RESEARCH ARTICLE

Association of post-traumatic acute respiratory distress syndrome on poor prognosis: A single-center study

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Abstract

Objective: To determine the association of post-traumatic acute respiratory distress syndrome (ARDS) on poor prognosis, and provide a theoretical basis for the treatment of patients with post-traumatic ARDS in clinical practice.

Methods: This was a retrospective study including trauma victims in the intensive care unit (ICU) of Daping Hospital. The patients were classified as having ARDS or non-ARDS, according to the Berlin definition. Subsequently, these patients were divided into subgroups, according to age, gender and injury site. The relationship between ARDS and prognosis was analyzed, including mechanical ventilation days, length of ICU stay, length of hospital stay, infection, sepsis, multiple organ dysfunction syndrome (MODS) and death.

Results: There were 507 trauma patients, out of which 287 (56.61%) cases were with ARDS. The duration of mechanical ventilation, ICU stay and hospital stay in the ARDS group was significantly longer than that in the non-ARDS group (5 days vs 3 days, 10 days vs 4 days, 30 days vs 27 days, respectively). In addition, ARDS was associated with an increased risk of nfection ($p<0.05$; OR=4.17; 95%CI=2.72–6.41), sepsis ($p<0.05$; OR=3.45; 95%CI=2.28–5.22), and MODS ($p<0.05$; OR=2.82; 95% CI=1.67–4.72), but had no significant association with mortality ($p>0.05$). Similar results were found in the subgroup analyses.

Conclusions: In conclusion, the prognosis of the patients with post-traumatic ARDS was worse; however, ARDS had little effect on death.

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Introduction

Trauma is a universal health problem. More than 2.8 million patients are hospitalized with traumatic injury annually in the United States.[1] In mainland China, trauma is the fifth most common cause of death after malignant tumours and cardiac, cerebral and respiratory diseases, and the annual incidence of death is over 400,000.[2]

Trauma patients are the main group in the intensive care unit (ICU), and have greater rates of complications than general surgery patients.[3] The post trauma complications are one of the causes of high mortality in the ICU. Acute respiratory distress syndrome (ARDS), sepsis and multiple organ dysfunction syndrome (MODS) are all serious complications after trauma. Among the complications of trauma, sepsis has the highest mortality rate and the highest cost, followed by ARDS.[3,4] Prior studies have examined the association between sepsis and sepsis-induced ARDS, indicating that the lung is the most vulnerable target organ during sepsis and that cases of sepsis are often complicated by ARDS. On the other hand, trauma patients with ARDS are prone to infections and septicaemia, which may be related to alterations in the surfactant of alveolar cells after trauma.[5] Unfortunately, there has been relatively little attention directed towards the connection between post-traumatic ARDS and the prognosis, especially in China, which became the research objective of this study. This is a necessary inquiry to obtain a larger understanding of the intervention strategies and the care strategies on the patients who develop ARDS post trauma.

Methods

This retrospective study was conducted from January 1, 2012 to December 31, 2017 in the ICU of Daping Hospital, Army Medical University. The data were collected in EXCEL2017 tables. The enrolment criteria included: 1) patients admitted to the ICU because of trauma, 2) patients above 16 years of age, 3) patients admitted within 24 hours after trauma and staying in the ICU longer than 2 days, 4) AIS (abbreviated injury scale) ≥3. The exclusion criteria included: trauma patients with incomplete clinical data.

Patients with trauma were divided into the ARDS group or the non-ARDS group, according to their oxygenation index, chest X-ray and other diagnostic parameters within 24h hours after admission to the ICU. Subsequently, the patients were divided into subgroups according to age,

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gender, and site of injury. The relationship between ARDS and its prognosis was analyzed, including mechanical ventilation days, length of ICU stay, length of hospital stay, infection, sepsis, MODS and death.

The sample size was calculated using the following formula.

$$n=\frac{\left(Z_{\alpha}\times\sqrt{2\times\bar{p}\bar{q}}+Z\beta\times\sqrt{p0q0+p1q1}\right)^{\wedge}2}{(p1-p0)^{\wedge}2}$$

Sample size was 2n. In the above formula, p0 and p1 were the estimated incidence in the control group and in the case group, respectively. α=0.05, Z_{α}=1.96, β=0.10, Z_{β}=1.28. In addition, q0=1-p0, p1= (OR×p0) / (1- p0+OR×p0), q1=1-p1, $\bar{p}$ =(p0+p1)/2, $\bar{q}$ =1- $\bar{p}$.

In our preliminary experiment, OR=2.0, p0 = 39.1%, so n=177 and the sample size was about 354.

