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Role of Presepsin (sCD14-ST) and the CURB65 scoring system in predicting severity and outcome of community-acquired pneumonia in an emergency department

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Summary
Introduction: CD14 is one of the leukocyte differentiation antigens, and is present in macrophages, monocytes, granulocytes and their cell membranes. Presepsin, namely soluble CD14-subtype (sCD14-ST) is produced by circulating plasma proteases activating cleavage of soluble CD14 (sCD14). The aim of this study is to investigate the role of Presepsin and the CURB65 scoring system in the evaluation of severity and outcome of CAP in an ED.
Method: A prospective, observational study was performed in an ED of an university teaching hospital from November 2011 to October 2012. A total of 359 patients with CAP and 214 patients with severe CAP (SCAP) were consecutively enrolled. Plasma Presepsin, lactate, serum PCT levels and leukocyte counts were measured and CURB65 score were calculated at admission enrollment.
Result: Plasma Presepsin levels were significantly higher in SCAP patients than in CAP patients ($P < 0.0001$), increasing correspondingly with the enhancement of CURB65 score. Patients with ARDS or DIC had obviously higher plasma Presepsin levels than those without ARDS or DIC (all $P < 0.0001$), and plasma Presepsin levels were significantly higher in non-survivors than in survivors at 28-day follow-up. In logistic regression analysis, CURB65 score was the independent predictor of ARDS, and Presepsin was the independent predictor of DIC, and Presepsin and CURB65 score were both the independent predictors of 28-day mortality. The AUCs showed Presepsin in combination with CURB65 score in predicting ARDS, SCAP and 28-day mortality

Abbreviations: ED, emergency department; CAP, community-acquired pneumonia; SCAP, severe CAP; DIC, disseminated intravascular coagulation; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PCT, procalcitonin; PSI, pneumonia severity index; CURB65 score, confusion, urea >7 mmol/L, respiratory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mmHg, and age ≥65 years; ROC curve, receiver operating characteristics curve; AUC, area under the ROC curve; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

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was superior to Presepsin or CURB65 score alone (all $P < 0.01$), Presepsin was better than CURB65 score and leukocyte in predicting DIC ($P < 0.01$).
Conclusion: Presepsin is a valuable biomarker in predicting severity and outcome in CAP patients in the ED and Presepsin in combination with CURB65 score significantly enhanced the predictive accuracy.

Introduction

Community-acquired pneumonia (CAP) is a common and potentially serious illness, and is considered to be the leading cause of deaths associated with infectious disease in developed countries [1]. Accurate, objective, and early disease severity assessment and prediction of outcome in patients with CAP are crucial for optimized management decisions regarding care setting, extent of assessment, and level of treatment.

Scoring systems have been used to evaluate the severity or outcome of CAP in recent years. At present, the Pneumonia Severity Index (PSI) and CURB65 have been the most widely used scoring systems. PSI is comprised of a 20-point score that classifies patients into five risk categories based on their risk of death within 30 days. This score was developed to identify patients at low risk of death, who could be recommended for outpatient treatment [2]. However, PSI is limited by the number of included variables, making it complex to use in a busy emergency department (ED) setting [3]. The CURB65 score consists of five predictors, including confusion, urea >7 mmol/L, respiratory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mm Hg, and age ≥65 years [4], and is significantly easier to use than PSI as a single point is awarded to each variable and is more easily applied in an ED setting. In addition, although CURB65 consists of a simple 5-point score, a comparison found no significant differences between PSI and CURB65 in predicting mortality in CAP patients [5]. Scoring systems are useful for optimizing and reducing unnecessary hospital admission rates, but they do not reflect aspects of the pathophysiology of disease. Thus, additional risk factors and prognostic biomarkers could potentially enhance the prognostic performance of these established risk scores in CAP patients.

CD14 is one of the leukocyte differentiation antigens, and is present in macrophages, monocytes, and granulocytes and their cell membranes. CD14 exists in two forms, membrane CD14 (mCD14) and soluble CD14 (sCD14) [6,7]. CD14 is a pattern recognition receptor for several conserved bacterial motifs, including lipopolysaccharide, the toxic moiety in the outer membrane of Gram-negative bacteria, and peptidoglycan and lipoteichoic acid, both major components of the Gram-positive bacteria cell wall [7—9]. Soluble CD14-subtype (sCD14-ST), or Presepsin, is produced by circulating plasma proteases activating cleavage of sCD14 [10], which is a new biomarker of sepsis.

Previous clinical studies have confirmed that Presepsin levels increased in sepsis and with severity of disease [11—13]. However, the correlation between Presepsin and CAP, one of the most common causes of sepsis, with high morbidity and mortality, has not yet been determined. Therefore, the aim of this study was to investigate the role of Presepsin and the CURB65 score in the assessment of severity, adverse medical events and 28-day mortality in CAP patients in an ED.

Materials and methods

Study institution and subjects

This prospective, observational study was conducted in the ED of Beijing Chao-Yang Hospital, an university teaching hospital with approximately 240,000—260,000 ED admissions per year. From November 2011 to October 2012, consecutive patients suspected of CAP at ED admission were enrolled.

