Presepsin 在急性呼吸窘迫综合征(ARDS)中的诊断和预后评估价值

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【摘要】 目的 明确 presepsin 血清浓度在急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)患者中的诊断和预后评估价值。**方法** 对 81 名 ARDS 患者、27 名心源性肺水肿(cardiogenic pulmonary edema,CPE)患者和 20 名健康者的血清 presepsin 水平进行研究。采用基于化学发光酶免疫分析法(CLEIA)的快速病理分析系统 PATHFAST®测定血清 presepsin 的水平,比较不同组别血清 presepsin 水平差异。ARDS 患者随访 28 天病死率,分析存活及非存活患者各项指标差异。**结果** ARDS 患者的 presepsin 平均值明显高于 CPE 患者[926.89(485.41～2 662.32) pg/mL *vs.* 376.21(247.16～568.52) pg/mL,$P<0.001$]。ARDS 患者中,感染组与非感染组无明显统计学意义[(934.74(456.44～3 322.51) pg/mL *vs.* 798.12(485.41～2 561.40) pg/mL,$P=0.079$]。ARDS 患者非存活组的 presepsin 水平明显高于存活组[3158.3(963.91～4 489.33) pg/mL *vs.* 729.09(398.05－1 467.24) pg/mL,$P<0.001$],多元 Logistic 回归分析表明 presepsin 水平是急性肺损伤 ARDS 患者 28 天死亡率的独立预测因子(OR=1.51,$P=0.027$)。**结论** Presepsin 是诊断 ARDS 的有效指标,也是 ARDS 患者短期死亡率的有效预测因子。

【关键词】 presepsin; 可溶性 CD14(sCD14); 急性呼吸窘迫综合征(ARDS); 诊断; 预测
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Diagnostic value and prognostic evaluation of presepsin for acute respiratory distress syndrome (ARDS)

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【Abstract】 Objective To assess the diagnostic and prognostic value of measuring presepsin in patients with acute respiratory distress syndrome (ARDS). **Methods** Plasma prsepsin was collected from 81 patients with ARDS, 27 patients with cardiogenic pulmonary edema (CPE) and 20 healthy volunteers at enrollment. Levels of presepsin were measured using the PATHFAST® analysis system based on a chemiluminescent enzyme immunoassay (CLEIA). The differences of plasma prsepsin were compared between different groups. The 28-day mortality were followed in ARDS patients, and the characteristics of the surviors and non-surviors were compared. **Results** ARDS patients had significantly higher median levels of presepsin compared to CPE patients [926.89 (485.41－2 662.32)

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pg/mL *vs.* 376.21 (247.16 – 568.52) pg/mL, $P<0.001$] at enrollment. The difference between infected and non-infected ARDS patients did not showed statistical significance [(934.74 (456.44 – 3 322.51) pg/mL *vs.* 798.12 (485.41 – 2 561.40) pg/mL, $P=0.079$). In ARDS patients, the presepsin levels of non-survivors was significantly higher than that of survivors [3 158.3 (963.91 – 4 489.33) pg/mL *vs.* 729.09 (398.05 – 1 467.24) pg/mL, $P<0.001$], and multivariate Logistic regression showed that presepsin (OR = 1.51, $P=0.027$) was the independent predictor for 28-day mortality in ARDS patients with acute lung injury (ALI). **Conclusions** Presepsin was an effective indicator in diagnosing ARDS, and it also was a strong prognostic marker for short-term mortality in ARDS.

【Key words】 presepsin; soluble CD14 (sCD14); acute respiratory distress syndrome (ARDS); diagnosis; prognosis

The differential diagnosis is challenging in cases requiring distinction between acute respiratory distress syndrome (ARDS) and cardiogenic pulmonary edema (CPE), which may delay initiation of critical treatment measures (for example, lung-protective ventilation, prone positioning, neuromuscular blockade). The diagnosis of ARDS requires the exclusion of left atrial hypertension, which is usually dependent on the clinical judgment along with echocardiography and invasive hemodynamic monitoring. BNP and NT-proBNP were proved useful in excluding CPE and identifying patients with ARDS, but renal dysfunction, aging in zcritically ill patients limit the discriminative role of them. The plasma levels of presepsin may be an excellent predictor of outcome in patients with ARDS or CPE.

