as the sum of fluid inputs and outputs beginning at admission into the ICU until the onset of ARDS. In patients who did not develop ARDS, the net fluid balance

was calculated for the day closest to the average time until progression to ARDS in the ARDS cohort. The Simplified Acute Physiology Score (SAPS) was calculated using physiologic data from the first 24 hours of admission. These data included age, heart rate, systolic ABP, temperature, respiratory rate, urine output, BUN, hematocrit, white blood count, glucose, potassium, sodium, bicarbonate, and Glasgow Coma score.

Statistical Analysis

Univariate and multivariate logistical regressions were performed to find correlations between predictor and outcome variables. The outcome of interest was development of ARDS after the onset of mechanical ventilation. In the univariate analysis, odds ratios were calculated per one standard deviation increase in predictor variables. Statistically significant variables ($p < 0.05$) were then considered for inclusion in a multivariate model if the variable contained less than 20% missing data. A backward stepwise logistic regression was performed to find the optimal model in which all contained variables were statistically significant predictors of ARDS, again with a p -value less than 0.05. SAPS and initial $\text{PaO}_2/\text{FiO}_2$ were forced into the multivariate model to control for severity of illness.

Finally, significant ventilator-related variables from univariate analyses were adjusted for severity of illness using the most significant non-ventilator variables found to be predictive of ARDS. A subsequent comparison of the unadjusted and adjusted odds ratios (with 95% confidence intervals) was performed. In multivariate analyses, missing values were filled using the averages from all patients who did not have ARDS at the outset of ventilation. All data analyses were performed using Matlab 7.2 and its supporting statistical toolboxes (<http://www.mathworks.com/products/matlab/>).

Results

1366 of 17,493 patients admitted between 2001 and 2005 required mechanical ventilation for greater than 48 hours in the ICU and had no record of congestive heart failure during their stay. The average age of these patients was 59 years and the mean duration of ICU stay was 13 days. When broken down by location, 29% of patients were in medical ICU, 28% in surgical ICUs, 28% in the cardiac surgery recovery unit, and 15% in coronary care units. The characteristics of this patient cohort are summarized in Table 1. Of 789 patients without ARDS on the first day of mechanical ventilation, 177 had worsening $\text{PaO}_2/\text{FiO}_2$, of these 152 (19%) had bilateral infiltrates and met ARDS criteria. On average, these patients developed ARDS 3.3 days after the initiation of mechanical ventilation (25% – 75% quartile: 0.8 – 4.3 days, median: 2.3 days). 324 of the 789 patients (41%) without ARDS at the outset received transfusion of blood products, including 101 (13%) who received platelets, 268 (34%) who received packed RBCs, and 146 (19%) who received fresh-frozen plasma. 577 patients had $\text{PaO}_2/\text{FiO}_2 < 200$ at the outset of ventilation and were excluded from logistic regression analyses.

Univariate continuous-variable logistical regression found the following variables to be associated with the development of ARDS: **P_{Plat}** (odds ratio 1.5 per standard deviation, 95% confidence interval 1.3 – 1.9), **PIP** (OR 1.5 per std, 95% CI 1.3 – 1.8), **patient weight** (OR 1.4 per std, 95% CI 1.2 – 1.7), **PEEP** (OR 1.4 per std, 95% CI 1.2 – 1.7), **sepsis** (OR 1.95, 95% CI 1.3 – 2.9), V_T (OR 1.4 per std, 95% CI 1.1 – 1.7), **transfusion of PRBCs** (OR 1.2 per std, 95% CI 1.1 – 1.4), **transfusion of plasma** (OR 1.3 per std, 95% CI 1.1 – 1.5), **net fluid balance** (OR 1.5 per std, 95% CI 1.3 – 1.8), **blood pH** (OR 0.8 per std, 95% CI 0.6 – 0.9), **albumin** (OR 0.8 per std, 95% CI 0.6 – 0.9), **respiratory compliance** (OR 0.8 per std, 95% CI 0.64 – 0.97) and **lactate** (OR 1.2 per std, 95% CI 1.0 – 1.4). In 448 patients with recorded height and tidal volume, V_T per predicted body weight was not found to be significantly associated ($p = 0.559$) with the development of ARDS. Table 2 shows the odds ratios and p -value statistics from univariate logistical regression, comparing patients who did and did not develop ARDS.