The diagnostic criteria for ARDS was referred to the Berlin definition[6] and for sepsis was referred to Sepsis 3.0.[7] The infections were diagnosed according to the microbiology results of blood or body fluids cultures obtained under sterile conditions. According to different diagnostic indices of circulation, respiration, nervous, blood, liver, kidney, stomach, intestinal system/organ, two or more dysfunctions occur simultaneously or sequentially, which was defined as MODS. At admission, SOFA (Sequential Organ Failure Assessment), ISS (Injury Severity Score), NISS (New Injury Severity Score), GCS (Glasgow Coma Scale), and APACHE II (Acute Physiological and Chronic Health Evaluation II) were all scored according to international general scoring standards.

The protocol for this study conformed to the standards of medical ethics, and was approved by the Ethics Committee of Daping Hospital. Informed consent was obtained from the patients or family members.

The data are presented as median (IQR, interquartile range) for numerical variables and numbers (%) for categorical variables. The differences were compared between the ARDS group and non-ARDS group. Numerical variables and categorical variables were tested by the non-parametric Mann-Whitney U test and chi-square test, respectively. After adjustment for possible influencing factors, multivariate logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for the association between ARDS and infection, sepsis, MODS, and death, using SAS 9.4 software for calculating and STATA10.0 for drawing. A p-value < 0.05 was considered statistically significant.

Results

A total of 2745 patients were registered in ICU of Daping Hospital from January 1, 2012 to December 31, 2017. Of these, 507 trauma patients met the inclusion criteria (Figure-1 showing study selection process), comprising of 376 males and 131 females. The median age of the patients was 48 years (40-63 yr), and the majority of the patients were male (376/507, 74.16%). From 2012 to 2017, the total incidence of ARDS in trauma patients in the ICU was 56.61% (287/507). Baseline characteristics and the clinical outcome of patients were compared between the ARDS group and the non-ARDS group, as shown in Table 1. There was no significant difference in age, admission time, blood transfusion and surgery (p> 0.05). However, the proportion of males was higher in the ARDS group than in the non-ARDS group (p< 0.05). Regarding the severity of trauma, the ISS, NISS and APACHE II scores were significantly higher in the ARDS group than the non-ARDS group, and the GCS

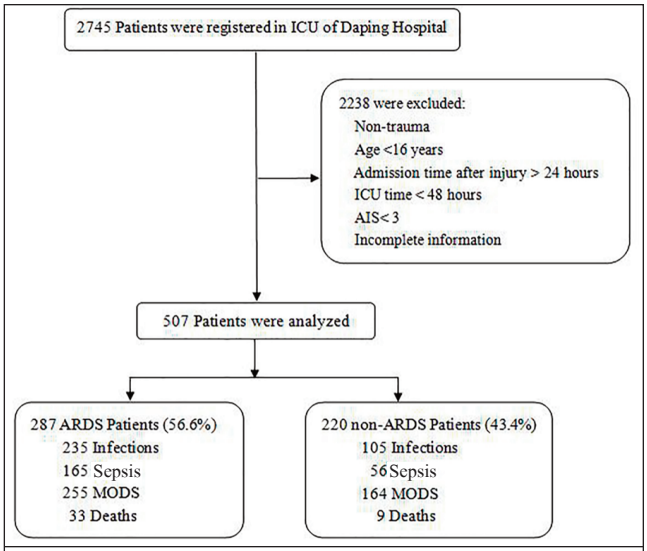

Figure-1: : Study selection process.

Table-1: Baseline characteristics of the patients.

Characteristic	Total (n=507)	ARDS (n=287)	Non ARDS (n=220)	*p*-value
Age(ys， M(IQR))	48(23)	49(21)	47(26)	0.122
Male (n,%)	376(74.16)	223(77.70)	153(69.55)	0.026*
ISS(M(IQR))	20(13)	22(12)	17(14)	＜0.001*
NISS(M(IQR))	27(17)	27(12)	22(15)	＜0.001*
APACHE II(M(IQR))	16(9)	17(9)	15(7)	0.003*
GCS(M(IQR))	13(6)	13(5)	14(5)	0.005*
AT(h, M(IQR))	8(11)	8(11)	7(10)	0.093
BT(n,%)	402(79.29)	227(79.09)	175(79.55)	0.959
Surgery (n,%)	371(73.18)	206(71.78)	165(75.00)	0.507

Note： M=median; IQR= interquartile range; AT= admission time; BT= blood transfusion.
From the data analysis of trauma types every year, it can be seen that the majority of trauma patients are those with traffic injury and fall injury, about 43.4% and 41.4%, respectively, as shown in Figure-2.