Exclusion criteria were as follows: age less than 18 years; terminal stage of disease (malignant cancer of any type, end-stage liver, or renal disease); hospitalized within 14 days before the onset of symptoms; cystic fibrosis; active pulmonary tuberculosis; severe immunosuppression; coagulopathy; systemic anticoagulant treatment; pretreatment outside hospital; and the patient or relatives did not consent to participate in the study. This study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital and written informed consent forms were obtained from all participants.

At enrollment, subject data, including name, age, sex, past medical history, and vital signs, were recorded. Laboratory examinations, including whole blood leukocyte count, blood gas analysis, blood biochemistry, and X-rays, were recorded within 24 h. The CURB65 scores were calculated on the basis of vital signs and laboratory findings [4].

Definition of CAP and SCAP, ARDS, and DIC

CAP was defined as the presence of a new infiltrate on a chest radiograph and at least one of the following signs and symptoms: cough, sputum production, dyspnea, core body temperature >38.0 °C, auscultatory findings of abnormal breath sounds, and rales [14]. Severe CAP (SCAP) was defined as having one of two major criteria (the need for invasive mechanical ventilation or vasopressors) or three of nine minor criteria (respiratory rate ≥30 breaths/min, PaO_2/FiO_2 ≤250 mm Hg, multilobar infiltrates, confusion, serum urea nitrogen level ≥20 mg/dL, white blood cell

count $\leq$4000 cells/mm^3, platelet count $\leq$100,000 cells/mm^3, core temperature $<$36 °C, and hypotension requiring aggressive fluid resuscitation) [1]. CAP was confirmed by an independent radiologist at admission to the ED.

According to the American-European Consensus Conference on Acute Respiratory Distress Syndrome (ARDS), the diagnostic criteria of ARDS are as follows: acute-onset symptoms, PaO_2/FiO_2 $<$200 mm Hg, bilateral infiltrates on chest radiography, and no clinical evidence of left atrial hypertension [15]. According to the criteria of the International Society on Thrombosis and Haemostasis subcommittee, disseminated intravascular coagulation (DIC) score is determined from platelet count, prothrombin time, fibrinogen, and fibrin degradation products; a score $\geq$5 is considered overt DIC and a lower score is considered non-DIC [16]. ARDS or DIC was diagnosed by two experienced physicians who did not participate in this study.

Measurement of Presepsin and other laboratory parameters

Venous blood samples were obtained at ED admission and collected in tubes containing heparin or ethylenediaminetetraacetate, and preserved by freezing at −80 °C after collection for analysis within 24 h. Plasma Presepsin concentrations were determined using a compact automated immunoanalyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Tokyo, Japan) based on a chemiluminescent enzyme immunoassay, and assay results were obtained within 17 min. This assay has a normal reference range of 60−365 pg/mL.

Serum procalcitonin (PCT) levels were measured by BioMerieux Mini VIDAS immunoassay analyzer (Block Scientific, Bohemia, NY, USA). A PCT level $<$0.05 ng/mL was regarded as normal. Plasma lactate levels were measured by blood gas analyzer (GEM Premier 3000, Instrumentation Laboratory, Lexington, MA, USA). The normal range was 0.7−2.5 mmol/L.

Outcome

For outcome assessment, a follow-up examination was planned at the 28th day after inclusion in the study. Patients who survived until follow-up were counted as survivors, whereas patients who died within the follow-up period were counted as non-survivors. Adverse medical outcome for this study was defined as the presence of ARDS, DIC, and death from any cause at the 28-day follow-up.

Statistical analysis

All data were analyzed by SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean $\pm$ standard derivation, and data with a skewed distributed as median (25−75th percentile). For multi-group comparisons, Kruskal−Wallis one-way analysis

Table 1 Baseline patient characteristics at enrollment.

Characteristics	CAP (n = 359)	SCAP (n = 214)	P-value
Patient demographics			
Age (years)	71 (59−78)	75 (69−80)	$<$0.001
Male sex, n (%)	221 (61.6%)	135 (63.1%)	0.716
ICU admission	33 (9.2%)	104 (48.6%)	$<$0.001
Ward admission	114 (31.8%)	79 (36.9%)	0.206
Outcome			
DIC, n (%)	39 (10.9%)	50 (23.4%)	$<$0.001
ARDS, n (%)	0 (0)	125 (58.4%)	$<$0.001
28-day mortality, n (%)	79 (22%)	117 (54.7%)	$<$0.001
Co-morbidities			
Hypertension	215 (59.9%)	121 (56.5%)	0.688
Diabetes mellitus	163 (45.4%)	101 (47.2%)	0.547
Chronic heart failure	168 (46.8%)	87 (40.7%)	0.635
COPD	125 (34.8%)	75 (35.0%)	0.672
Cerebrovascular disease	68 (18.9%)	29 (13.6%)	0.258
Chronic renal dysfunction	88 (24.5%)	52 (24.3%)	0.266
Neoplastic disease	35 (9.7%)	20 (9.3%)	0.811
Laboratory parameters			
Presepsin (pg/mL)	400.0 (231.5−691.5)	689.0 (395.5−1225.5)	$<$0.001
Lactate (mmol/L)	2.2 (1.7−2.5)	2.9 (2.2−6.4)	$<$0.001
PCT (ng/mL)	0.29 (0.05−1.5)	1.28 (0.25−8.98)	$<$0.001
Leukocyte count ($\times$ 10^9/L)	10.83 (7.61−14.87)	12.76 (8.59−18.42)	0.003
Risk assessment			
CURB65 score	2 (1−3)	4 (3−4)	$<$0.001
CURB score	1 (1−2)	3 (2−3)	$<$0.001