CD14, a cluster of differentiation (CD) marker protein expressed on the surface of various cells including monocytes, macrophages, neuutrophils, and B cells, is a multifunctional cell surface glycoprotein. CD14 is thought to be the lipopolysaccharide-binding protein (LPS-LBP) complex receptor, which exists either in a glycosylphosphatidylinositol (GPI)-anchored membrane form (mCD14), or in a circulating soluble form (sCD14)[1-2]. Circulating plasma proteases activate a cleavage of sCD14, generating a 13-kDa truncated N-terminal fragment of 64 amino acid residues named sCD14 subtype (sCD14-ST) or presepsin[1]. Recent studies showed that plasma presepsin levels were significantly increased in septic patients, and were positively correlated with the severity of sepsis[3-7]. In addition, *in vitro* studies indicated that sCD14 could interact with human bronchial epithelia cells (HBECs) to augment the production of IL-8 and IL-6[8]. Blockade of CD14 may attenuate the development of acute lung injury and suppress the activation of macrophage function after LPS challenge [9]. Thus, the aim of the present study was to investigate the plasma levels of presepsin and analyze its value in patients with ARDS.

Materials and methods

Research object The prospective, observational trial was undertaken from Jan., 2013 to Jun., 2014. A total of 108 consecutive patients with ARDS or CPE admitted into ICU of Zhongshan Hospital, Fudan University (Shanghai, China) were included. Exclusion criteria included age<18 years, pregnant women, immunosuppression due to medication or disease and patients on haemodialysis. Healthy volunteers ($n=20$, free from pulmonary or cardiac disease) were defined as normal individuals. The study protocol was approved by the Ethics Committee of Zhongshan

Hospital in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participating people or their legal representatives.

Diagnostic criteria Patients were enrolled within 6 h from the time of admission to the ICU. Two intensivists who were blinded to the results of presepsin reviewed all the other available clinical information integrated with progression of the disease and response to therapy, then made the final diagnosis of ARDS or CPE. Patients with ARDS met the following consensus definition: a known clinical result or new or worsening respiratory symptoms within 1 week; bilateral opacities which were not fully explained by effusions, lobar/lung collapse, or nodules; respiratory failure not fully explained by cardiac failure or fluid overload; severe hypoxemia with a ratio of arterial oxygen partial pressure and inspiratory oxygen fraction (PO_2/FiO_2) less than 300 with positive end expiratory pressure (PEEP) $\geqslant$5 cm H_2O[10]. Patients with CPE was diagnosed by a combination of clinical signs (gallop rhythm, jugular venous distension, systolic hypertension); radiographic (cardiothoracic ratio$>$0.53 and vascular pedicle width$>$65 mm), electrocardiographic (new ST-segment and T-wave changes), laboratory (elevated troponin T $>$ 0.1 ng/mL), and hemodynamic findings [pulmonary arterial occlusion pressure (PAOP)$\geqslant$18 mmHg, decreased ejection fraction $<$ 45%, presence of severe left-sided valvular heart disease, such as aortic or mitral stenosis or regurgitation]; and the response to appropriate therapy (preload/afterload reduction, treatment of ischemia or inotropic agents)[11].