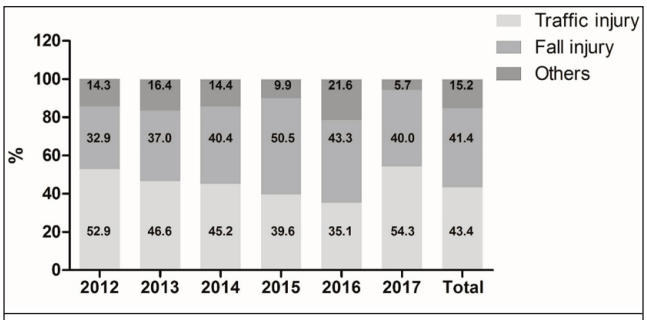

Figure-2: : The composition ratio of trauma types.

Table-2: Relationship between post-traumatic ARDS and prognosis (Numerical variables).

	Total (n=507)	ARDS (n=287)	Non ARDS (n=220)	*p*-value
Mechanical ventilation days (d, M(IQR))	4(7)	5(9)	3(3)	<0.001*
ICU LOS(d, M(IQR))	6(12)	10(14)	4(6)	<0.001*
LOS (d, M(IQR))	28(29)	30(28)	27(30)	0.017*

Note： M=median; IQR= interquartile range; LOS= length of stay.

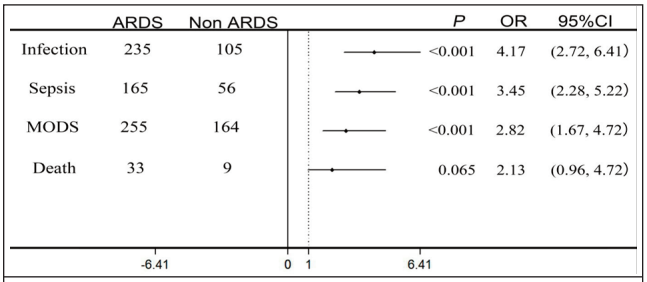

Figure-3: : Relationship between post-traumatic ARDS and prognosis (Categorical variables).

value indicating vital signs was significantly lower in the ARDS group than the non-ARDS group ($p< 0.05$).

The composition ratio of trauma types is shown in Figure 2.

The prognosis of patients with post-traumatic ARDS is listed in Table 2. The duration of mechanical ventilation, the duration of ICU stay and the duration of hospital stay of patients in the ARDS group were 5days(9 d),10 days (14 d) and 30 days (28 d), respectively, while those in the non-ARDS group were 3days(3 d), 4 days (6 d) and 27days (30 d), respectively. The difference between the two groups was statistically significant ($p<0.05$).

We also investigated the relationship between ARDS and infection, sepsis, MODS and death, as shown in Figure-3. The association of ARDS with the risk of infection, sepsis, MODS and death was assessed after adjusting for potential confounding variables such as gender, ISS, NISS, GCS and APACHE II. The results showed that ARDS was associated with an increased risk of infection ($p<0.05$; OR=4.17; 95%CI=2.72–6.41), sepsis (P <0.05; OR=3.45; 95%CI=2.28–5.22), and MODS ($p< 0.05$; OR=2.82; 95%CI=1.67–4.72), but had no significant association with death ($p>0.05$).

Table-3: Relationship between post-traumatic ARDS and prognosis (Numerical variables) in subgroups.

Variables	Subgroups	Total (n=507)	ARDS (n=287)	Non-ARDS (n=220)	*p*-value
Mechanical ventilation days （d, median(IQR)					
Age	<65 years	4(7)	5(8)	3(3)	<0.001*
	≥65 years	4(13)	6(14)	3(3)	0.037*
Gender	Male	4(8)	5(9)	3(4)	<0.001*
	Female	3(7)	4(10)	3(2)	0.003*
Injury site	Thoracic trauma	4(7)	4(9)	3(5)	0.001*
	Non-thoracic trauma	2(5)	5(9)	2(3)	<0.001*
Length of ICU stay （d, median(IQR)					
Age	<65 years	7(11)	10(13)	4(5)	<0.001*
	≥65 years	5(12)	10(18)	3(4)	<0.001*
Gender	Male	7(12)	10(14)	4(6)	<0.001*
	Female	6(9)	9(12)	4(4)	<0.001*
Injury site	Thoracic trauma	8(12)	10(14)	5(9)	<0.001*
	Non-thoracic trauma	5(9)	10(15)	3(5)	<0.001*
Length of stay (LOS) （d, median(IQR)					
Age	<65 years	29(28)	30(27)	28(28)	0.210
	≥65 years	23(33)	32(35)	16(25)	0.053
Gender	Male	29(29)	30(27)	28(31)	0.203
	Female	25(29)	31(36)	21(21)	0.087
Injury site	Thoracic trauma	30(27)	31(27)	29(28)	0.330
	Non-thoracic trauma	27(30)	29(31)	25(31)	0.076