CAP: community-acquired pneumonia; SCAP: severe CAP; DIC: disseminated intravascular coagulation; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary diseases; PCT: procalcitonin; CURB65: confusion, urea $>$7 mmol/L, respiratory rate $\geq$30 breaths per minute, systolic pressure $<$90 mm Hg or diastolic pressure $\leq$60 mm Hg, and age $\geq$65 years.

of variance was applied, and two-group comparisons were performed nonparametrically using the Mann—Whitney *U* test. To compare the predictive value of Presepsin, PCT, leukocyte, lactate, and CURB65 score on ARDS, DIC, and 28-day mortality, receiver operating characteristic (ROC) curves were constructed and the areas under the ROC curves (AUC) were determined. On the basis of optimal thresholds determined according to ROC curve analysis, prognostic parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−)) were also calculated. For comparisons of AUCs, the *Z* test formula $Z=(A_1-A_2)/(SE_1^2+SE_2^2-rSE_1SE_2)^{1/2}$ was applied, and the test standard was $Z_{0.05}=1.96$, $Z_{0.01}=2.58$. Binary logistic regression analysis was applied to determine the independent predictors of ARDS, DIC, SCAP, and 28-day mortality. All statistical tests were two-tailed, and $P<0.05$ was considered statistically significant. Spearman correlation analysis was applied to determine the correlation between Presepsin, PCT, leukocyte, lactate, and CURB65 score.

Results

Characteristics of enrolled subjects

Between November 2011 and October 2012, 573 patients were enrolled after excluding 57 patients with missing clinical data and who were finally diagnosed with a disease other than CAP, 36 patients lost to follow-up, and 25 patients who did not consent to participate in the study. The enrolled patients were followed for 28 days or until death. There were no significant differences between CAP and SCAP groups with respect to sex and co-morbidities. The characteristics, coexisting illness, hospital admission, and associated laboratory findings of enrolled subjects are listed in Table 1.

Comparison of Presepsin levels between patients with CAP and SCAP, survivors and non-survivors at the 28-day follow-up

The median Presepsin level, PCT level, leukocyte count, and lactate level in each group are shown in Table 1. Plasma Presepsin levels at ED admission were significantly higher in patients with SCAP than in patients with CAP (689.0 [395.5—1225.5] pg/mL *vs* 400.0 [231.5—691.5] pg/mL, $P<0.0001$), and in non-survivors than survivors at the 28-day follow-up (699.0 [373.0—1250.0] pg/mL *vs* 410.5 [242.3—697.0] pg/mL, $P<0.0001$). Plasma Presepsin levels were markedly higher in non-survivors than in survivors in each group (CAP group, 588.0 [333.0—891.0] pg/mL *vs* 361.0 [218.0—589.0] pg/mL, $P<0.0001$; SCAP group, 781.0 [437.0—1427.0] pg/mL *vs* 520.0 [352.0—1014.5.0] pg/mL, $P=0.004$) (Fig. 1).

Comparison of plasma Presepsin levels on the basis of CURB65 score

CAP patients were divided into groups according to three CURB65 score risk categories: low (0—1), moderate (2), and high (≥3) risk, Median Presepsin levels were 353.0 [196.0—685.0] pg/mL, 385.0 [230.8—613.5] pg/mL, and 588.0 [362.0—1020.0] pg/mL, respectively, in each group. Median Presepsin levels were significantly higher in CAP patients with CURB65 (≥3) than CURB65 (0—1) or CURB65 (2) (all $P<0.0001$). There was no significant differences between CURB65 (0—1) and CURB65 (2) groups ($P=0.317$) (Fig. 2).

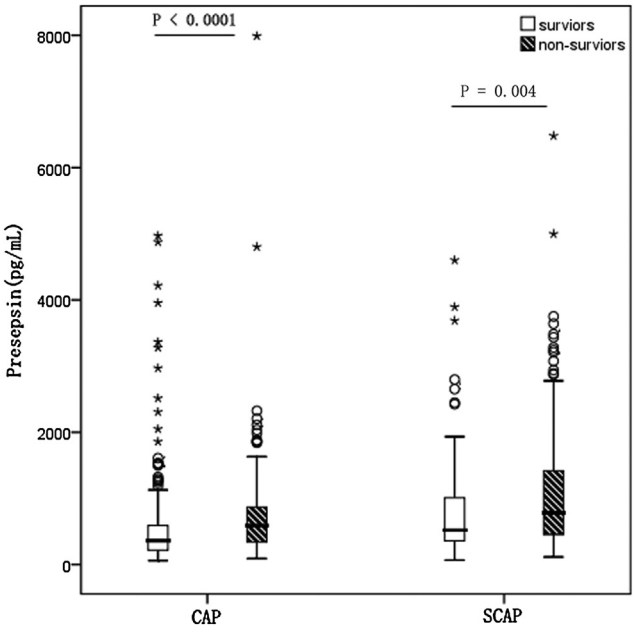

Figure 1 Comparison of plasma Presepsin levels in patients with CAP and SCAP, survivors and non-survivors at the 28-day follow-up between two groups. Lines denote median values, boxes represent 25—75th percentiles and whiskers indicate the range.

