

# Epidemiological features and risk factor analysis of children with acute lung injury

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**Background:** Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) represents a devastating complication observed in critical care medicine. The purpose of this study is to investigate the epidemiological aspects of ALI/ARDS in pediatric intensive care unit (PICU) and risk factors of mortality.

**Methods:** Patients with ALI/ARDS in PICU of Beijing Children's Hospital, a tertiary medical center from November 1, 2005 to October 31, 2006 were included in this prospective study. We identified the risk factors for underlying diseases and mortality during a 3-month follow-up using multivariate logistic regression analysis.

**Results:** In 562 critically ill patients admitted to PICU of Beijing Children's Hospital, there were 15 ALI-non ARDS patients and 29 ARDS patients, resulting in an incidence of 7.8% (44/562). The mortality rate of ARDS was 24.1% (7/29) and that of ALI/ARDS was 18.2% (8/44). At a 3-month follow-up, 12 patients died after being discharged from PICU and the total mortality rate was 45.5% (20/44). ALI/ARDS patients with pulmonary disease had better outcomes than those with extra-pulmonary involvements ( $P < 0.05$ ). Discharge against medical advice, low  $\text{PaO}_2/\text{FiO}_2$  during hospital stay and high  $\text{PaCO}_2$  on PICU admission were risk factors of mortality.

**Conclusions:** ARDS has a high mortality rate in PICU, especially in those with extra-pulmonary diseases. In addition to aggressive medical management of comorbidity, lung protection and avoidance of discharge against medical advice will decrease the mortality.

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**Key words:** acute lung injury; acute respiratory distress syndrome; children; epidemiology; risk factor

## Introduction

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) remains the ultimate challenge in pediatric intensive care unit (PICU). As the disease process evolving, ALI/ARDS is defined as acute hypoxic respiratory failure resulting from pulmonary or extra-pulmonary causes except cardiogenic factors. ARDS has recently been recognized as one of the most common causes of death because of severe acute respiratory syndrome and high pathogenic avian influenza infection. ARDS has posed great threats to public health, and deserves more study in pediatric critical care community. Clinical research into ALI/ARDS is dominated by studies in adult patients. Pediatric ALI/ARDS cases have been reported in the literature since 1967.<sup>[1]</sup> Here, we report a one-year prospective survey of ALI/ARDS in PICU of Beijing Children's Hospital to describe the epidemiology and risk factors for ALI/ARDS.

## Methods

### Patients

All critically ill children admitted for ALI/ARDS in PICU of Beijing Children's Hospital between November 1, 2005 and October 31, 2006 were screened. The recruited children met the following inclusion criteria: (1) age between 29 days and 18 years; and (2) domestic pediatric critical index score (PCIS)  $\leq 90$  or fulfilling the American Guidelines for Admission of Pediatric Intensive Care Units (PICUs). Exclusion criteria were: (1) patients younger than 29 days or older than 18 years (Premature infants with corrected gestational age less than 43 weeks were also excluded); (2) patients with PCIS  $> 90$  and failed to meet the American Guidelines for Admission of PICU; (3) patients with central

respiratory failure, neuromuscular diseases, cyanotic congenital heart disease or signs of cardiogenic pulmonary edema (Echocardiography within 24 hours after admission indicated ejection fraction <50% or fractional shortening <30% and left atria or ventricle enlargement). ALI/ARDS was defined according to the criteria of the American European Consensus Conference (1994).<sup>[2]</sup>

### Study design

Data were collected from the patients who met the inclusion criteria, which included age, gender, height, weight, contact information, diagnosis of primary disease, oxygenation index, PCIS, and modified lung injury score (LIS).<sup>[3]</sup> Data concerning laboratory test, chest radiography, length of hospital stay, duration of mechanical ventilation, and ventilator setting were also recorded until transfer or discharge of patients. All laboratory tests were carried out according to the clinical indications.

In patients who required mechanical ventilation, low-tidal-volume ventilation setting was implemented (Normal tidal volume ranged from 6 to 8 mL/kg, maximizing at 10 mL/kg).