Figure 2 examines the distribution of day one P_{plat} and the increasing percentage of patients developing ARDS with increasing pressure. Figures 3, 4, and 5 show similar analyses for PIP, V_T , and patient weight respectively.

Risk factors found to be significant in univariate analysis were considered for multivariate regression analysis if the variable had less than 20% missing data. In the final multivariate model, **PIP** (odds ratio 1.31 per standard deviation, $p = 0.006$), **transfusion of plasma** (OR 1.26 per std, $p = 0.006$), **high fluid balance** (OR 1.3 per std, $p = 0.003$), and V_T (OR 1.25 per std, $p = 0.030$) remained significantly associated with the development of new ARDS. Sepsis and PEEP were of borderline significance ($p = 0.055$ and 0.058 respectively). This final multivariate model, in which $\text{PaO}_2/\text{FiO}_2$ and SAPS were included to control for severity of illness, is shown in Table 3.

Finally, in order to further define significant ventilator related risk factors for the development of ARDS, significant ventilator related variables from univariate analysis (PIP, P_{plat} , V_T , PEEP,) were adjusted for significant physiologic risk factors ($\text{PaO}_2/\text{FiO}_2$, pH, sepsis, respiratory compliance, transfusion of plasma and net fluid balance). In this analysis, **PIP** (OR 1.43 per std, $p < 0.001$), **P_{plat}** (OR 1.37 per std, $p = 0.007$), **PEEP** (OR 1.22 per std, $p = 0.016$), **V_T** (OR 1.33 per std, $p = 0.006$), remained significantly associated with the development of ARDS (Table 4).

Discussion

This retrospective cohort study sheds new light on the risk factors for ARDS in patients ventilated ≥ 48 hours in the ICU. Approximately 19% of patients who did not have ARDS at the outset of mechanical ventilation and no record of CHF during their hospitalization later developed ARDS. The association between initial ventilator settings and new ARDS suggests that ventilator-associated lung injury may be a preventable illness in some cases. Ventilation with high airway pressures and tidal volume is an important risk factor for respiratory failure. In our analysis high PIP, P_{plat} , PEEP and V_T remained predictive of new ARDS after adjusting for $\text{PaO}_2/\text{FiO}_2$, sepsis, pH, respiratory compliance, net fluid balance and transfusion of blood plasma. Pressure and volume are related through respiratory compliance, and in this cohort, PIP and V_T had a small but significant correlation ($R^2 = 0.05$, $p < 0.001$). The multivariate model demonstrated that PIP and V_T were significant predictors of ARDS independently of each other. This may be due to the variations in respiratory compliance that allow high pressures to be injurious in some cases and high volumes to be injurious in others. In general, the finding that ventilator pressures and tidal volumes play a role in the development of ARDS is supported by existing literature which emphasizes the adverse effects of high airway and transpulmonary pressures^{5,16,17,18}.

Tidal volume per predicted body weight was not significantly associated with ARDS ($p = 0.559$), contradicting previous studies⁹ which recognize this to be the most important ventilator-related risk factor for ARDS. It is possible that this discrepancy is influenced by the lower percentage of recorded height data and imprecision in making this measurement for the current cohort. Further studies should be conducted to clarify this discrepancy.

Plateau pressure was significantly associated with ARDS in univariate regression analysis and after adjusting for severity of illness. However, P_{plat} was excluded from the multivariate model by the backward-search algorithm while PIP was included. This is likely explained by the phenomenon where variables that are correlated (such as PIP and P_{plat}) have low significance levels or high p-values when they are introduced into the same multivariate model. A backward-stepwise logistic regression algorithm would simply remove the less significant variable, in this case P_{plat} , while searching for the optimal multivariate model. Due to differences in airway

resistance, P_{plat} and PIP do not correlate perfectly ($R^2 = 0.55$, $p < 0.001$). However, a high PIP is likely to produce a high P_{plat} that can cause alveolar damage.