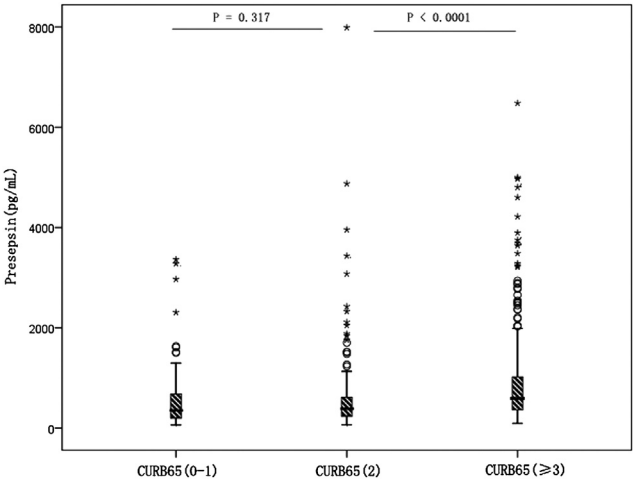

Figure 2 Comparison of plasma Presepsin levels according to three CURB65 score categories. Lines denote median values, boxes represent 25—75th percentiles, and whiskers indicate the range. CURB65 = confusion, urea >7 mmol/L, respiratory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mm Hg, and age ≥65 years.

Comparison of plasma Presepsin levels in patients with and without ARDS, with and without DIC, and in survivors and non-survivors with ARDS or DIC at the 28-day follow-up

Plasma Presepsin levels at ED admission were significantly higher ($P < 0.0001$) in patients with ARDS than without ARDS (777.0 [423.8—1307.0] pg/mL *vs* 416.0 [253.0—753.3] pg/mL), and in patients with DIC than without DIC (723.0 [441.0—1542.5] pg/mL *vs* 427.0 [266.5—779.5] pg/mL). Plasma Presepsin levels were significantly higher in non-survivors compared with survivors at 28-day follow-up in CAP patients with ARDS (844.5 [499.5—1409.3] pg/mL *vs* 506.0 [355.0—1020.0] pg/mL, $P = 0.024$) or DIC (833.0 [623.0—2145.3] pg/mL *vs* 503.0 [230.5—1097.5] pg/mL, $P = 0.001$) (Fig. 3).

Performance of various parameters for predicting ARDS, DIC, SCAP, and 28-day mortality

The AUCs of Presepsin, PCT, leukocyte, lactate, and CURB65 score for predicting ARDS, DIC, SCAP, and 28-day mortality in CAP patients are demonstrated in Table 2. AUCs of Presepsin for predicting ARDS, DIC, SCAP, and 28-day mortality were 0.684, 0.658, 0.679, and 0.672, respectively; AUCs of CURB65 were 0.824, 0.570, 0.903, and 0.703, respectively; AUCs of Presepsin in combination with CURB65 were 0.847, 0.916, and 0.731 for predicting ARDS, SCAP, and 28-day mortality, respectively, and these AUCs were greater than those of Presepsin alone or CURB65 score alone (all $P < 0.01$). The AUCs of Presepsin were significantly higher than those of leukocyte count or CURB65 score for predicting DIC (all $P < 0.01$), and there were no significant differences compared with PCT and lactate (all $P > 0.05$). The detailed results are presented in Table 2. The optimal cutoff value, sensitivity, specificity, PPV, NPV, LR+, and LR− on the basis of the ROC curves are presented in Table 3.

Independent predictors of ARDS, DIC, SCAP, and 28-day mortality

Sex, age, Presepsin level, PCT level, leukocyte count, lactate level, and CURB65 score were included in a binary logistic regression model to determine the independent predictors of ARDS, DIC, SCAP, and 28-day mortality. CURB65, lactate level, and age were found to be independent predictors of ARDS. Presepsin level, lactate level, and age were

