# Survival Predictors in Patients with Acute Respiratory Distress Syndrome and Underlying Chronic Respiratory Diseases

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**Introduction:** Acute respiratory distress syndrome (ARDS) is a syndrome of severe hypoxemia with various risk factors. Chronic respiratory diseases are chronic diseases of the airways and lungs. In most of the large trials of ARDS, patients with chronic respiratory diseases were excluded. The aim of this study was to investigate the outcomes of patients with both ARDS and chronic respiratory diseases.

**Material and Methods:** We retrospectively collected patients documented with ARDS and chronic respiratory diseases at a tertiary care center from October 2012 to May 2015. Baseline clinical features, severity and causes of ARDS, parameters of mechanical ventilator use and the survival outcome were recorded.

**Results:** We enrolled 73 patients with ARDS and chronic respiratory diseases; 47.9% had COPD. The overall hospital mortality rate was 67.1% (49/73). In patients with mild, moderate and severe ARDS, the hospital mortality rates were 76.4% (13/17), 58.1% (18/31), and 72% (18/25), respectively ($p$=0.23). There was no significant difference in positive end-expiratory pressure, peak airway pressure and dynamic driving pressure between non-survivors and survivors. Tidal volume was significantly higher in non-survivors than in survivors (8.0 ± 1.7 ml/kgw vs. 7.2 ± 1.6 ml/kgw, $p$=0.03). In multivariate logistic regression, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, $p$=0.03).

**Conclusions:** In this study on patients with ARDS and underlying chronic respiratory diseases, the hospital mortality rate was relatively high. Lower tidal volume was identified as the significant and independent predictive factor for hospital survival. ***(Thorac Med 2019; 34: 230-239)***

Key words: chronic respiratory disease, acute respiratory distress syndrome, outcome, low tidal volume

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## Introduction

Acute respiratory distress syndrome (ARDS) is a syndrome of heterogeneity with various risk factors resulting in severe hypoxemia; pneumonia is the leading cause of ARDS [1]. According to the Berlin definition, and using the $PaO_2/FiO_2$ ratio, the severity of ARDS is classified into mild, moderate and severe, with hospital mortality rates of 34.9%, 40.3% and 46.1%, respectively [2]. In terms of therapy or management for ARDS, evidence shows that a lung protective strategy with lower tidal volume and higher positive end-expiratory pressure (PEEP), early neuromuscular blockade use and prone positioning could improve survival for ARDS patients [3-7].

Chronic respiratory diseases are diseases of the airways and other structures of the lungs. Major chronic respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease, occupational lung diseases and pulmonary hypertension [8-9]. These chronic respiratory diseases contribute to dyspnea, activity limitation, and impairment of gas exchange, and patients with these diseases are prone to acute exacerbation due to pneumonia [10-13]. It is not surprising that patients with chronic respiratory diseases may suffer from ARDS simultaneously. The largest epidemiological study of ARDS to date, the LUNG SAFE study, found that patients with underlying COPD comprised 21.7% of the ARDS population, but the outcome of this specific group was not well addressed [1]. Previous large randomized controlled trials of ARDS excluded patients with underlying chronic respiratory diseases [4,7]. Furthermore, it is not well known whether the lung protective strategy with low tidal volume for ARDS is effective for patients with underlying chronic respiratory diseases. Thus, the aim of this study was to investigate the outcomes of patients with both ARDS and chronic respiratory diseases.

## Materials and methods

### *Study design and data collection*

The study population was extracted from a prospective observational cohort at Chang Gung Memorial Hospital, Linkou Branch, from October 2012 to May 2015 [14]. Patients were enrolled in the study once they met the Berlin definition of ARDS [2]. Patients under 18 years of age were excluded. Information including demographics, baseline clinical features, laboratory data, severity of ARDS, and causes of ARDS was recorded upon ICU admission. Patient severity within 24 hours of ARDS diagnosis was documented as the Charlson Comorbidity Index (CCI) [15], Acute Physiology and Chronic Health Evaluation (APACHE) II score [16], and Sequential Organ Failure Assessment (SOFA) score [17]. Parameters of mechanical ventilation were recorded within the first 24 hours after recognizing ARDS, and included tidal volume, $PaO_2/FiO_2$ ratio, PEEP and peak airway pressure.

