A Prospective Study of Presepsin as an Indicator of the Severity of Community-Acquired Pneumonia in Emergency Departments: Comparison with Pneumonia Severity Index and CURB-65 Scores

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ABSTRACT

Despite widely used severity indices such as the pneumonia severity index (PSI) and CURB-65, a rapid, easy-to-detect biological marker is required for assessment of community-acquired pneumonia (CAP) severity. We aimed to investigate the ability of presepsin to differentiate between high- and low-risk patients, categorized according to PSI and CURB-65 scores. This prospective study was performed in an emergency department (ED) with 90 CAP patients. Whole blood presepsin levels were measured with a point-of-care test instrument. Using PSI and CURB-65 scores, we classified patients into outpatient (low-score group of PSI and CURB-65) and inpatient (high-score group of PSI and CURB-65) management groups. Presepsin levels were significantly higher in CAP patients with the high-score groups compared to the corresponding low-score groups. Presepsin correlated well with low- and high-score PSI (ROC AUC: presepsin, 0.726; PCT, 0.614; CRP, 0.544) and CURB-65 groups (ROC AUC: presepsin, 0.669; PCT, 0.645; CRP, 0.602). Presepsin is a valuable biomarker for assessing and classifying CAP severity.

Keywords: presepsin, soluble CD14 subtype, community-acquired pneumonia, pneumonia severity index, CURB-65

Soluble cluster of differentiation (CD)14 subtype (sCD14-ST; 64 amino acids, 13 kDa), or *presepsin*, is a small soluble peptide generated from soluble CD14 released in response to bacterial infection. Presepsin is known to function as a regulatory factor that can modulate immune responses by interacting with T and B cells.[1] Currently, the results of many clinical studies[2-5] have indicated that presepsin is a promising novel marker used for early diagnosis, risk stratification, prognosis prediction, and monitoring of response to antibiotic therapies for sepsis. The results of many other studies[3,6-8] have confirmed that increased presepsin levels in patients with sepsis correlate well with the severity of the disease—even better than well-known infectious markers such as procalcitonin (PCT).

Community-acquired pneumonia (CAP), an infectious and potentially serious illness, is commonly treated at emergency departments (EDs) and is the leading cause of death from infectious disease. CAP, which has a high prevalence in patients receiving treatment in the intensive-care unit (ICU), has a reported inpatient mortality rate of 5.7% to 14.0%.[9,10] Immediate and accurate assessment of disease severity is critical in patients with CAP, particularly in EDs, because doing so enables clinicians to rapidly select optimal management options, such as admission or outpatient discharge, and the extent of evaluation. It is important to

Abbreviations

CD, cluster of differentiation; sCD14-ST, cluster of differentiation 14 subtype; PCT, procalcitonin; CAP, community-acquired pneumonia; EDs, emergency departments; ICU, intensive-care unit; PSI, Pneumonia Severity Index; CURB-65, confusion of new onset (defined as an Abbreviated Mental Test Score of ≤8), blood urea nitrogen level > 7 mmol/L (19 mg/dL), respiratory rate of ≥ 30 breaths/minute, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, age 65 years or older; CBC, complete blood count; EDTA, ethylenediaminetetraacetate; POC, point-of-care; CRP, C-reactive protein; ROC, receiver operating characteristic; AUCs, areas under the curves; SPSS, Statistical Program for the Social Sciences; WBC, white blood cells; eGFR, estimated glomerular filtration rate; OR, odds ratio

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ensure that patients get the appropriate level of treatment because overtreatment can cause unnecessary complications, whereas undertreatment can cause prolonged pain.

The Pneumonia Severity Index (PSI) and CURB-65 (**c**onfusion of new onset [defined as an Abbreviated Mental Test Score of 8 or less], **b**lood urea nitrogen level > 7 mmol/L (19 mg/dL), **r**espiratory rate of ≥ 30 breaths/minute, **b**lood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, age **65** years or older) are the most widely used severity indices for assessment of CAP. The PSI was introduced in 1997 and uses 20 variables to calculate a patient score, which is used to classify patients into 5 risk groups (I–V) on the basis of 30-day mortality rates; patients are further classified into 2 treatment groups: low risk, outpatient treatment group I–II; high risk, inpatient treatment group III–V.[11]

Although the PSI has been widely adopted, it evaluates too many variables to be useful in an emergency situation. To overcome this limitation of the PSI, the British Thoracic Society introduced CURB-65, an alternative scoring system, which was subsequently modified by Lim and colleagues[10] in 2003. CURB-65 is much simpler to use than PSI because it uses only 5 variables (1 point each) to classify patients into 2 treatment groups: low risk, outpatient treatment group, score 0–1; high risk, inpatient treatment group, score 3–5.[12] The use of CURB-65 is now widely recommended because it predicts mortality in patients with CAP as accurately as the complex PSI index does.[10] Although both indices can identify patients at low or high risk of death, who may be suitable for outpatient or inpatient treatment, respectively, additional biological markers that can be rapidly and easily measured are required to differentiate patients with different risks in emergency situations. Therefore, the aim of this study was to investigate the ability of presepsin to differentiate between patients at high-risk and low-risk of CAP in an ED setting, categorized according to PSI and CURB-65 scores.