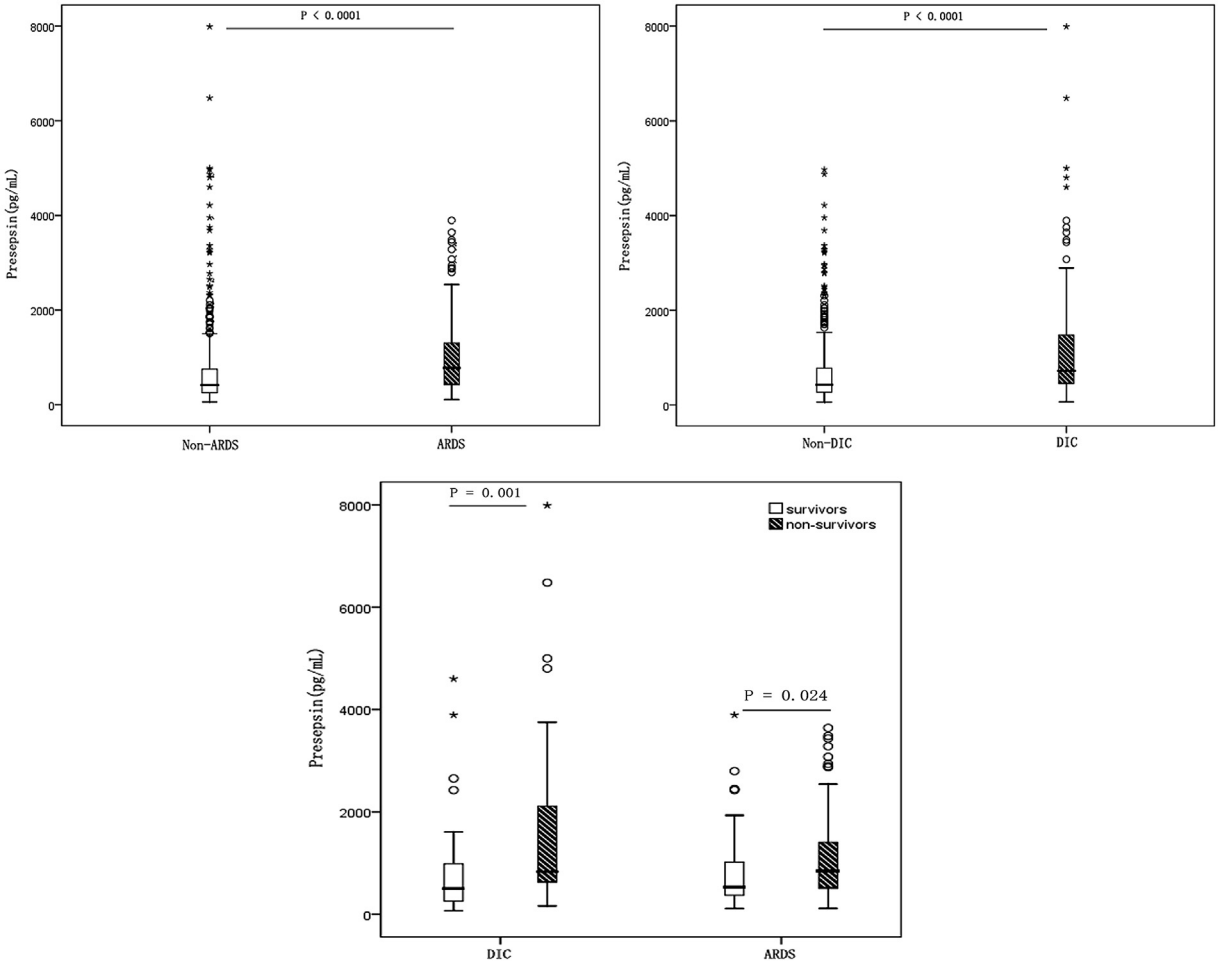

Figure 3 Plasma Presepsin levels in patients with ARDS and non-ARDS, and with and without DIC, survivors and non-survivors at the 28-day follow-up with ARDS or DIC. Lines denote median values, boxes represent 25—75th percentiles and whiskers indicate the range.

Table 2 AUCs of various parameters for predicting ARDS, DIC, SCAP and 28-day mortality.

	Variable	AUC	SE	*P*-value	95% CI	
					Lower limit	Upper limit
ARDS	Presepsin	0.684	0.026	0	0.632	0.735
	PCT	0.699	0.025	0	0.649	0.748
	Leukocyte	0.531	0.031	0.292	0.470	0.592
	Lactate	0.714	0.027	0	0.660	0.768
	CURB65	0.824	0.019	0	0.787	0.862
	Presepsin + CURB65	0.847*	0.017	0	0.813	0.881
DIC	Presepsin	0.658#	0.033	0	0.593	0.724
	PCT	0.645	0.034	0	0.579	0.710
	Leukocyte	0.488	0.037	0.711	0.415	0.560
	Lactate	0.669	0.034	0	0.603	0.735
	CURB65	0.570	0.033	0.036	0.505	0.634
	Presepsin + CURB65	0.648※	0.034	0	0.581	0.715
SCAP	Presepsin	0.679	0.023	0	0.634	0.724
	PCT	0.665	0.023	0	0.619	0.710
	Leukocyte	0.575	0.026	0.003	0.525	0.625
	Lactate	0.695	0.024	0	0.649	0.741
	CURB65	0.903	0.013	0	0.877	0.928
	Presepsin + CURB65	0.916*	0.012	0	0.894	0.939
28-day mortality	Presepsin	0.672	0.024	0	0.026	0.719
	PCT	0.683	0.023	0	0.637	0.729
	Leukocyte	0.581	0.026	0.001	0.530	0.632
	Lactate	0.703	0.023	0	0.657	0.748
	CURB65	0.703	0.022	0	0.659	0.747
	Presepsin + CURB65	0.735*	0.021	0	0.689	0.773

*compared with Presepsin or CURB65, all $P < 0.01$; #compared with Leukocyte or CURB65, all $P < 0.01$; ※compared with CURB65, $P < 0.01$; AUC: areas under the receiver operating curve; SE: Standard Error; CI: Confidence Interval. PCT: procalcitonin; CURB65: confusion, urea >7 mmol/L, respitatory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mm Hg, and age ≥65 years.

Table 3 Performance characteristics of multivariable in predicting ARDS, DIC, SCAP and 28-day mortality.