The prognosis of patients with post-traumatic ARDS in subgroups is listed in Table 3. The duration of mechanical ventilation and duration of ICU stay of patients in the ARDS group were longer than the non-ARDS group in the subgroups of age, gender and injury site ($p<0.05$). However, there was no significant difference in the duration of LOS between ARDS patients and non-ARDS patients in the subgroups of age, gender, and injury site ($p>0.05$). This is likely to be attributable to effective use of antibiotics and further improved strategies of late care.

As shown in Figure-4, the patients with ARDS were more likely to develop infection, sepsis and MODS, but not death, than those with non-ARDS at different subgroups of age, gender and injury site, which was basically consistent with Figure-3. Interestingly, there was no significant difference in the risk of MODS between the ARDS group and the non-ARDS group in the subgroup of over 65 years old ($p=0.238$), as well as the subgroup of female (P=0.237).

Figure-4 shows the relationship between post-traumatic ARDS and prognosis (Categorical variables) in subgroups (A: post-traumatic ARDS and infection, in different subgroup of age, gender and injury site, the risk of infection with ARDS patients was significantly higher than that with

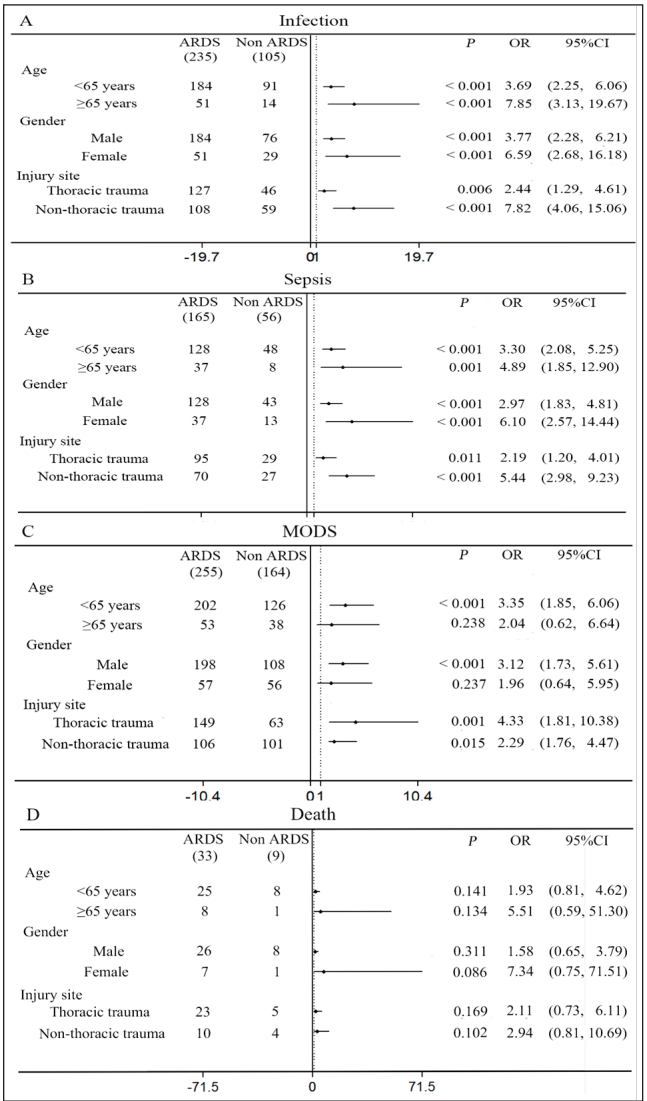

Figure-4: : Relationship between post-traumatic ARDS and prognosis (Categorical variables) in subgroups.

non-ARDS patients； B: post-traumatic ARDS and sepsis, in different subgroup of age, gender and injury site, the risk of sepsis with ARDS patients was significantly higher than that with non-ARDS patients； C: post-traumatic ARDS and MODS, in different subgroup of injury site, the risk of MODS with ARDS patients was significantly higher than that with non-ARDS patients, while in the subgroup of older than 65 years or female, there was no significant difference in the risk of MODS between the ARDS patients and the non-ARDS patients； D: post-traumatic ARDS and death, in different subgroup of age, gender and injury site, there was no significant difference in the risk of death between the ARDS patients and the non-ARDS patients)