Measures and indexes Patients underwent an initial clinical assessment at enrollment. Invasive hemodynamic monitoring, echocardiogram, pulmonary function and CT angiography were performed according to the treating physician. Insertion of a Swan-Ganz catheter was required when the diagnosis was uncertain. Comorbidities, ventilatory data, hemodynamic and laboratory findings were recorded at enrollment. Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ score, Lung Injury Score (LIS) and the Sequential Organ Failure Assessment (SOFA) score were also calculated. The primary clinical risk factor for ARDS was classified as direct pulmonary (pneumonia, aspiration) or indirect non-pulmonary (sepsis, hemorrhagic shock, resuscitation, multiple transfusion). For some analysis, the causes of ARDS were classified into infected group (infection as the cause) and non-infected group (all other causes, including hemorrhagic shock, aspiration, resuscitation and multiple transfusion). In addition, the degree of hypoxemia of ARDS was divided into mild ($200 < PO_2/FiO_2 \leqslant 300$), moderate ($100 < PO_2/FiO_2 \leqslant 200$) and severe ($PO_2/FiO_2 \leqslant 100$). Patients were followed for the end point of 28-day mortality over a 28-day period after enrollment.

Blood samples for determination of presepsin were collected at enrollment and 4 days later for all subjects and were centrifugated within the next 1 hour. Plasma samples were frozen at −80 ℃ for further analysis. Levels of presepsin were measured using the PATHFAST® analysis system (Mitsubishi Chemical Medicine Corporation, Japan) based on a chemiluminescent enzyme immunoassay (CLEIA) which has a normal reference range of 60−365 pg/mL.

Statistics analysis Continuous variables are presented as $\bar{x} \pm s$ or median (with interquartile range), and categorical variables as numbers and percentages. Unpaired Student's *t*-test or Mann-Whitney test were used between groups for continuous variables and chi-square for categorical variables. If the difference among multiple groups was indicated significant by the Kruskal-Wallis test, then the Mann-Whitney test was used to further evaluate the difference between them.

Correlations among continuous variables were assessed by the Spearman rank analysis. Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of presepsin to diagnose ARDS. Value of presepsin was used to predict 28-day mortality. The optimal cutoff value was determined when the Youden index reached the maximum value. Logistic regression was assessed by univariate and multivariate analysis to identify independent predictors of outcome. All probabilities were two tailed and $P<0.05$ was regarded as significant. Data were statistically analyzed with SPSS 16.0 software.

Results

Patient characteristics A total of 128 subjects including 81 patients with ARDS, 27 patients with CPE and 20 healthy volunteers were enrolled in the study. Causes of ARDS included pneumonia in 35 patients (43.2%), non-pulmonary sepsis in 19 (23.5%), aspiration in 10 (12.3%), resuscitation in 7 (8.6%), hemorrhagic shock in 6 (7.4%) and multiple transfusion in 4 (4.9%). Causes of CPE included congestive heart failure in 14 patients (51.9%), myocardial infarction/ischemia in 7 (25.9%) and acute volume overload in 6 (22.2%).

Baseline Characteristics of the study population were presented in Tab 1 stratified according to the final diagnosis. Echocardiographic data was obtained in 79 patients (73.1%), and hemodynamic data in 40 patients (37.0%). Compared with patients with ARDS, patients with CPE were more likely to have a history of atrial fibrillation and higher PO_2/FiO_2. Echocardiographic and hemodynamic data indicated patients with CPE had lower left ventricular ejection fraction (LVEF) and higher PAOP.

Presepsin values Patients with ARDS had significantly higher median levels of presepsin [926.89 (485.41 - 2 662.32) pg/mL] compared with CPE patients [376.21 (247.16 - 568.52) pg/mL, $P<0.001$, Tab 1] and with healthy subjects [116.23 (92.26 - 145.65) pg/mL, $P<0.001$] at enrollment. There was no significant difference between CPE patients and healthy subjects in terms of presepsin value ($P=0.189$). The area under ROC curve for presepsin in relation to the final diagnosis of ARDS from CPE was 0.803 ± 0.042 (Fig 1A). At a cut point >618.58 pg/mL, presepsin provided a specificity of 81.5% and a sensitivity of 70.4% for the diagnosis of ARDS. When the analysis was restricted to 87 patients (80.6%) without renal dysfunction (creatinine clearance>60 mL/min), the AUC for presepsin improved to 0.835 ± 0.051.