High PEEP was associated with development of ARDS in univariate regression, but this relationship becomes less significant after adjusting for peak pressure and $\text{PaO}_2/\text{FiO}_2$. Thus, high PEEP may be responsible for higher airway pressures and may be a marker of sicker patients. Historically, PEEP is thought to be lung protective^{12,13} and is often used to recruit collapsed alveoli^{19,20}. However, the data presented from this cohort do not point to the protective nature of PEEP.

Transfusion of blood products is a recognized risk factor for ARDS^{21,22,23}. The exact mechanism of transfusion-related ARDS is unclear, though studies suggest granulocyte and human leukocyte antigen antibodies are important factors^{24, 25}. In this study, univariate analyses identified transfusion of packed red blood cells and plasma to be significant risk factors for ARDS ($p = 0.007$ and $p < 0.001$ respectively) while transfusion of platelets was of borderline significance ($p = 0.051$). In the multivariate model, plasma remained a significant risk factor ($p = 0.006$) while PRBCs and platelets were excluded from the model due by the backward search algorithm. These results support the conclusion that transfusion of blood products, especially of plasma, is an important risk factor for ARDS.

Conservative fluid management has been proposed as a strategy to reduce lung fluid in patients with acute lung injury²⁶. Results from this study support the hypothesis that an elevated fluid balance is a risk factor for the development of ARDS. High net fluid balance was moderately associated with low albumin ($R^2 = 0.10$, $p < 0.001$). This association may be caused by disruption of oncotic balance in circulating blood due to high fluid balance, or more likely by the effects of capillary leak in the critically ill that leads to decreased plasma oncotic pressure, hypotension, and an increased demand for fluid administration. Capillary leak produces exudates and hyaline membrane formation in the alveoli while hydrostatic pulmonary edema produces transudation without hyaline membranes. In this study, however, there is no way to definitively distinguish between the two effects. Nevertheless, the final multivariate model shows that high net fluid balance is an ARDS risk factor independent of ventilator settings, transfusion of plasma, and severity of illness.

Physiological risk factors for new ARDS include blood acidemia, hypoalbuminemia, low respiratory compliance, and high lactate. Low pH and high lactate are characteristic of metabolic acidosis - a condition known to be predictive of acute lung injury in severely traumatized patients²⁷. Although high lactate and low pH were associated with the development of ARDS in univariate analyses, these relationships become secondary in the multivariate context (neither variable was selected for the final multivariate model). This result suggests that the practice of using the ventilator to correct for acidosis may be a potentially harmful intervention. Hypoalbuminemia, another factor known to be predictive of ARDS²⁸, disrupts the oncotic balance between fluids in the pulmonary circulation and lung alveoli. In the critically ill, hypoalbuminemia may be a marker of leaky capillaries rather than a cause of hydrostatic edema. Low albumin was significantly associated with ARDS in univariate analysis, but the variable was not included in multivariate analysis due to insufficient data (31% missing). High patient weight was also associated with higher odds of developing ARDS. However, weight is significantly correlated with set tidal volume ($R^2 = 0.19$, $p < 0.001$), and to a lesser extent with set peak pressure ($R^2 = 0.05$, $p < 0.001$). Thus heavier patients may require higher ventilator pressures to deliver the same tidal volume, producing the observed though indirect association with ARDS due to the ventilator.