	Variable	Cutoff values	Sensitivity	Specificity	PPV	NPV	LR+	LR-
ARDS	Presepsin	468.5 pg/mL	72.6%	57.8%	32.4%	88.4%	1.72	0.47
	PCT	1.21 ng/mL	60.8%	70.8%	36.7%	86.6%	2.08	0.55
	Leukocyte	12.515 × 10^9/L	52.0%	58.9%	26.1%	81.5%	1.27	0.81
	Lactate	2.55 mmol/L	67.2%	71.7%	39.8%	88.7%	2.37	0.46
	CURB65	3.5 scores	65.6%	84.8%	54.7%	89.8%	4.32	0.41
DIC	Presepsin	591.5 pg/mL	64.0%	65.5%	25.6%	90.8%	1.86	0.55
	PCT	1.285 ng/mL	57.3%	69.0%	25.4%	89.8%	1.85	0.62
	Leukocyte	22.61 × 10^9/L	13.5%	93.6%	27.9%	85.5%	2.11	0.92
	Lactate	2.85 mmol/L	59.6%	73.1%	29.0%	90.8%	2.22	0.55
	CURB65	3.5 scores	33.7%	75.2%	20.0%	86.1%	1.36	0.88
SCAP	Presepsin	498.5 pg/mL	63.4%	64.4%	51.5%	74.7%	1.78	0.57
	PCT	1.125 ng/mL	53.7%	72.7%	54.0%	72.5%	1.97	0.64
	Leukocyte	12.515 × 10^9/L	53.3%	62.4%	45.8%	69.1%	1.42	0.75
	Lactate	2.65 mmol/L	56.1%	78.3%	60.6%	74.9%	2.59	0.56
	CURB65	3.5 scores	65.0%	96.9%	92.7%	82.3%	20.97	0.04
28-day mortality	Presepsin	556.0 pg/mL	60.2%	68.4%	50.0%	76.6%	1.91	0.58
	PCT	0.955 ng/mL	58.7%	71.1%	51.3%	76.8%	2.03	0.58
	Leukocyte	14.17 × 10^9/L	43.9%	71.6%	44.6%	71.1%	1.55	0.78
	Lactate	2.45 mmol/L	76.0%	66.3%	54.0%	84.2%	2.26	0.36
	CURB65	2.5 scores	77.6%	57.3%	48.6%	83.1%	1.82	0.39

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio, LR-: negative likelihood ratio. PCT: procalcitonin; CURB65: confusion, urea >7 mmol/L, respiratory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mm Hg, and age ≥65 years.

Table 4 Independent factors predicting ARDS, DIC, SCAP and 28-day mortality.

	Variable	B	SE	Wald	df	*P*-value	OR	95% CI	
								Lower limit	Upper limit
ARDS	Presepsin	0	0	0.140	1	0.708	1.000	1.000	1.000
	PCT	0.003	0.004	0.683	1	0.409	1.003	0.995	1.012
	Leukocyte	−0.018	0.014	1.691	1	0.193	0.982	0.955	1.009
	Lactate	0.115	0.035	10.719	1	0.001	1.122	1.047	1.202
	CURB65	1.136	0.142	84.049	1	0.000	3.691	2.792	4.879
	Sex	0.169	0.252	0.449	1	0.503	0.503	0.723	1.939
	Age	−0.026	0.011	5.607	1	0.018	0.018	0.954	0.996
	Constant	−3.850	0.817	22.188	1	0	0.021		
DIC	Presepsin	0	0	11.894	1	0.001	1.000	1.000	1.001
	PCT	0.006	0.004	3.098	1	0.078	1.006	0.999	1.014
	Leukocyte	0.005	0.008	0.311	1	0.577	1.005	0.989	1.021
	Lactate	0.087	0.032	7.324	1	0.007	1.091	1.024	1.162
	CURB65	0.196	0.117	2.819	1	0.093	1.217	0.968	1.531
	Sex	0.151	0.258	0.344	1	0.557	1.163	0.702	1.928
	Age	−0.025	0.009	6.756	1	0.009	0.976	0.958	0.994
	Constant	−1.517	0.618	6.020	1	0.014	0.219		
SCAP	Presepsin	0	0	0.255	1	0.614	1.000	1.000	1.000
	PCT	0.009	0.005	3.235	1	0.072	1.009	0.999	1.020
	Leukocyte	−0.001	0.015	0.006	1	0.936	0.999	0.970	1.028
	Lactate	0.204	0.048	18.125	1	0.000	1.226	1.116	1.346
	CURB65	2.421	0.220	121.098	1	0.000	11.255	7.313	17.322
	Sex	0.540	0.281	3.690	1	0.055	1.715	0.989	2.975
	Age	−0.025	0.013	3.667	1	0.056	0.976	0.951	1.001
	Constant	−7.015	1.048	44.810	1	0	0.001		
28-day mortality	Presepsin	0	0	7.602	1	0.006	1.000	1.000	1.001
	PCT	0.007	0.004	3.345	1	0.067	1.007	0.999	1.015
	Leukocyte	0.022	0.014	2.583	1	0.108	1.022	0.995	1.049
	Lactate	0.056	0.031	3.348	1	0.067	1.058	0.996	1.123
	CURB65	0.531	0.097	30.147	1	0.000	1.701	1.407	2.056
	Sex	−0.154	0.199	0.603	1	0.437	0.857	0.580	1.265
	Age	0	0.008	0	1	0.988	1.000	0.984	1.017
	Constant	−2.851	0.612	21.719	1	0	0.058		

SE: Standard Error; OR: Odds ratio; CI: Confidence Interval. PCT: procalcitonin; CURB65: confusion, urea>7 mmol/L, respiratory rate ≥30 breaths per minute, systolic pressure <90 mm Hg or diastolic pressure ≤60 mm Hg, and age ≥65 years.

independent predictors of DIC. CURB65 and lactate level were independent predictors of SCAP. Presepsin and CURB65 were independent predictors of 28-day mortality. The detailed results are presented in Table 4.

