Research Article

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Serological ferritin, 100A12, procalcitonin and APACHEII score in prediction the prognosis of acute respiratory distress syndrome

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Abstract: Objective The aim of the present work was to investigate the prognostic value of serological ferritin, 100A12, procalcitonin (PCT) and APACHEII score in predicting death risk for patients with acute respiratory distress syndrome (ARDS).

Methods Forty eight ARDS patients were recruited from Feb. 2016 to Jan. 2019 from Lishui People's Hospital. According to their prognosis (survival or death within 28 days), these 48 patients were further divided into the survival group (n=28) and death group (n=20). The serological levels of S100A12, PCT and ferritin of the 48 ARDS patients were examined within 24 hours after hospitalization. Demographic characteristics, serum S100A12, PCT and ferritin were compared between the two groups, and diagnostic analysis was performed to evaluate the clinical efficacy of these markers in predicting the death of ARDS patients.

Results The serum S100A12, ferritin and APACHEII scores of the death group were significantly higher than those of the survival group ($p < 0.05$). However, serum PCT levels were not statistically different between the

two groups ($p > 0.05$). The death prediction sensitivity for serum S100A12, PCT, ferritin and APACHEII score were 65.0 (40.78-84.61)%, 60.00(36.05-80.88) %, 75.0(50.90-91.34)% and 85.0(62.11-96.79)% respectively. The death prediction specificity for serum S100A12, PCT, ferritin and APACHEII score were 75.0(55.13-89.31)%, 60.00(36.05-80.88)%, 64.29(44.07-81.36)% and 82.14(63.11-93.94)%, respectively. The area under the ROC curve (AUC) for serum S100A12, PCT, ferritin and APACHEII score were 0.68(0.51-0.84), 0.63(0.46-0.79), 0.71(0.56-0.86) and 0.91(0.83-0.99) respectively.

Conclusion Serological ferritin, 100A12, PCT and APACHEII scores can be used as biomarkers to predict the death risk of ARDS patients.

Keywords: ARDS; S100A12; procalcitonin; ferritin; prognosis.

Introduction

Acute respiratory distress syndrome (ARDS) is an inflammation syndrome that can be caused by severe trauma, infection, shock and non-cardiogenic disease [1-4]. The main pathological changes associated with ARDS are alveolar exudative hemorrhage, interstitial edema and alveolar endothelial dysfunction [5-7]. It had been reported that there are 190,600 ARDS seen in the United States every year, with a fatality rate of 40%-60% [8]. There is no comprehensive data on the incidence of ARDS in China. However, Eworuke et al. [9] estimate the incidence of ARDS to be about 59 cases for every 100,000 people, with an annual increase of about 670,000 ARDS patients according to the data from the U.S. With the continuous development of medical technology, the prognosis of ARDS has been improved; however, the mortality rate of ARDS still remains as high as 50%, and 80% of the deaths occur just 2-3 weeks after disease onset [8]. Therefore, early diagnosis, effective treatment and the

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identification of biomarkers that can accurately evaluate the incidence and prognosis of ARDS are crucial for improving the prognosis of ARDS.

Inflammatory factors play an important role in the pathogenesis of ARDS. Serum ferritin, a 480 KDa macromolecule, is synthesized by hepatocytes and reticular endothelial cells. The main inflammatory mediators causing lung injury are proteases and oxygen free radicals. Oxygen free radicals primarily include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl free radical ($-OH$). As ferritin is an acute phase protein, elevated ferritin levels are reflective of the degree of inflammation in the body. Therefore, ferritin levels can be used to assess disease severity and the lesion progress, thus predicting the prognosis of ARDS patients. S100A12 belongs to the S100 protein family and plays a regulatory role in the inflammatory process. Procalcitonin is a glycoprotein composed of 116 amino acid residues. Procalcitonin is a inflammatory mediator capable of stimulating cyclic adenosine monophosphate production in monocytes, suggesting that its action may be specific and comparable with that of calcitonin [10]. Studies have shown that S100A12 and PCT are closely associated with ARDS [11, 12]. PCT has been reported as a potential biomarker for evaluating ARDS prognosis, but the clinical values of serum ferritin, S100A12, and PCT in predicting death risk of ARDS patients remains unclear.

Material and methods

Patients

Forty eight ARDS patients were recruited from Feb. 2016 to Jan. 2019 from Lishui People's Hospital. According to their prognosis (survival or death within 28 days), the 48 ARDS cases were further divided into the survival group (n=28) and death group (n=20). Patient inclusion criteria were: 1) ARDS diagnosis meets the relevant criteria as established by the European Society of Serious Medical Sciences; 2) Emergency onset with 24 hours and oxygenation index < 200 mmHg; 3) Chest X-ray showed patchy shadow in both lungs; 4) Age more than 18 years old; 5) No long-term use of hormones or immunosuppressants. Case exclusion criteria were: 1) Cases in which hospitalization lasted for less than 24 hours; 2) Patients with chronic pulmonary diseases, malignant tumors or immune system diseases; 3) ARDS patients with symptoms caused by tuberculosis or bronchial asthma; 4) Pregnant or lactating women; 5) Patients taking immunosuppressive drugs. The study

was approved by the Medical Ethics Committee of Lishui People's Hospital.