We acknowledge the following limitations in the current study. First, although data were validated at collection by the bed-side nurses and respiratory therapists, they were not collected

by scientific investigators and thus may contain errors. The large size of the database should correct for such random errors, assuming inaccuracies are random rather than systematic. Secondly, we assume random variability in initial ventilator settings, but there always exists the possibility that higher pressures and tidal volumes were chosen deliberately to correct underlying hypoxemia, acidemia, and non-cardiogenic pulmonary edema. It has been proposed that the association between ventilator settings and development of ARDS may be driven by a group of sicker patients who were ventilated at higher tidal volumes and pressures. To test this possibility, we examined significant ventilator variables before and after being adjusted for severity of illness at baseline. The odds ratios for the ventilator settings decreased slightly after such adjustments while retaining significant 95% confidence intervals. This suggests that the observed relationship between ventilation settings and development of ARDS may be in part due to sicker patients with lower lung compliance (due to pneumonia or another respiratory illness). Thirdly, although we used a large patient population in this study, data were not complete in all records. The variables with the least complete data included height (40% missing), albumin (31%), ALT (30%) and lactate (15%). All other variables had less than 7% missing data. The absence of height in many records prevented us from calculating tidal volume per predicted body weight in many patients. The diagnosis of sepsis and pneumonia were based solely on ICD9 codes, making it difficult to determine whether the disease appeared before or after ARDS. Microbiology reports were unavailable at the time of this study, and future studies should use more than ICD9 codes to identify the underlying illness. Fourth, the final multivariate model only explains a small fraction of the total variance observed ($R^2 = 0.11$). This suggests that the risk factors thus identified cannot be used, by themselves, to predict the development of ARDS with great sensitivity and specificity. Further, it points to the possibility that there exist additional risk factors for ARDS, genetic or environmental, that yet to be identified. Finally, $\text{PaO}_2/\text{FiO}_2$ values were available only when arterial blood gases were measured, and the accuracy of our patient classifications (no ARDS or ARDS at the outset of ventilation) depended on the presence and validity of these values. In general, any misclassification would bias towards the null hypothesis, making it more difficult to show a relationship between initial ventilator settings and worsening gas exchange in the lungs. Future studies could use pulmonary artery wedge pressure or biomarkers such as BNP in addition to $\text{PaO}_2/\text{FiO}_2$ values and chest x-ray reports when diagnosing ARDS. Most importantly, a randomized trial is needed to verify the suggestion that high ventilator pressures play a causal role in the development of ARDS.

Conclusions

Development of new onset ARDS is a relatively common complication (152 of 798) in patients mechanically ventilated ≥ 48 hours in the ICU. In this study, high airway pressure and tidal volume were the most important ventilator-associated risk factors for the development of new ARDS. Transfusion of blood products, especially of fresh-frozen plasma, and high net fluid balance are also strongly associated with new ARDS. Thus it may be possible to reduce the occurrence of ARDS with careful ventilator and fluid management. Prospective randomized prospective studies are needed to support this hypothesis. Meanwhile, practitioners should consider avoiding these potentially injurious interventions in patients without acute lung injury at the onset of mechanical ventilation.

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Figure 1
Patient distribution from the MIMIC-II database. Gray boxes indicate patients examined in this study.

Figure 2
 . Distribution of initial plateau pressure in 789 patients without ARDS at the outset of ventilation (top), and risk of developing ARDS as a function of plateau pressure (152 eventually developed ARDS).

Figure 3. Distribution of initial peak inspiratory pressures (PIP) in 789 patients without ARDS at the outset of ventilation (top), and risk of developing ARDS as a function of PIP (152 eventually developed ARDS).

Figure 4.

Distribution of initial tidal volume in 789 patients without ARDS at the outset of ventilation (top), and risk of developing ARDS as a function of tidal volume (152 eventually developed ARDS).

Figure 5. Distribution of weight in 789 patients without ARDS at the outset of ventilation (top), and risk of developing ARDS as a function of weight (152 eventually developed ARDS).

Table 1

Characteristics of patient cohort, grouped by initial lung health.