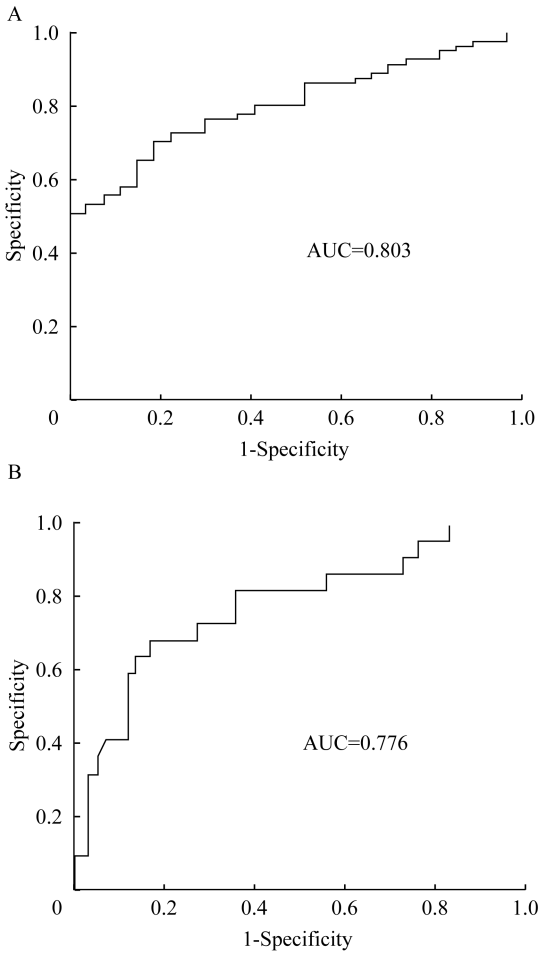
Patients with ARDS were classified into infected group (52 patients, 64.2%) and non-infected group (29 patients, 35.8%). The median presepsin levels at enrollment were 934.74 (456.44 - 3 322.51) pg/mL and 798.12 (485.41 - 2 561.40) pg/mL respectively, without statistical significance ($P=0.079$). In the infected group, there was no marked difference in presepsin levels between Gram-positive and Gram-negative bacterial infection. Furthermore, the presepsin levels of non-infected patients with ARDS were significantly higher than that of patients with CPE [798.12 (485.41 - 2 561.40) pg/mL *vs.* 376.21 (247.16 - 568.52) pg/mL, $P=0.004$]. There was no significant difference between pulmonary and non-pulmonary group in terms of presepsin value.

ARDS patients were divided into mild ($n=21$), moderate ($n=48$) and severe ($n=12$) group according to the degree of hypoxemia. There was no significant difference in presepsin value between mild and moderate group [769.62 (428.86 - 1 291.51) pg/mL *vs.* 944.90 (419.45 - 2 183.10) pg/mL, $P=0.633$]. However, the presepsin value of moderate group was significantly lower than that of severe group [944.90 (419.45 - 2 183.10) pg/mL *vs.* 3 681.32 (948.25 - 4 629.63) pg/mL, $P=0.003$] (Fig 2).