Correlation of Presepsin with PCT, leukocyte, lactate, and CURB65 score

A Spearman analysis of the correlation of Presepsin level with PCT level, leukocyte count, lactate level, and CURB65 score found that the correlation coefficients of Presepsin were 0.444, 0.163, 0.339, and 0.301, respectively (all $P < 0.01$), which suggested significant positive correlations.

Comparison of survival rate in patients above or below the Presepsin cutoff for predicting 28-day mortality in CAP patients

To demonstrate the capacity of Presepsin for risk stratification in CAP patients, a comparison of survival using Kaplan–Meier survival curves was performed. CAP patients with plasma Presepsin levels above the cutoff (556.0 pg/mL) had significantly lower survival rates compared with patients with levels below this cutoff (50.0% *vs* 76.6%; $P < 0.0001$) (Fig. 4).

Discussion

This study demonstrated that plasma Presepsin levels were markedly different in CAP and SCAP patients, and were significantly higher in SCAP patients than in CAP patients at ED admission. In addition, plasma Presepsin levels increased with an increase in CURB65 score, and reached the highest levels in CAP patients with a CURB65 score ≥3. Additionally, in CAP and SCAP patients, there were significantly higher plasma Presepsin levels in non-survivors than in survivors. The present study suggested that the contribution of plasma Presepsin levels to the evaluation of CAP patients varied according to severity of CAP, and was a good parameter for reflecting the severity and prognosis of CAP patients.

Taking into account the importance of CAP in terms of morbidity and mortality, early identification of patients at

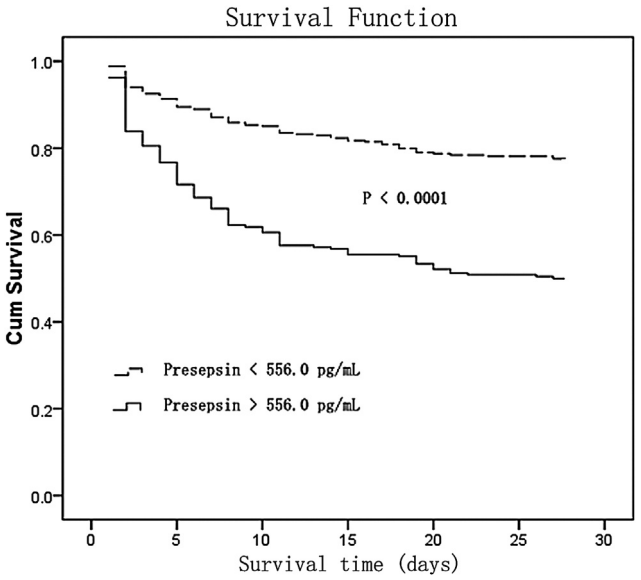

Figure 4 Kaplan—Meier curves for Presepsin in CAP patients at the 28-day follow-up. Solid lines represent non-survivors, and dashed lines represent survivors.

high risk is a key point in improving outcome. To the best of our knowledge, this is the first study to assess the usefulness of plasma Presepsin levels for CAP complications. The ARDS, the more severe form of acute lung injury (ALI), is one of the most serious complications of CAP. In the United States, ALI and ARDS affect 150,000—200,000 patients per year, resulting in a burden of 3.6 million hospital days per year and a mortality rate of 30—40% [17,18]. Furthermore, early prediction and timely intervention for ARDS are crucial for improving prognosis in CAP patients. Previous studies on biomarkers have demonstrated that specific biomarkers were associated with increased disease severity and poorer clinical outcomes in patients with ALI/ARDS [19,20]. sCD14, a new infection-related biomarker, is present in the circulation and other body fluids, and levels of sCD14 in plasma increase during inflammation and infection [21]. Martin et al. [22] found that sCD14 levels were markedly increased in bronchoalveolar lavage (BAL) fluid from patients with ARDS, and concluded that sCD14 contributed to the inflammatory process in the lung. In the present study, we found that plasma Presepsin (sCD14-ST) levels were significantly higher in CAP patients with ARDS than in those without ARDS, which was in line with the previous study of BAL fluid in ARDS patients. Additionally, we also found that there were significantly higher plasma Presepsin levels in non-survivors than in survivors with ARDS. Taken together, the plasma Presepsin level was closely associated with the incidence of ARDS in CAP patients, and was a good parameter to reflect 28-day mortality in these patients.

Coagulation abnormalities are frequent in patients with severe infections. DIC is characterized by widespread activated coagulation and suppression of fibrinolysis, resulting in intravascular fibrin formation and thrombotic occlusion of microvessels [23—26]. It is now accepted that DIC can originate from and cause damage to the microvasculature, which can produce organ dysfunction if sufficiently severe, and that DIC reflects an inflammatory disorder of the microvasculature [24]. Therefore, earlier diagnosis and treatment of DIC would contribute to a better outcome in patients with this disorder [27]. Similarly, the present study also indicated that plasma Presepsin levels were significantly higher in DIC patients than in non-DIC patients, and there were significantly higher plasma Presepsin levels in non-survivors compared with survivors, suggesting plasma Presepsin levels were a better predictor of DIC in CAP patients, and higher plasma Presepsin levels indicated an adverse medical outcome.