	All ventilated >48 hrs (n = 1366) ^a	no ARDS at outset (n = 789) ^a	ARDS at outset (n = 577) ^a
Age (yrs)	59 ± 18 (16 – 99)	60 ± 19 (16 – 99)	58 ± 18 (16 – 92)
Male gender, n (%)	787 (58%)	437 (56%)	350 (61%)
Height (cm)	170 ± 16.7	169 ± 19	170 ± 13.3
Weight (kg)	81 ± 23	79 ± 23	82 ± 22
SAPS ^b	9.3 ± 2.9	9.2 ± 2.9	9.4 ± 3
Length of stay (days) ^c	13.1 ± 10.1	12 ± 8.8	14.6 ± 11.4
Length of mechanical ventilation (days) ^d	10 ± 9.6	9 ± 8.2	11.2 ± 11

SAPS, Simplified Acute Physiology Score;

^a excludes patients with congestive heart failure according to ICD-9 codes;^b SAPS score based on data from first 24 hours of admission;^c length of stay in a single care unit;^d length of continuous mechanical ventilation.

Univariate logistical analysis of risk factors for ARDS in 789 patients without ARDS at the outset of mechanical ventilation.

Table 2

	ARDS (n = 153)	Non-ARDS (n = 636)	p Value	Odds Ratio per STD (95% confidence interval)	Missing values (out of 789)
Age (years)	57.9 ± 18.2	60.3 ± 19.1	0.163	0.88 (0.74 – 1.05)	5 (1%)
Male gender (n, %)	92 (61%)	345 (54%)	0.126	1.15 (0.96 – 1.38)	5 (1%)
Weight (kg)	85.7 ± 24.2	77.4 ± 22.4	<0.001	1.39 (1.18 – 1.65)	36 (5%)
Height (inches)	67.8 ± 11.8	66.4 ± 5.6	0.120	1.22 (0.95 – 1.56)	314 (40%)
SAPS	9.5 ± 3	9.2 ± 2.8	0.235	1.11 (0.93 – 1.33)	0 (0%)
Sepsis (%) ^a	49 (32%)	125 (20%)	<0.001	1.95 (1.31 – 2.88)	0 (0%)
Pneumonia (%) ^a	67 (44%)	232 (36%)	0.081	1.38 (0.96 – 1.97)	0 (0%)
Creatinine (mg/dL)	1.3 ± 1.3	1.2 ± 1.2	0.110	1.14 (0.97 – 1.33)	0 (0%)
Lactate (mmol/L)	3.2 ± 2.5	2.7 ± 2.4	0.044	1.19 (1.00 – 1.41)	117 (15%)
PaO ₂ /FiO ₂ (mmHg)	302.3 ± 110.5	355.9 ± 114.9	<0.001	0.56 (0.45 – 0.70)	0 (0%)
pH	7.3 ± 0.1	7.4 ± 0.1	0.003	0.77 (0.65 – 0.91)	0 (0%)
Albumin (g/dL)	2.5 ± 0.7	2.7 ± 0.6	0.011	0.76 (0.62 – 0.94)	247 (31%)
Compliance (mL/cmH ₂ O)	41.9 ± 14.7	45.7 ± 18.5	0.024	0.79 (0.64 – 0.97)	61 (8%)
ALT (units/L)	131.1 ± 350.7	155.4 ± 538.1	0.641	0.95 (0.75 – 1.19)	238 (30%)
Bicarbonate (mmol/L)	22.9 ± 5.7	23.6 ± 5.3	0.158	0.88 (0.73 – 1.05)	0 (0%)
PaCO ₂ (mmHg)	40.5 ± 11.1	39.6 ± 10.9	0.342	1.09 (0.92 – 1.29)	0 (0%)
PaO ₂ (mmHg)	235.5 ± 125.5	226.4 ± 118.1	0.399	1.08 (0.90 – 1.28)	0 (0%)
Tidal volume (mL)	650.5 ± 119.7	616.9 ± 112.8	0.001	1.36 (1.12 – 1.64)	41 (5%)
Tidal volume/PBW (mL/kg)	10 ± 2.8	10.1 ± 2.4	0.559	0.94 (0.76 – 1.16)	341 (43%)
High Inspiratory Pr. (cmH ₂ O)	48.2 ± 7.3	47.2 ± 7.4	0.143	1.14 (0.96 – 1.36)	20 (3%)
PIP (cmH ₂ O)	33.8 ± 9	30 ± 8.2	<0.001	1.53 (1.28 – 1.84)	43 (5%)
Plateau Pressure (cmH ₂ O)	25.4 ± 5.9	22.5 ± 6.3	<0.001	1.54 (1.28 – 1.85)	55 (7%)
PEEP (cmH ₂ O)	6.6 ± 2.8	5.8 ± 2	<0.001	1.35 (1.15 – 1.58)	18 (2%)
Resp rate total (breaths/min)	21.3 ± 6.2	21.4 ± 6.2	0.779	0.97 (0.82 – 1.17)	17 (2%)
Packed RBCs (packets)	2.2 ± 4.7	1.2 ± 3.5	0.007	1.23 (1.06 – 1.43)	0 (0%)
Plasma (packets)	0.9 ± 1.7	0.5 ± 1.2	<0.001	1.30 (1.12 – 1.51)	0 (0%)
Platelets (packets)	0.3 ± 1.0	0.2 ± 0.7	0.051	1.16 (1.00 – 1.35)	0 (0%)
Net Fluid Balance (L)	10.6 ± 11.5	6.7 ± 7.2	<0.001	1.48 (1.26 – 1.75)	37 (0.5%)