Tab 1　Baseline characteristics of patients with ARDS or CPE

Characteristics	ARDS (n = 81)	CPE (n = 27)	P
Demographics			
Age (y)	65 (61 - 69)	69 (58 - 75)	0.334
Male [n (%)]	49 (60.5)	17 (63.0)	0.820
BMI (kg/m^2)	22 (19 - 23)	20 (18 - 24)	0.316
Comorbidities [n(%)]			
Post-operation	18 (22.2)	7 (25.9)	0.693
Atrial fibrillation	5 (6.2)	6 (22.2)	**0.017**
Coronary artery disease	9 (11.1)	6 (22.2)	0.148
Chronic obstructive pulmonary disease	12 (14.8)	2 (7.4)	0.508
Hypertension	17 (21.0)	7 (25.9)	0.593
Diabetes	15 (18.5)	4 (14.8)	0.884
Chronic kidney disease	10 (12.3)	5 (18.5)	0.422
Cirrhosis	6 (7.4)	2 (7.4)	0.671
APACHE-Ⅱ score	16 (14 - 19)	16 (13 - 18)	0.383
SOFA score	10 (8 - 11)	9 (7 - 11)	0.287
Ventilatory data			
Arterial pH	7.41 (7.33 - 7.48)	7.42 (7.30 - 7.48)	0.931
Arterial lactate (mmol/L)	1.2 (0.8 - 1.9)	1.1 (0.5 - 1.8)	0.570
PO_2/FiO_2	123 (89 - 170)	170 (158 - 225)	**0.039**
Echocardiography			
Patients examined [n (%)]	58 (71.6)	21 (77.8)	0.531
LVEF (%)	56 (52 - 62)	48 (43 - 54)	**0.042**
Hemodynamics			
Patients examined [n (%)]	26 (32.1)	14 (51.9)	0.066
PAOP (mmHg)	14 (8 - 16)	22 (20 - 25)	**0.041**
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.12 (2.68 - 3.35)	2.75 (2.36 - 3.06)	0.127
SvO_2(%)	62 (55 - 66)	68 (61 - 75)	0.086
Laboratory findings			
White blood cell (10^9/L)	12.8 (7.8 - 17.6)	11.6 (6.8 - 13.9)	0.764
Platelet (10^9/L)	170 (87 - 278)	152 (107 - 335)	0.912
APTT (s)	38 (36 - 44)	36 (32 - 43)	0.652
Bilirubin (μmol/L)	10.8 (6.5 - 15.2)	9.6 (6.1 - 13.2)	0.765
Glucose (mmol/L)	6.3 (5.1 - 6.9)	6.5 (5.4 - 7.0)	0.476
Albumin (g/L)	29.2 (26.8 - 32.6)	32.0 (28.7 - 33.0)	0.527
Creatinine (μmol/L)	69 (57 - 112)	91 (68 - 121)	0.068
Presepsin (pg/mL)	926.89 (485.41 - 2 662.32)	376.21 (247.16 - 568.52)	**<0.001**
Length of ICU stay (d)	8 (6 - 14)	6 (4 - 10)	0.315

ARDS: Acute respiratory distress syndrome; CPE: Cardiogenic pulmonary edema; BMI: Body mass index; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; SOFA: Sequential organ failure assessment; PO_2/FiO_2: Aratio of arterial oxygen partial pressure and inspiratory oxygen fraction; LVEF: Left ventricular ejection fraction; PAOP: Pulmonary artery occlusion pressure; SvO_2: Oxygen saturation of venous blood; APTT: Activated partial thromboplastin time. Data were presented as median (interquartile range) for continuous variables and number (%) for categorical variables.



Receiver operating characteristic curves for presepsin in (A) diagnosing ARDS from cardiogenic pulmonary edema and (B) predicting 28-day mortality in patients with ARDS. AUC: Area under the curve.

Fig 1 Presepsin for disease diagnosis and mortality prediction

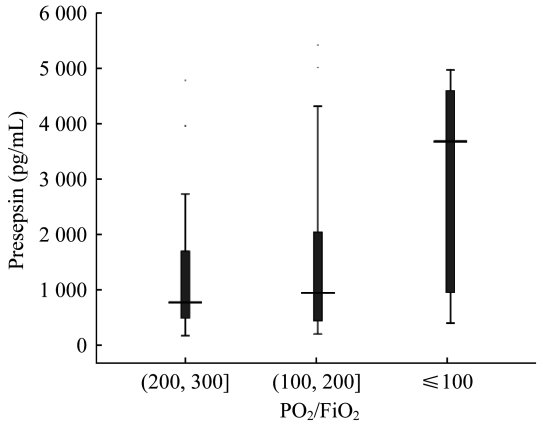


Fig 2 Presepsin levels in patiens with ARDS classified by PO_2/FiO_2

In patients with ARDS, presepsin levels were correlated with serum creatinine ($r = 0.71$, $P < 0.001$), APACHE Ⅱ score ($r = 0.63$, $P = 0.031$), SOFA score ($r = 0.61$, $P = 0.023$) and PO_2/FiO_2 ($r = -0.52$, $P = 0.029$) at enrollment.