### Statistical analysis

Proportion was used as descriptive statistics for categorical variables, mean  $\pm$  standard deviation for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. For normally distributed quantitative data, Student's *t* test was applied to evaluate the difference between the two groups. Qualitative data were tested with the Chi-square test. Wilcoxon's rank-sum test was used for analysis of non-normally distributed quantitative data. To analyze mortality, a backward stepwise logistic regression model was used to choose variables that were associated with mortality and considered clinically important. Consequently, age, sex, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, initial lung injury score, and arterial carbon dioxide tension were included. The SPSS 12.0 software was used for all statistical analyses, and a two-sided *P*<0.05 was considered statistically significant.

### Results

In 562 critically ill patients admitted to PICU of Beijing Children's Hospital, a total of 44 patients met the inclusion criteria. Among them, 15 patients had ALI-non ARDS (34.1%) and 29 had ARDS (65.9%). Their gender and age at the first clinical visit are presented in the Table. Among 30 patients of 0-3 years old, 15

were ARDS patients. All the patients of 3-7 years old (*n*=2) and those of more than 7 years old (*n*=12) were diagnosed with ARDS.

### Etiology of ALI/ARDS

The most common causes of ALI/ARDS were pneumonia (52%) and sepsis (36%), followed by multiple trauma (5%), lung contusion (5%) and drowning (2%). Sepsis was associated with leukemia, congenital immunodeficiency disease, lymphoma, systemic lupus erythematosus, etc.

According to the causes, ALI/ARDS patients were divided into a pulmonary disease group (direct lung damage, *n*=26) and an extra-pulmonary disease group (indirect lung damage, *n*=18). The survival rate was higher in the pulmonary disease group than in the extra-pulmonary disease group (69.2% vs. 33.3%).

### Outcome and risk factors

Eight ALI/ARDS patients died during hospital stay and 36 survived at discharge. In-hospital mortality was 18.2% (8/44) for patients with ALI/ARDS, and 24.1% (7/29) for patients with ARDS. The prevalence rate of self-discharge against medical advice was 50% (22/44), which was attributed to socioeconomic factors (63.6%, 14/22), uncontrollable diseases (27.3%, 6/22) and other factors (9.1%, 2/22).

The primary causes of hospital mortality included multiple organ failure (50%, 4/8), respiratory failure (25%, 2/8) and uncontrollable diseases (25%, 2/8). The uncontrollable diseases included malignant diseases (leukemia, lymphoma) and congenital diseases (metabolic disease, immunodeficiency disease).

Among the 36 patients who survived after discharge from the hospital, 21 patients survived, 12 died within 28 days after discharge, and 3 were lost to follow-up. The lost 3 patients were considered survivors because of the improvement of their clinical manifestations

**Table.** Baseline characteristics of children with ALI/ARDS (*n*=44)

Variables	ALI (non-ARDS)	ARDS	<i>P</i>
Cases	15	29	
Age (y)	0.58 (0.25-1)*	4.81 (0.5-8)*	0.013
Sex ratio (M/F)	12:3	20:9	0.673
ICU length of stay (d)	8.26 $\pm$ 6.46	10.83 $\pm$ 10.63	0.398
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	225.90 $\pm$ 117.33	58.69 $\pm$ 10.90	<0.001
Lung injury score	1.51 $\pm$ 0.51	2.73 $\pm$ 0.81	<0.001
In-hospital mortality	6.7% (1/15)	24.1% (7/15)	<0.001
28-day mortality	20.0% (3/15)	58.6% (17/29)	0.015

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; PaO<sub>2</sub>: arterial oxygen tension; FiO<sub>2</sub>: fraction of inspired oxygen. \*: Since the age was skewedly distributed, it was described as median (interquartile range).

and no requirement of mechanical ventilation at the time of discharge. The total mortality rate at the end of the follow-up was 45.5% (20/44). Thus there were 20 patients in the non-survival group and 24 in the survival group. There was no significant difference in age and sex between the two groups ( $P=0.320$  and  $0.457$ , respectively).