^a Odds ratios calculated for the presence of the disease.^b STD, standard deviation of variable in all 789 patients without ARDS at the outset.

Table 3

Multivariate analysis of ARDS risk factors in 789 patients without ARDS at the outset. Optimal multivariable model reached from backward search on statistically significant variables derived from univariate analysis. SAPS and PaO₂/FiO₂ ratio were added to control for severity of illness. In this final model, $R^2 = 0.11$ (proportion of total variance explained by the model).

	Mean	Standard deviation	Odds ratio per STD (95% confidence interval)	<i>p</i> Value (adjusted)
Net Fluid Balance (L) ^a	7.4	8.2	1.30 (1.09 – 1.56)	0.003
PIP (cmH ₂ O)	30.7	8.2	1.31 (1.08 – 1.59)	0.006
Plasma transfusion (# packets) ^b	0.5	1.4	1.26 (1.07 – 1.49)	0.006
V _T (mL)	623.5	111.9	1.25 (1.02 – 1.52)	0.030
Sepsis ^c	-	-	1.57 (1.00 – 2.45)	0.055
PEEP (cmH ₂ O)	5.9	2.2	1.18 (0.99 – 1.39)	0.058

SDT, standard deviation; PIP, peak inspiratory pressure; V_T, tidal volume; PEEP, positive end-expiratory pressure.

^a Net fluid balance before onset of ARDS (fluid balance on day 3 of mechanical ventilation was used for patients who did not develop ARDS).

^b Transfusion of blood products on day one of mechanical ventilation

^c Odds ratio calculated for presence of sepsis as underlying illness.

Analysis of ventilator-associated risk factors for ARDS (unadjusted = univariate, adjusted = controlled for initial PaO₂/FiO₂, blood pH, static respiratory compliance, presence of sepsis, transfusion of plasma, and net fluid balance) in 789 patients without ARDS at the onset of mechanical ventilation.

Table 4

	Mean	Standard deviation	odds ratio per STD (unadjusted)	p Value (unadjusted)	odds ratio per STD (adjusted)	p Value (adjusted)
PIP (cmH ₂ O)	30.7	8.2	1.53 (1.28 – 1.84)	<0.001	1.43 (1.17 – 1.74)	<0.001
Pplat (cmH ₂ O)	23.1	6.3	1.54 (1.28 – 1.85)	<0.001	1.37 (1.09 – 1.73)	0.007
PEEP (cmH ₂ O)	5.9	2.2	1.35 (1.15 – 1.58)	<0.001	1.22 (1.04 – 1.44)	0.016
Tidal volume (mL)	623.5	111.9	1.36 (1.12 – 1.64)	0.001	1.33 (1.09 – 1.62)	0.006

SDT, standard deviation; PIP, peak inspiratory pressure; Pplat, plateau pressure; V_T, tidal volume; PEEP, positive end-expiratory pressure.