The mortality was 27.2% in patients with ARDS. Compared with survivors, non-survivors had significantly higher APACHE Ⅱ score, SOFA score, arterial lactate and lower PO_2/FiO_2 (Tab 2). The presepsin levels of non-survivors were significantly higher than that of survivors [3 158.30 (963.91 - 4 489.33) pg/mL *vs.* 729.09 (398.05 - 1 467.24) pg/mL, $P < 0.001$] at enrollment. ROC curve was drawn to evaluate the value of presepsin to predict 28-day mortality and the AUC was calculated as 0.776 ± 0.062 (Fig 1B). The optimal cutoff value for predicting death was > 2 024.9 pg/mL, which gave specificity of 83.1% and sensitivity of 68.2%. Kaplan-Meier curve was drawn according to the value of 2 024.9 g/mL for as a cut-point to describe death over 28 days follow-up (Fig 3). There was a significant difference in the occurrence of death ($P < 0.001$).

Univariate logistic regression analysis showed that APACHE Ⅱ score, SOFA score, PO_2/FiO_2 and plasma presepsin levels at enrollment were the common predictors of 28-day mortality in patients with ARDS. Multivariate logistic regression analysis showed SOFA score (OR = 1.81, P = 0.033) and presepsin (OR = 1.51, $P = 0.027$) remained the independent predictor for mortality after adjustment for risk factors (APACHE Ⅱ score, PO_2/FiO_2) (Tab 3).

In ARDS patients whose plasma presepsin level increased over 4 days had a trend toward an increased risk of death compared with those whose plasma level decreased over time (mortality: 36.1% *vs.* 18.1%, $P = 0.024$). The association between increasing presepsin and death was statistically significantin patients with ARDS (OR = 1.42, $P = 0.035$).

Tab 2　Baseline characteristics of patients with ARDS according to survival

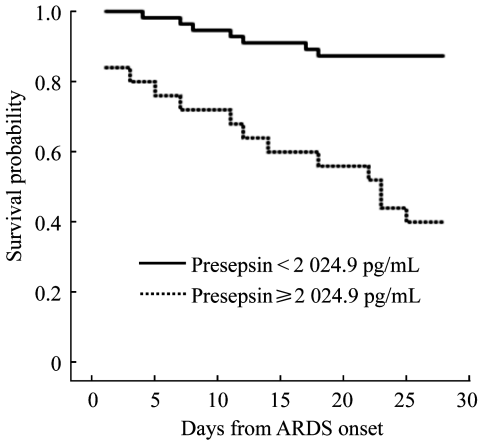
Characteristics	Non-survivors (n = 22)	Survivors (n = 59)	P
Demographics			
Age (y)	70 (64 - 75)	70 (65 - 75)	0.873
Male [n (%)]	13 (59.1)	36 (61.0)	0.875
BMI (kg/m^2)	22 (21 - 25)	21 (19 - 23)	0.211
Main cause of ARDS [n (%)]			
Pneumonia	9 (40.9)	26 (44.1)	0.799
Non-pulmonary sepsis	8 (36.4)	11 (18.6)	0.094
Aspiration	4 (18.2)	6 (10.2)	0.552
Resuscitation	4 (18.2)	3 (5.1)	0.155
APACHE-Ⅱ score	18 (15 - 25)	16 (13 - 18)	**0.008**
SOFA score	12 (10 - 14)	9 (8 - 11)	**0.001**
LIS score	1.3 (0.9 - 1.8)	1.0 (0.6 - 1.8)	0.240
Ventilatory data			
Arterial pH	7.33 (7.25 - 7.47)	7.42 (7.38 - 7.48)	0.128
Arterial lactate (mmol/L)	3.2 (1.6 - 5.6)	1.8 (1.2 - 2.6)	**0.039**
PO_2/FiO_2	138 (89 - 203)	176 (150 - 214)	**0.005**
Echocardiography			
Patients examined [n (%)]	16 (72.7)	42 (71.2)	0.891
LVEF (%)	52 (47 - 56)	54 (49 - 59)	0.455
Hemodynamics			
Patients examined [n (%)]	10 (45.5)	16 (44.1)	0.116
PAOP (mmHg)	13 (10 - 15)	12 (8 - 14)	0.322
Cardiac index (L · min^{-1} · m^{-2})	2.77 (2.36 - 3.15)	3.02 (2.58 - 3.38)	0.257
SvO_2(%)	59 (54 - 65)	65 (58 - 69)	0.229
Laboratory findings			
White blood cell (10^9/L)	13.5 (5.85 - 18.4)	12.7 (8.4 - 16.8)	0.571
Platelet (10^9/L)	169 (65 - 256)	159 (111 - 307)	0.066
APTT (s)	37 (33 - 42)	36 (32 - 43)	0.809
Bilirubin (μmol/)	12.8 (9.6 - 15.6)	10.2 (7.6 - 13.6)	0.218
Glucose (mmol/L)	6.2 (5.4 - 7.6)	6.1 (5.2 - 7.1)	0.362
Albumin (g/L)	30.1 (25.4 - 32.8)	29.4 (26.9 - 32.6)	0.206
Creatinine (μmol/L)	92 (75 - 126)	73 (56 - 92)	0.079
Presepsin (pg/mL)	3 158.3 (963.91 - 4 489.3)	729.09 (398.05 - 1 467.2)	**<0.001**