Materials and Methods

Study Population

This prospective observational study was conducted in an ED of Kyungpook National University Hospital, Daegu, South Korea, from July 2015 through January 2016. The study population consisted of adult patients with suspected CAP on arrival at the ED. Finally, 90 patients with confirmed CAP were enrolled—61 men and 29 women. CAP was defined as the presence of new infiltrations on a chest radiographic image with at least 1 of the following signs and symptoms: cough, sputum production, dyspnea, core body temperature higher than 38.0°C, auscultatory findings of abnormal breath sounds, and rales.[13] We calculated PSI and CURB-65 scores for the risk assessment of CAP, primarily to differentiate between outpatient (low-score group: PSI class I–II, CURB-65 score 0–1) and inpatient (high-score group: PSI class III–V, CURB-65 score 2–5) management.

All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Measurement Methods

For presepsin level and complete blood count (CBC) measurements, we collected venous blood specimens in ethylenediaminetetraacetate (EDTA)–containing tubes and mixed the contents gently. Presepsin was immediately measured in whole-blood specimens by using a point-of-care (POC) test instrument (PATHFAST, Mitsubishi Chemical Medience Corporation), based on the principle of noncompetitive chemiluminescence enzyme immunoassay, which operates continuously for 24 hours. Presepsin and CBC measurements were performed separately using each whole-blood specimen because a previous report[14] indicated potential cross-interference due to the strength of mixing methods. Also, other serum specimens were obtained for measurement of the widely used infection markers C-reactive protein (CRP) and PCT.

Statistical Analysis

We used the Kolmogorov–Smirnov test to assess the normality of distribution of the investigated parameters. Continuous variables are expressed as median (interquartile range) for non-normally distributed data. Group differences for continuous variables were evaluated using the Mann-Whitney *U* test. To assess the differences in biomarker levels between different groups, we performed independent

t tests. The receiver operating characteristic (ROC) curve and areas under the curves (AUCs) were analyzed for PSI and CURB-65 groups using presepsin and PCT measurements, to assess the differentiation power between the 2 patient groups. Multivariable analysis with stepwise logistic regression was used to identify independent predictors of increased presepsin levels. $P < .05$ was regarded as statistically significant. All the statistical analyses were performed by using Statistical Program for the Social Sciences (SPSS) software, version 20.0 (SPSS Inc) and Analyze-It software, version 4.80 (Analyze-It Software Ltd).

Results

Baseline Characteristics and Between-Group Comparisons

A comparison of several variables between the low- and high-score groups according to PSI and CURB-65 indices revealed that presepsin was a superior marker to differentiate between the 2 different management groups (**Table 1**). White-blood-cell (WBC) counts, platelet counts, and CRP levels were not significantly different between the patients within each group. When comparing biological markers between the 2 PSI-based groups, only presepsin levels were significantly different, with presepsin levels being significantly higher in the high-score group than in the low-score group. When comparing biological markers between the 2 CURB-65–based groups, PCT and presepsin levels were significantly higher among the 2 scoring groups. In both cases, we discovered that PSI and CURB-65 scores were correlated with each other.

Discriminating Power of Presepsin between the 2 Groups

In the results of our ROC analysis, presepsin was the most informative biomarker for the identification of outpatient and inpatient groups, correlating well with low and high PSI (ROC AUC: presepsin, 0.726; PCT, 0.614; CRP, 0.544) and CURB-65 groups (ROC AUC: presepsin, 0.669; PCT, 0.645; CRP, 0.602) (**Figures 1A** and **1B**). PCT levels were not significantly different between the 2 PSI groups; however, they were significantly different between the 2 CURB-65 groups (**Figures 2A** and **2B**). Presepsin levels were significantly different between the 2 groups for PSI- and CURB-65–based classification (**Figures 2C** and **2D**).

The Differences of Age and Estimated Glomerular Filtration Rate [eGFR] between the 2 Groups

The results of multivariate analysis indicated that neither older age (odds ratio [OR], 1.031, $P = .09$) nor lower eGFR (OR, 0.987, $P = .17$) were independent predictors of an increase in presepsin.

Discussion

In the present study, we compared the performance of presepsin with that of classical severity indices, for the immediate risk classification of patients with CAP, and with the performance of classical biological markers such as CRP and PCT.

Among potential markers, CRP, one of the acute-phase proteins synthesized by the liver, is known to have good sensitivity but low specificity for detecting infection. PCT is a much more specific marker for infection and is better correlated with infection progression than CRP is. However, because PCT levels are increased not only by infection but also in other conditions like major surgical procedures, trauma, and burns, it has a high false-positivity rate. Presepsin has recently emerged as a promising marker to overcome these disadvantages of PCT; presepsin levels correlate well with infectious-disease progression.