Discussion

ARDS was first described as a clinical syndrome in 1967.[8] Because of its high incidence, high mortality and complex pathogenesis, ARDS has always been a difficult and key point in critical care, and involves progressive respiratory failure characterized by intractable hypoxaemia and respiratory distress. The result of a recent meta-analysis of the incidence of ARDS in trauma patients showed that the overall incidence of ARDS was about 8.4% in America and Europe[9,10] which is far below our figure (above 50%). This may be related to the characteristics of Chongqing,[11] which is an industrialized city in the western part of China. It is generally known that the main causes of trauma-related admissions in hospitals worldwide are road traffic accidents (RTA).[12] The road traffic situation of Chongqing is very complex, coupled with the rapid development of construction industry in recent years, making the incidence rate of traffic injuries and industrial accidents very high in Chongqing. Our results also showed that the proportion of trauma patients with traffic injury and fall injury was as high as 85% (Figure-2). The other reason may be related to the inconsistency of diagnostic criteria in different countries, because there is lack of adherence to a standard approach for identifying ARDS in trauma patients, which contributes to variability.

To our knowledge, limited research has focused on post-traumatic ARDS and its poor prognosis, especially in China. Post-traumatic ARDS has been considered to increase the severity of disease, and therefore the prognosis is considered to be worse. However, there is no evidence of an alteration of prognosis in patients with post-traumatic ARDS in China. As great progress has been made in the clinical treatment of ARDS, especially in the development and implementation of lung protective mechanical ventilation strategies, lung opening strategies and fluid management strategies, the ventilator days, LOS in ICU and LOS in hospital of ARDS patients have decreased over time,[10] but they were still longer than that of non-ARDS patients.[13] This is consistent with our findings in post-traumatic ARDS. Ventilator associated pneumonia (VAP) is the most common hospital acquired infection (HAI) in the ICU.[14] VAP can significantly prolong the duration of mechanical ventilation and the length of ICU and hospital stay.[15] Infection is the precursor of sepsis. Respiratory tract infections are the most common cause of sepsis.[16] With the occurrence of infection, the risk of sepsis and MODS increases correspondingly. However, contrary to expectation, post-traumatic ARDS does not increase the risk of death. This result is in line with the findings of Thomas, whose reports showed that the mortality rate of polytrauma patients was not affected by thoracic trauma and ARDS.[17] It is probable that mortality in polytrauma patients was influenced by a combination of ARDS and the severity of thoracic trauma.[18,19] Wu identified that the

presence of lung contusion was among the risk factors affecting mortality in post-traumatic ARDS.[20] Unfortunately, we did not analyze the severity of ARDS and the types of chest trauma.

To further understand the relationship between ARDS and its prognosis in patients, the subgroup analyses were performed, including age, gender and injury site. With the development of the country, the phenomenon of population on aging is obvious in China. As patients age, co-morbidities tend to increase, and the prognosis becomes more complicated. In addition, Gender, as a potential factor of affecting the prognosis of trauma patients, has received increasing attention recently. This is a controversial issue. Most laboratory studies based on the animal model of trauma supported the protective role of oestrogen.[21] However, clinical studies failed to consistently reproduce these laboratory findings. Some supported that the protective effect of female sex on outcomes of trauma patients,[22] some demonstrated no substantial differences[23] and others even provided opposing evidences.[24,25] Finally, thoracic trauma has been reported as an important risk factor for the development of ARDS, and increases the odds of ARDS occurrence.[18]

This needs further analysis. First, infection should be categorized into in situ infection and secondary infection. In addition, some types of non-thoracic trauma such as abdominal injury and cranio-cerebral injury can lead to higher infection rates. Therefore, the locations and types of infection and injury should also be investigated.

However, this study has some potential limitations, such as the lack of further classification of ARDS and infection, and some time-related biases in the medical strategy. Nevertheless, these results still provided a theoretical basis for the treatment of patients with post-traumatic ARDS in clinical practice.

Conclusions

Our analysis of a single center trauma database found that patients with post-traumatic ARDS had poorer prognosis than non-ARDS patients. This was reflected in a longer duration of mechanical ventilation, of ICU stay and of hospitalization, and in a higher incidence of infection, sepsis and MODS.

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Abbreviations

ARDS= acute respiratory distress syndrome, MODS= multiple organ dysfunction syndrome, ICU= intensive care unit, IQR= interquartile range, AIS= abbreviated injury scale, ISS= injury severity score, NISS= new injury severity score, SOFA= sequential organ failure assessment, APACHE II=acute physiology and chronic health evaluation II, GCS= Glasgow Coma Scale, LOS= length of stay, OR=odds ratio, CI=confidence interval.

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