Abbreviations are the same as Tab 1.

Tab 3　Logistic regression analysis of mortality prediction for patients with ARDS

Factor	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
APACHEⅡ (per point)	1.25 (1.05 - 2.18)	**0.028**		
PO_2/FiO_2[a] (per one-log)	0.76 (0.42 - 0.91)	**0.046**		
SOFA score (per point)	1.65 (1.32 - 2.97)		1.81 (1.23 - 2.55)	**0.033**
Presepsin[a] (per one-log)	1.78 (1.25 - 3.68)	**0.027**	1.51 (1.16 - 3.16)	**0.027**
Increase in presepsin[b]	1.56 (1.23 - 2.25)	**0.036**	1.42 (1.16 - 1.98)	**0.035**

ARDS: Acute respiratory distress syndrome; OR: Odds ratio; PO_2/FiO_2: A ratio of arterial oxygen partial pressure and inspiratory oxygen fraction. The APACHE Ⅱ uses a point score based on initial values of 12 routine physiological measurements, patient age, and medical history to provide a general measure of disease severity in a patient. The SOFA score calculates a summary value for the degree of dysfunction of six sets of organs (respiratory, coagulation, liver, cardiovascular, central nervous system and renal). [a]Log-transformed; [b]Referent group: Subjects whose presepsindecreased over 4 days.



Kaplan-Meier survival probability by presepsin value above or below the cutoff point of 2 024.9 pg/mL. ARDS: Acute respiratory distress syndrome.

Fig 3 Survival probability by presepsin value

Discussion

There were no identified biomarkers or tools with high-quality evidence for differentiating ARDS from CPE, because there is no objective gold standard for diagnosing ARDS or CPE. In our study, we found that patients with ARDS had significant higher median levels of presepsin compared with patients with CPE. Presepsin may be useful in identifying patients with ARDS and CPE. In this way, ARDS and CPE can be identified early and treated correctly and effectively.

Univariate Logistic regression analysis showed that APACHE Ⅱ score, SOFA score, PO_2/FiO_2 and plasma presepsin levels at enrollment were the common predictors of 28-day mortality in patients with ARDS. As we all known, APACHE Ⅱ, SOFA score, PO_2/FiO_2 were associated with poor outcome. In some studies, the initial oxygenation abnormality defined by the PO_2/FiO_2 ratio did not predict mortality unless it was grossly abnormal[23]. Studys supported the use of SOFA score as an aid to identify patients with increased risk of in-hospital mortality among patients hospitalized with infection. In our study, presepsin levels of non-survivors was significantly higher than survivors. Multivariate logistic regression analysis showed presepsin at enrollment was the independent predictor for 28-day mortality.