Ethical approval: The research related to human use complies with all relevant national regulations and institutional policies, was performed in accordance the tenets of the Helsinki Declaration, and has been approved by Lishui People's Hospital's institutional review board.

Informed consent: Informed consent has been obtained from all individuals included in this study

Serum S100A12, PCT and ferritin detection

When the subjects were enrolled in the study, 5 mL venous blood was collected and centrifuged at a speed of 3 000 r/min for 10 minutes. The supernatant was collected and stored at - 20°C for reserve. Serum levels of S100A12 and PCT were detected by ELISA (S100A12 kit, Abnova Company, USA; PCT kit, Wuhan Youersheng Commercial and Trade Co., Ltd.) Serum ferritin levels were detected by radioimmunoassay in accordance with the manufacturer's instructions.

Statistical analysis

STATA11.0 statistical software (<http://www.stata.com>) was used for data analysis. The measurement data was expressed by $\bar{x} \pm s$, and the comparison between groups was made using the Student's *t*-test of the sample mean. The enumeration data was expressed by a relative number, and the comparison between groups was made based on the χ^2 test. Regarding the death prediction for ARDS patients, sensitivity, specificity, and the area under the ROC curve(AUC) were calculated according to the Bayes' theorem. $P < 0.05$ is statistical different.

Results

Demographic characteristics of the two groups

According to prognosis (survival or death within 28 days), the 48 ARDS cases were divided into a survival group (n=28) and a death group (n=20). The general characteristics of the two groups are shown in **Table 1**. There was no statistical difference between the groups with regards to age, gender, primary disease, etc.

Table 1: Demographic characteristics of the death and survival groups in patients with ARDS.

Factors	Survival (n=28)	Death (n=20)	t/chi-square	P-value
Age(year)	62.3±8.6	64.7±9.2	0.93	0.36
Gender			0.09	0.76
Male	17	13		
Female	11	7		
Primary disease			0.30	0.98
Pulmonary infection	15	11		
Trauma	4	3		
Surgery	3	2		
Pancreatitis	2	2		
Others	4	2		
Diabetes			0.87	0.35
Yes	4	5		
NO	24	15		
Coronary heart disease			1.95	0.16
Yes	3	5		
NO	25	15		
Hypertension			0.22	0.64
Yes	8	7		
NO	20	13		
Drinking			0.20	0.66
Yes	13	8		
NO	15	12		
Smoking			0.12	0.73
Yes	14	11		
NO	14	9		

Serological level of S100A12, procalcitonin, ferritin and APACHEII score distribution

The serum S100A12, ferritin and APACHEII scores of the death group were significantly higher than those of the survival group ($p < 0.05$). However, serum procalcitonin levels were not statistically different between the two groups ($p > 0.05$), **Table 2**. The distribution of serum S100A12, PCT, ferritin and APACHEII score are demonstrated by **Figure 1**.

Table 2: Comparison of serum S100A12, PCT, ferritin and APACHEII score in the death and survival groups.

Serum markers	Survival (n=28)	Death (n=20)	t	p-value
S100A12(ng/mL)	148.70± 30.10	172.80± 46.01	2.20	0.03
PCT(ng/mL)	8.50± 3.37	7.20± 2.68	1.42	0.16
Ferritin(ng/mL)	396.80± 136.20	505.20± 153.10	2.58	0.01
APACHEII	22.37± 6.98	37.96± 10.47	6.19	<0.001

Death prediction of serum S100A12, procalcitonin, ferritin and APACHEII score

The death prediction sensitivity for serum S100A12, PCT, ferritin and APACHEII score were 65.0 (40.78-84.61)%, 60.00(36.05-80.88)%, 75.0(50.90-91.34)% and 85.0(62.11-96.79)% respectively. The death prediction specificity for serum S100A12, PCT, ferritin and APACHEII score were 75.0(55.13-89.31)%, 60.00(36.05-80.88)%, 64.29(44.07-81.36)% and 82.14(63.11-93.94)%, respectively, **Table 3**. The area under the ROC curve (AUC) for serum S100A12, PCT, ferritin and APACHEII score were 0.68(0.51-0.84), 0.63(0.46-0.79), 0.71(0.56-0.86) and 0.91(0.83-0.99) respectively, **Figure 2**.