We retrospectively collected patients from the database with documented chronic respiratory diseases. Beside the baseline clinical information, severity and causes of ARDS, and mechanical ventilator settings, a chart review for the exact diagnosis of the chronic respiratory disease was performed. Survival outcome was recorded. The chronic respiratory diseases were defined as asthma, COPD, bronchiectasis, interstitial lung disease and pulmonary hypertension. The specific diagnoses of the patients with chronic respiratory diseases were made based on in-patient and outpatient medical records, pulmonary function tests, and radiologic imaging (chest X-ray or computed tomography). The local Institutional Review Board for Human Research approved the study (CGMH IRB No. 102-1729B), and the need for informed consent was waived.

***Management of ARDS***

The mechanical ventilator settings of the patients with ARDS included a lung protective ventilation strategy using a low tidal volume of 4-8 ml/kg of predicted body weight (PBW), and a PEEP setting guided by a low PEEP-$FiO_2$ table for volume-controlled or pressure-controlled ventilation [4]. Pulse oximetry was used to monitor oxygenation by $SpO_2$, and the $FiO_2$ level was adjusted to maintain $SpO_2$ at more than 90%. The PiCCO plus monitor (version 5.2.2; Pulsion Medical System AG, Muenchen, Germany) was used to evaluate hemodynamics and lung water, if indicated by the clinical condition of the patient.

***Statistical analysis***

All statistical analyses were performed with SPSS software version 22 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). Independent Student's $t$ test was used to compare continuous variables, presented as mean ± SD, between survivors and non-survivors. Categorical data was compared via Chi square test. A p value <0.05 was regarded as statistically significant. To identify factors related to survival, univariate analysis was performed first, and the variables with a significance of $p<0.2$ were included for multivariate logistic regression with forward elimination of data.

## Results

During the research period, 22,470 hospitalized adult patients undergoing invasive mechanical ventilation were screened; of this total, 1,034 (4.6%) met the criteria of ARDS. Seventy-three (7.1%) of the ARDS patients had documented chronic respiratory diseases, and their overall hospital mortality rate was 67.1% (49/73). Among patients with mild, moderate and severe ARDS, the hospital mortality rates were 76.4% (13/17), 58.1% (18/31), and 72% (18/25), respectively ($p=0.23$). A comparison of the demographic data and characteristics of the non-survivors (n=9) and survivors (n=24) is shown in Table 1. The main cause of ARDS was pneumonia (90.4%). The most common chronic respiratory disease was COPD (n=35, 47.9%), followed by asthma (n=15, 20.5%), interstitial lung disease (n=12, 16.4%) and bronchiectasis (n=5, 6.8%).

Patient disease severity upon admission to the intensive care unit (ICU) and the parameters of mechanical ventilation on the first day of intubation are listed in Table 2. The SOFA score of the non-survivors was higher than that of the survivors (9.4±3.3 vs. 7.7±2.2, $p=0.02$). Using the Berlin definition, there were 17 (23.3%) patients with mild ARDS, 31 (42.5%) with moderate ARDS and 25 (34.2%) with severe ARDS. Tidal volume of the non-survivors was significantly higher than that of the survivors (8.0±1.7 ml/kgw, PBW vs. 7.2±1.6 ml/kgw, PBW, $p=0.03$). There was no significant difference in PEEP, peak airway pressure and dynamic driving pressure between the non-survivors and survivors. There was no significant difference between the two groups in terms of those who had received renal replacement therapy, including intermittent hemodialysis (14.3% vs.

Table 1. Demographics and Characteristics of Hospital non-Survivors and Survivors Among ARDS Patients with Chronic Respiratory Diseases

| Variables | Total (n=73) | Non-survivors (n=49) | Survivors (n=24) | *p* value |
|---|---|---|---|---|
| Age (years) | 74.5 ± 12.1 | 74.6 ± 10.0 | 74.3 ± 15.8 | 0.95 |
| Gender (male %) | 58 (79.5%) | 42 (85.7%) | 16 (66.7%) | 0.06 |
| Body mass index (kgw/m$^2$) | 22.9 ± 4.6 | 22.9 ± 4.1 | 22.7 ± 5.5 | 0.83 |
| Smoking history (%) | 33 (45.2%) | 26 (53.1%) | 7 (29.2%) | 0.09 |
| Charlson Comorbidity Index | 2.7 ± 1.7 | 2.8 ± 1.6 | 2.6 ± 2.0 | 0.69 |
| Cause of chronic respiratory disease (%) | | | | 0.15 |
| COPD | 35 (47.9%) | 23 (46.9%) | 12 (50.0%) | |
| Asthma | 15 (20.5%) | 11 (22.4%) | 4 (16.7%) | |
| Bronchiectasis | 5 (6.8%) | 1 (2.0%) | 4 (16.7%) | |
| Interstitial lung disease | 12 (16.4%) | 10 (20.4%) | 2 (8.3%) | |
| Others | 6 (8.2%) | 4 (8.2%) | 2 (8.3%) | |
| Causes of ARDS (%) | | | | |
| Pneumonia | 66 (90.4%) | 43 (87.8%) | 23 (95.8%) | |
| Sepsis | 9 (12.3%) | 7 (14.3%) | 2 (8.3%) | |
| Aspiration | 1 (1.4%) | 1 (2.0%) | 0 (0.0%) | |
| Postoperative complication | 1 (1.4%) | 1 (2.0%) | 0 (0.0%) | |
| Trauma | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| TRALI | 2 (2.7%) | 2 (4.1%) | 0 (0.0%) | |
| Diffuse alveolar hemorrhage | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Acute pancreatitis | 1 (1.4%) | 0 (0.0%) | 1 (4.2%) | |
| Others | 2 (2.7%) | 2 (4.1%) | 0 (0.0%) | |