Previous studies have proposed that ALI and ARDS are closely linked to systemic activation of inflammation and coagulation, and that simultaneous activation of inflammation and coagulation occur in the early stage of ALI and ARDS [28,29]. In our study, ARDS or DIC was confirmed at ED admission, and plasma Presepsin levels were elevated in ARDS and DIC patients at the same time, thus plasma Presepsin levels reflected the early pathophysiological condition of ARDS and DIC patients.

Accurate, objective models of prognosis for CAP could help physicians assess patient risk and improve the decisions about hospitalization [2]. Recent interest has focused on scoring systems in combination with biomarkers for assessment of severity and evaluation of prognosis of CAP patients. The CURB65 scoring system, a simplified assessment tool developed by the British Thoracic Society, focuses on only five predictors, and is easier to remember and apply [4,30]. To improve the predictive accuracy of clinical severity scores, some biomarkers have been proposed to provide more detailed and complementary information. Previous studies have confirmed that precursor levels of adrenomedullin, endothelin-1, atrial natriuretic peptide, antidiuretic hormone, and PCT levels on admission and during follow-up showed high prognostic accuracy for mortality and serious complications in CAP patients [31], but to date, Presepsin has not been investigated as a factor for prediction of adverse medical events and complica tions.

The current study had several strengths. First, the CURB65 score had high specificity (84.8%) and NPV (89.8%), and was an independent predictor of ARDS. Although Presepsin was not an independent predictor of ARDS, the Presepsin level significantly increased the AUC of the CURB65 score for predicting ARDS. Presepsin had a high NPV (88.4%), and simultaneously displayed a positive correlation with CURB65 score. Thus, the CURB65 score in combination with Presepsin significantly improved the accuracy of predicting ARDS, and lower than the cutoffs of 468.5 pg/mL for Presepsin and 3.5 scores for CURB65 may help rule out the possibility of ARDS. Similarly, the CURB65 score demonstrated high specificity (96.9%) and PPV (92.7%) for predicting SCAP. Presepsin also significantly increased with CURB65 score, and enhanced the accuracy of the CURB65 score in predicting SCAP, and higher than the cutoffs of 498.5 pg/mL for Presepsin and 3.5 scores for CURB65 may help predict the possibility of SCAP. Second, in this study, we also found that Presepsin had a high NPV (90.8%) and was an independent predictor of DIC, but Presepsin in conjunction with CURB65 score did not increase the AUC. This indicated that Presepsin

alone may predict DIC, with levels lower than a cutoff of 591.5 pg/mL possibly ruling out the possibility of DIC. Third, we further found that although the AUCs of Presepsin and CURB65 score were a little low for predicting 28-day mortality (0.672 and 0.703, respectively), Presepsin in conjunction with CURB65 score markedly increased the AUC (0.735). In addition, multivariable regression analysis found that both were independent predictors of 28-day mortality, and Presepsin in conjunction with CURB65 score significantly elevated the predictive accuracy. Kaplan—Meier survival curves demonstrated that CAP patients with plasma Presepsin levels above a cutoff of 556.0 pg/mL had significantly lower survival rates compared with patients with levels below this cutoff. Thus, lower than the cutoffs of 556.0 pg/mL for Presepsin and 2.5 scores for CURB65 may exclude the possibility of death. Fourth, we found that although AUCs of lactate for predicting ARDS, DIC, SCAP, and 28-day mortality in CAP patients were slightly higher than that of Presepsin, there were no significant differences. Additionally, our present study found that blood lactate was also a better predictor of mortality in CAP patients, which was in line with previous studies [32—34]. Presepsin levels were positively correlated with lactate levels, further validating Presepsin as a biomarker reflecting prognosis in CAP patients.

Limitations

There were some limitations in our study. First, our study was a single-center study, so the results may not be applicable to other EDs. Second, CAP patients were mainly enrolled from the critical care unit of the ED, and suffered from multiple chronic diseases, so had high mortality (CAP group 22%, SCAP group 54.7%), and hence may not represent the overall population of CAP patients. Third, only plasma Presepsin levels at ED enrollment were measured, and the dynamic changes of Presepsin were unknown. Fourth, it was difficult to obtain pathogen samples in an ED setting, so there was a lack of etiological evidence of CAP. For this reason, a multicenter clinical study including etiology will be needed to further investigate the serial changes in Presepsin levels in CAP patients.

Conclusion

The present study suggests that Presepsin is a promising biomarker for reflecting the severity of CAP. Presepsin has predictive value for predicting ARDS, DIC, SCAP, and 28-day mortality, and is an independent predictor of DIC and 28-day mortality in CAP patients. Presepsin in combination with CURB65 score may improve the predictive accuracy for ARDS, SCAP, and 28-day mortality. Presepsin is a valuable biomarker in predicting severity and outcome in CAP patients in the ED.

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Authors' contributions

Chun-Sheng Li designed the study and obtained research funding. Bo Liu, Qin Yin, Yun-Xia Chen, and Yun-Zhou Zhao conducted the study and collected the data. Bo Liu analyzed the data, performed the statistical analysis, and drafted and revised the manuscript. Chun-Sheng Li takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

Competing interests

The authors declare they have no competing interests.

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