Variables with a significant difference between the ALI/ARDS survivors and non-survivors included PaCO<sub>2</sub> on PICU admission ( $P=0.008$ ), LIS ( $P=0.036$ ), minimum PaO<sub>2</sub>/FiO<sub>2</sub> during the hospital stay ( $P=0.010$ ) and self-discharge against medical advice ( $P<0.001$ ). In the risk factors of mortality identified, discharge against medical advice (OR=87.651, 95%CI=7.300-1052.494), low PaO<sub>2</sub>/FiO<sub>2</sub> during the hospital stay (OR=0.967, 95%CI=0.941-0.994), and high PaCO<sub>2</sub> on PICU admission (OR=1.093, 95%CI=1.009-1.184) were the most significant ones shown by multivariate stepwise logistic regression analysis.

## Discussion

In this study, ALI/ARDS patients accounted for 7.8% (ARDS for 5.2%) of all patients admitted to the PICU of Beijing Children's Hospital. This finding is consistent with the average ALI/ARDS incidence in PICU reported elsewhere.<sup>[4-9]</sup> The reported ARDS prevalence is about three times higher than that of China in 2004,<sup>[10]</sup> and the relatively higher ALI/ARDS prevalence may be correlated to a higher percentage of severe cases in PICU.

The reported mortality rates of ARDS varied from 34% to 70%<sup>[11-14]</sup> because of different inclusion criteria and mortality calculation. The mortality in our study was 45.5%. Interestingly, there were striking differences between the reported data and ours. The in-hospital mortality rates were 18.2% and 24.1% for ALI and ARDS respectively, which are considerably lower than those reported previously,<sup>[15-21]</sup> but consistent with those reported by other four studies published after 2000.<sup>[9,13,22,23]</sup> This wide disparity in mortality could be related to many factors including medical referral system, admission and discharge criteria of PICU, severity of illness, socioeconomic status of patients, quality of patient care, and resource availability. Notably, our findings differ significantly from those mentioned above in that some patients had to abandon treatments for reasons that made the in-hospital mortality different from 28-day mortality. It is possible that the factors influencing the mortality of in-hospital vs. 28-day are the coverage of medical insurance and the capability to afford medical expenses.

This study revealed that pneumonia was the main cause of ALI/ARDS. The second cause of ALI/

ARDS was non-pneumonia related sepsis, accounting for approximately 10% of the patients. Since most pneumonia cases also met the diagnostic criteria for pulmonogenic sepsis, we came to the conclusion that sepsis is the leading cause of ALI/ARDS. Risk factors of ALI/ARDS include sepsis, chronic liver disease, extra-pulmonary organ failure, low PaO<sub>2</sub>/FiO<sub>2</sub>, hypoalbuminemia and old age.<sup>[7-9,16,19,24-26]</sup> In our study the principal risk factor of ALI/ARDS mortality was discharge against medical advice, followed by low PaO<sub>2</sub>/FiO<sub>2</sub> and high PaCO<sub>2</sub> on PICU admission.

No coverage of medical insurance and low socioeconomic status of patients contributed to delayed treatment or discharge against medical advice. Some patients with a great chance of survival who chose to terminate their treatment would make the mortality rate higher and the identification of risk factors difficult, for instance, multiple organ failure.

Limited by the low incidence of the disease and the small sample size, this study can only provide a preliminary conclusion and further investigation with a large sample is necessary. The prognosis of ALI/ARDS with pulmonary and extra-pulmonary origin is still unclear. In this study, ALI/ARDS patients with pulmonary disease had better outcome than those with extra-pulmonary involvement. The difference in prognosis was thought to be related to both the underlying diseases and the fact that most patients with extra-pulmonary disease also had other diseases such as leukemia, immune deficiency syndrome, and lymphoma, which caused immunocompromized conditions making sepsis patients susceptible to ARDS and even life-threatening multiple organ dysfunction syndrome (MODS). In cases of ALI/ARDS caused by pulmonary diseases, the lower incidence of severe complications or MODS was probably due to the improved survival rate. This indicated that MODS may be a morbidity-related risk factor for ALI/ARDS, but a definite conclusion still needs a large-sample study.

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