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; TRALI: transfusion-related acute lung injury. All values are expressed as No. of patients (%) or mean ± SD. **p*-value <0.05

8.3%, *p*=0.47) and continuous renal replacement therapy (14.3% vs. 4.2%, *p*=0.19), and extracorporeal membrane oxygenation (4.1% vs. 4.2%, *p*=0.99).

Logistic regression analysis was carried out to determine the possible predictive factors for survival among patients with chronic respiratory diseases. After univariate logistic regression analysis, gender, smoking, SOFA score, and tidal volume were selected as variables for multivariate analysis. In the multivariate logistic regression test, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, *p*=0.03) (Table 3).

## Discussion

Among the 73 patients with both ARDS and chronic respiratory diseases, the hospital mortality rate was as high as 67.1%. In addition, after multivariate logistic regression analysis, lower tidal volume was identified as the significant and independent predictive factor for hospital survival.

Little has been reported regarding mortality

Table 2. Severity and Mechanical Ventilator Settings of Hospital Non-survivors and Survivors Among ARDS Patients with Chronic Respiratory Diseases

| Variables | Total (n=73) | Non-survivors (n=49) | Survivors (n=24) | *p* value |
|---|---|---|---|---|
| APACHE II score | 24.2 ± 6.5 | 24.8 ± 6.4 | 23.3 ± 6.7 | 0.34 |
| SOFA score | 8.8 ± 3.0 | 9.4 ± 3.3 | 7.7 ± 2.2 | 0.02* |
| Severity of ARDS (%) | | | | 0.35 |
| Mild | 17 (23.3%) | 13 (26.5%) | 4 (16.7%) | |
| Moderate | 31 (42.5%) | 18 (36.7%) | 13 (54.2%) | |
| Severe | 25 (34.2%) | 18 (36.7%) | 7 (29.2%) | |
| $PaO_2/FiO_2$ (mmHg) | 140.3 ± 69.5 | 140.8 ± 71.3 | 139.2 ± 67.3 | 0.93 |
| Tidal volume (ml/kgw, PBW) | 7.8 ± 1.7 | 8.0 ± 1.7 | 7.2 ± 1.6 | 0.03* |
| PEEP (cm $H_2O$) | 9.7 ± 2.0 | 9.8 ± 1.9 | 9.6 ± 2.1 | 0.67 |
| Peak airway pressure (cm $H_2O$) | 29.2 ± 4.7 | 28.8 ± 4.7 | 29.4 ± 5.1 | 0.38 |
| Dynamic driving pressure (cm $H_2O$) | 19.5 ± 4.6 | 19.0 ± 4.5 | 20.3 ± 4.8 | 0.28 |
| ECMO (%) | 3 (4.1%) | 2 (4.1%) | 1 (4.2%) | 0.99 |

ARDS: acute respiratory distress syndrome; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: Sequential Organ Function Assessment; $PaO_2/FiO_2$: alveolar oxygen pressure/fraction of inspiratory oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; ECMO: extra-corporeal membrane oxygenation. All values are expressed as No. of patients (%) or mean ± SD. **p*-value <0.05

in patients with both ARDS and chronic respiratory diseases. In the ALIEN study, the hospital mortality rate in a multi-center cohort in Spain was 47.8%, and the outcome was associated with age, $PaO_2/FiO_2$, and plateau pressure at 24 hours after diagnosis of ARDS [18-19]. In the LUNG SAFE study, the hospital mortality rate was 39.6%, and older age, lower PaO2/$FiO_2$, and higher SOFA score were negative predictors for survival among ARDS patients [1,20]. However, in our study, patients with underlying chronic respiratory diseases coexisting with ARDS had a hospital mortality rate up to 67.1%, which is considerably higher than that in the ALIEN study (47.8%) and the LUNG SAFE study (39.6%). The possible explanation for the relatively high mortality rate in these subgroups of patients with ARDS might be the limited reserved lung function in underlying chronic respiratory diseases before ARDS develops.