CD14 plays a role in monocyte activation, signal transduction, leukocyte aggregation, and cyte adhesion on endothelial cells[12]. Blockade of CD14 with monoclonal antibodies prevents the monocyte synthesis of tumor necrosis factor-α (TNF-α)[13]. Presepsin which generated by circulating plasma proteases activating cleavage of soluble CD14 is associated with phagocytosis and cleavage of microorganisms. It has been found that presepsin levels in patients with systemic and localized bacterial infections were significantly higher than those in patients with non-bacterial infectious diseases[5]. Beyond that, sCD14 levels were specifically increased in serum and bronchoalveolar lavage fluid (BALF) of children with pneumonia compared with cystic fibrosis, asthma and healthy subjects[14]. ARDS is characterized by extensive neutrophil influx into the lungs, production of proinflammatory mediators, and damage of lung epithelial and endothelial surfaces[15]. Martin, *et al*[16] found that sCD14 increased in BALF and serum of patients with ARDS. In the present study, the presepsin levels in patients with ARDS were significantly higher than patients with CPE. In addition, the difference in presepsin levels between infected and non-infected patients with ARDS was not significant. CD14 is an essential receptor in LPS-induced lung inflammation, meanwhile, it also exists in a soluble form (sCD14) which is able to mediate LPS-activation of cells devoid of membrane CD14 expression, such as epithelial and endothelial cells[17-19]. sCD14 can reconstitute the whole (physiological and biological) response to inhaled LPS in the lung. The augment of the endogenous concentration of sCD14 can enhance neutrophil inflammation in response to inhaled LPS[20]. Moreover, the release of IL-8 and IL-6 from human bronchial epithelial cells (HBECs) was increased in a concentration-dependent manner upon stimulation with sCD14 both in the presence and absence of LPS[8].

sCD14 is deemed to act as a key component in pulmonary inflammation, meanwhile, may represent a promising marker and therapeutic target in respiratory diseases. Pulmonary edema and neutrophil emigration after LPS challenge were attenuated by blocking CD14 using an anti-CD14 monoclonal antibody[8]. A significant decrease in protein leakage into BAL fluid was also induced by CD14 blockade[21]. Our study showed that presepsin was the independent predictor for 28-day mortality in ARDS patients. Beyond that, patients whose plasma presepsin level decreased over 4 days had a decreased risk of death compared with those whose plasma level increased over time. The decreasing trend could be related to an early clearance or to a reduced production of presepsin as a consequence of the appropriate treatment. It is conceivable that early measurement of circulation presepsin will help in monitoring the appropriateness of the early therapy adopted.

CD14 has been shown to be a specific receptor of LPS, a compound from the outer cell wall of Gram-negative bacteria. In addition, CD14 may function as a receptor for peptidoglycan, the major cell wall component of Gram-positive bacteria[1-2]. The elevated value of sCD14 in Gram-positive septic patients could thus be due to enhanced liberation of sCD14 caused by cytokines such as TNF-α[22]. This may be the reason why there is no marked difference in presepsin levels between Gram-positive and Gram-negative bacterial infection in our study.

There are several limitations to our study. Firstly, the study sample was small in size and was a single-center study, thus restricting generalizability. Secondly, we did not take in-depth analysis of the relation between presepsin levels and the therapy implemented. Finally, we did not test the concentration of presepsin in alveolar fluid and compare with other biomarkers of ARDS.

In conclusion, our findings suggested that presepsin was a biomarker which could distinguish ARDS from CPE. Furthermore, it was a strong predictor for short-term mortality in ARDS. The clinical indications of presepsin in diagnosis and prognosis should be validated in large-scale patients with ARDS.

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