Discussion

ARDS is one of the most commonly diagnosed serious complications for patients with critical illnesses and mechanical ventilation [13, 14]. It is primarily characterized by acute onset, progressive dyspnea and intractable hypoxemia, with high morbidity and mortality. The pathogenesis of ARDS is complex and unclear, but studies have shown it's development is closely related to inflammation [15, 16]. When acute lung injury occurs, exogenous factors stimulate alveolar macrophages to synthesize and release a variety of inflammatory factors. This can stimulate the body to produce chemokines, oxygen free radicals and proteases, aggravate inflammation, promote the formation of pulmonary hyaline membrane and increase the permeability of pulmonary capillaries, ultimately leading to the development of ARDS [17, 18]. Previous publications [19-21] found neutrophils to play an important role in the pathogenesis of ARDS. For example, after activation of a large number of neutrophils *in vivo*,

Table 3: Death prediction efficacy of serum S100A12, PCT, ferritin and APACHEII score in patients with ARDS.

Marker	Sensitivity(95%CI)	Specificity(95%CI)	AUC(95%CI)	Likelihood ratio	Cut-off value
S100A12	65.0 (40.78-84.61)%	75.0(55.13-89.31)%	0.68(0.51-0.84)	2.6	164.2
PCT	60.00(36.05-80.88) %	60.7(40.58-78.50)%	0.63(0.46-0.79)	1.66	7.1
Ferritin	75.0(50.90-91.34)%	64.29(44.07-81.36)%	0.71(0.56-0.86)	2.1	422.1
APACHEII	85.0(62.11-96.79)%	82.14(63.11-93.94)	0.91(0.83-0.99)	4.8	28.3

Figure 1: The distribution of serum S100A12, PCT, ferritin and APACHEII score in patients with ARDS.

inflammatory factors and oxygen free radicals are released through “respiratory burst” to aggravate inflammation and lung injury.

The relative molecular weight of ferritin is 480 000. It contains trivalent iron ions and can catalyze the reaction between superoxide anions and hydrogen peroxide to produce highly toxic hydroxyl radicals and expand the oxidative stress reaction in a high-risk population [22]. Proinflammatory factors released by ARDS (IL-8, IL-6, TNF- α , etc.) can promote the synthesis of ferritin [23]. Therefore, the increase of serum ferritin in ARDS is due to the increase in oxidative stress reflux, the release of pro-inflammatory cytokines, and the aggravation of lung

injury, and can therefore be used as a marker for ARDS severity. Patients with high risk factors for ARDS and high serum ferritin levels are more likely to develop ARDS [24]. Sharkey et al. [23]. confirmed that the serum level of ferritin was positively correlated with the ARDS patient mortality. This elevated serum ferritin in ARDS patients may be due to : (1) Iron ions, which directly participate in immune regulation, aggregating in the reticuloendothelial system; (2) Tissue damage and cell lysis; (3) Direct damage to the body’s tissue caused by inflammation; (4) Reduced speed and quantity of circulatory iron transport due to liver injury; (5) Pre-inflammatory cytokines (IL-1 β , TNF, IL-6).

Figure 2: The ROC of serum S100A12, PCT, ferritin and APACHEII score in predicting the death of patients with ARDS.

As a member of the S100 protein family, S100A12 is mainly expressed in the cytoplasm of neutrophils. In cases of acute lung injury occurs, serum S100A12 is persistently over-expressed and specifically binds to advanced glycation end product receptor (RAGE). NF- κ B can be activated in this process, producing a large number of cytokines that cause pathological lung injury [12]. PCT is a relatively stable precursor of calcitonin, as well as a marker of inflammatory response. When a systemic inflammatory response occurs, serum PCT levels increase significantly.

In our present work, we found that the serum S100A12, ferritin and APACHEII score of the death group of ARDS cases were significantly higher than those of the survival group ($p < 0.05$). However, serum PCT levels were not statistically different between the two groups ($p > 0.05$). The death prediction sensitivity for serum S100A12, PCT, ferritin and APACHEII score were 65.0 %, 60.00 %, 75.0(50.90-91.34)% and 85.0% respectively. The death

prediction specificity for serum S100A12, PCT, ferritin and APACHEII score were 75.0%, 60.00%, 64.29% and 82.14%, respectively. The APACHEII score had the highest prediction sensitivity and specificity.

In conclusion

Serological ferritin, 100A12, PCT and APACHEII score were all relatively elevated in the death group, meaning that they can be utilize as biomarkers to predict the death risk of ARDS patients. However, the sample size of this experiment was relatively small with limited statistical power. Therefore, the conclusions presented here should be followed up by large-scale, multicenter clinical studies for further validation..

Conflict of interest: Authors state no conflict of interest

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