It is well known that ventilator-induced lung injury can lead to multiple organ failure, the primary cause of death in patients suffering from ARDS [21]. To reduce lung injury subsequent to systemic inflammation, lower tidal volume ventilation emerged as the key management for ARDS. Meta-analysis and systematic reviews have shown that lower tidal volume was associated with improved survival outcome in patients with ARDS [22-24]. However, in a landmark trial of lower tidal volume in ARDS, patients with severe chronic respiratory diseases were excluded [4]. Thus, the issue of the optimal tidal volume for the group of patients with chronic respiratory diseases complicated with ARDS has not yet been addressed. Moreover, an increase of 1 ml/kg in initial tidal volume was associated with an increase in mortality of 23-26% in patients with ARDS [25-26]. In our

Table 3. Univariate and Multivariate Logistic Regression Analyses of Clinical Variables Associated with Hospital Survival Among ARDS Patients with Chronic Respiratory Diseases

| Parameters | β coefficient | Standard error | Odds ratio (95% CI) | *p* value |
|---|---|---|---|---|
| Univariate | | | | |
| Age (years) | -0.00 | 0.02 | 0.99 (0.96-1.04) | 0.94 |
| Gender (Male) | -1.10 | 0.60 | 0.33 (0.10-1.07) | 0.07 |
| Body mass index (kgw/$m^2$) | -0.01 | 0.06 | 0.99 (0.89-1.10) | 0.83 |
| Smoking history | -1.01 | 0.53 | 0.36 (0.13-1.03) | 0.06 |
| COPD | 0.12 | 0.50 | 1.13 (0.43-3.00) | 0.94 |
| Charlson Comorbidity Index | -0.07 | 0.15 | 0.94 (0.70-1.25) | 0.65 |
| APACHE II score | -0.04 | 0.04 | 0.96 (0.89-1.04) | 0.34 |
| SOFA score | -0.22 | 0.10 | 0.80 (0.66-0.98) | 0.03* |
| Severity of ARDS | | | | |
| Mild (reference) | - | - | - | - |
| Moderate | 0.85 | 0.68 | 2.35 (0.62-8.87) | 0.21 |
| Severe | 0.23 | 0.73 | 1.26 (0.31-5.23) | 0.74 |
| ECMO | 0.02 | 1.25 | 1.02 (0.09-11.86) | 0.99 |
| $PaO_2/FiO_2$ (mmHg) | 0.00 | 0.00 | 1.00 (0.99-1.00) | 0.92 |
| Tidal volume (ml/kgw, PBW) | -0.34 | 0.16 | 0.71 (0.52-0.98) | 0.04* |
| PEEP (cm $H_2O$) | -0.06 | 0.13 | 0.94 (0.73-1.22) | 0.66 |
| Peak airway pressure (cm $H_2O$) | 0.05 | 0.06 | 1.05 (0.94-1.17) | 0.38 |
| Dynamic driving pressure (cm $H_2O$) | 0.06 | 0.06 | 1.06 (0.95-1.19) | 0.28 |
| Multivariate | | | | |
| Gender (male) | -0.90 | 0.77 | 0.41 (0.09-1.83) | 0.24 |
| Smoking history | -0.54 | 0.65 | 0.58 (0.16-2.05) | 0.40 |
| SOFA score | -0.21 | 0.11 | 0.81 (0.66-1.00) | 0.06 |
| Tidal volume (ml/kgw, PBW) | -0.42 | 0.19 | 0.66 (0.45-0.97) | 0.03* |

ARDS: acute respiratory distress syndrome; CI: confidence interval; APACHE: Acute Physical and Chronic Health Evaluation; SOFA: Sequential Organ Function Assessment; $PaO_2/FiO_2$: alveolar oxygen pressure/fraction of inspiratory oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure. *p-value < 0.05

study focusing on patients with ARDS and underlying chronic respiratory diseases, the tidal volume used with hospital survivors was significantly lower than that used with non-survivors (7.2 ± 1.6 ml/kgw vs. 8.0 ± 1.7 ml/kgw, *p*= 0.03). Furthermore, tidal volume was identified as the significant and independent predictive factor for survival (odds ratio 0.65, 95% confidence interval 0.44-0.95, *p*=0.03). Thus, a lung protective strategy may be an important way to manage ARDS patients with chronic respiratory diseases.

The role of initial severity of ARDS in predicting mortality is controversial. In the LUNG SAFE study, severity of ARDS was significantly correlated with hospital mortality (34.9% in mild, 40.3% in moderate and 46.1% in severe ARDS patients, *p*<0.001) [1]. However, some studies investigating the evolution of disease severity after ARDS onset found that the baseline definition does not necessarily provide reliable predictions of mortality [19,27-29]. Villar *et al.* reported significant differences between mortality and severity when reclassified by response to a standard ventilator setting at 24 hours after ARDS onset ($p$<0.0001) [27]. In the current study, the distribution of severity of ARDS and $PaO_2/FiO_2$ ratio on day 1 was not significantly different between non-survivors and survivors (140.8 ± 71.3 mmHg vs 139.2 ± 67.3 mm Hg, $p$=0.93). Moreover, a disproportional relationship between mortality rate and severity of ARDS was found in our study (mortality rates of 76.4%, 58.1%, 72% in mild, moderate and severe ARDS, $p$=0.23), despite its statistical insignificance. It is very likely that the initial classification of ARDS is insufficient to determine the severity and outcome of new onset lung injury, especially for patients with underlying chronic respiratory diseases. In these patients, the $PaO_2/FiO_2$ ratio may not actually reflect the severity of the underlying disease. For example, in obstructive airway diseases, severity of disease was classified using FEV1 instead of the $PaO_2/FiO_2$ ratio [11-13]. However, underlying chronic respiratory diseases may also have an impact on the $PaO_2/FiO_2$ ratio via development of hypoxemia. Taking all the above into consideration, the severity of ARDS may not represent the outcome in patients with underlying chronic respiratory disease.

There are some limitations in our study. First, this was a single-center study with a small sample size, which may not be representative of the actual population of patients with chronic respiratory diseases and ARDS. Second, our study was retrospective in design, not prospective. Although a study on outcomes of patients with chronic respiratory diseases suffering from ARDS seems impossible to perform prospectively, enrollment of more patients may provide more details in terms of clinical information, hemodynamic evaluation and outcome evaluation. Third, in this study, not all patients received a pulmonary function test prior to the ARDS diagnosis, which may have led to slight difference in categorization of chronic respiratory diseases. However, all of these patients had an imaging study and detailed chart review to assist in reaching the diagnosis of chronic respiratory disease. Further prospective and multi-centered research should be conducted to validate our results.

## Conclusion

In this study on patients with ARDS and underlying chronic respiratory diseases, the hospital mortality rate was relatively high. Lower tidal volume was identified as the significant and independent predictive factor for hospital survival. A lung protective strategy may be an important way to manage the ARDS patients with chronic respiratory diseases.

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# 急性呼吸窘迫症候群併有慢性肺疾病患之存活預測因子

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**背景**：急性呼吸窘迫症候群的嚴重缺氧由許多因子造成。慢性肺疾乃呼吸道或肺部之慢性疾病。急性呼吸窘迫症候群的部分大型研究中慢性肺疾病患是被排除的。本篇研究中，我們針對罹患急性呼吸窘迫症候群的慢性肺疾病患，研究其存活預測因子。

**方法**：我們回溯性蒐集2012年10月至2015年5月所有入住一醫學中心有急性呼吸窘迫症候群的慢性肺疾病患。我們記錄了臨床資訊、急性呼吸窘迫症候群嚴重度及成因、呼吸器參數和存活預後等資料。

**結果**：本在73位有急性呼吸窘迫症候群及慢性肺疾的病患中，COPD 佔 47.9%。院內死亡率為67.1% (49/73)。在輕度、中度、重度急性呼吸窘迫症候群中，死亡率各為76.4% (13/17), 58.1% (18/31), 72% (18/25) ($p$=0.23)。吐氣末正壓、尖峰氣道壓力及動態驅動壓力在未存活與存活病患中並無差異，但未存活者有較高的潮氣容積(8.0 ± 1.7 ml/kgw vs. 7.2 ± 1.6 ml/kgw, $p$=0.03)。多因子羅吉氏迴歸分析中，只有潮氣容積為有意義且獨立的院內存活預測因子 (勝算比0.65, 95%信賴區間0.44-0.95, $p$=0.03)。

**結論**：本研究中，罹患急性呼吸窘迫症候群的慢性肺疾病患有很高的院內死亡率，而較低的潮氣容積是有意義且獨立的存活預測因子。*(胸腔醫學 **2019; 34: 230-239**)*

關鍵詞：慢性肺疾，急性呼吸窘迫症候群，預後，低潮氣容積

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