In the results of a previous study,[1] presepsin levels were shown to increase earlier than CRP or PCT levels did, peaking at 3 hours and remaining elevated for at least 5 hours; therefore, presepsin can be used as an early marker for the detection of infectious diseases. Also, presepsin can be measured easily using a whole-blood specimen, without additional procedures such as centrifugation to obtain serum specimens, and with a fully automated POC instrument that can operate continuously for 24 hours. The results are obtained within 17 minutes, which is essential for clinicians in EDs, where rapid test results are critical.

As previously reported,[6] the degree of increase in presepsin levels is proportional to the severity of infection. In another

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Table 1. Baseline Characteristics of Patients in the 2 Risk Groups According to PSI and CURB-65 Indices[a]

Variable	PSI Low-Score Group (PSI Class I–II) (*n* = 34)	PSI High-Score Group (PSI Class III–V) (*n* = 56)	*P* Value	CURB-65 Low-Score Group (CURB-65 Score 0–1) (*n* = 63)	CURB-65 High-Score Group (CURB-65 Score 2–5) (*n* = 27)	*P* Value
Age, y	56 (40–65)	78 (72–82)	<.001	66 (51–76)	80 (75–83)	<.001
CURB-65/PSI	0 (0–1)	1 (1–2)	<.001	0 (0–1)	1 (1–2)	<.001
WBCs (×10^3/μL)	12,305 (10,200–16,161)	10,770 (7897–15,768)	.32	11,020 (8242–15,048)	12,700 (9180–19,855)	.16
Platelet (× 10^3/μL)	264.5 (208.3–327.7)	243.5 (189.0–332.2)	.24	246.0 (195.8–316.7)	253.0 (214.5–349.0)	.43
Presepsin (ng/L)	382.5 (251.5–598.0)	655.0 (437.7–1160.2)	.001	458.0 (265.3–766.7)	658.0 (487.8–1227.3)	.01
CRP (mg/dL)	12.3 (6.1–17.5)	12.7 (7.0–21.8)	.49	10.9 (5.5–18.3)	13.6 (8.1–23.7)	.13
PCT (ng/mL)	0.11 (0.10–0.64)	0.41 (0.10–1.50)	.06	0.16 (0.10–0.64)	0.44 (0.11–2.00)	.03
eGFR (mL/min)	95.54 (84.35–117.69)	65.93 (53.98–80.18)	<.001	86.12 (69.59–106.20)	55.79 (42.43–74.48)	<.001

Abbreviations: PSI, pneumonia severity index; CURB-65, confusion of new onset (defined as an Abbreviated Mental Test Score of ≤8), blood urea nitrogen level > 7 mmol/L (19 mg/dL), respiratory rate of ≥ 30 breaths, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, age 65 y or older; WBCs, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; eGFR, estimated glomerular filtration rate.
[a]*Data are presented as median (interquartile range).*

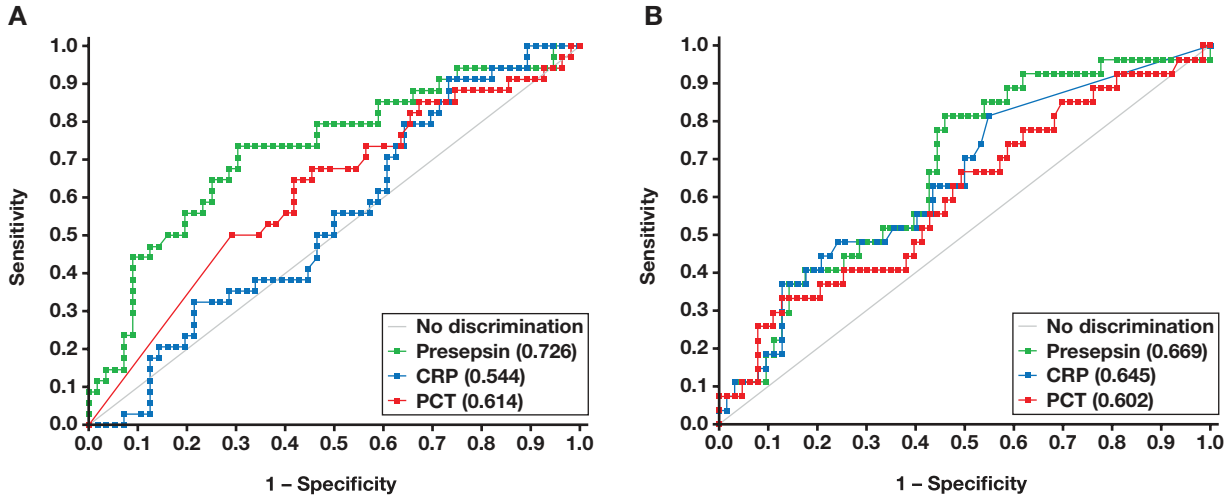

Figure 1

Receiver operating characteristic (ROC) curve and the corresponding areas under the curves (AUCs) of presepsin, procalcitonin (PCT), and C-reactive protein (CRP) for the discrimination of the 2 risk groups according to the Pneumonia Severity Index (PSI) (**A**) and according to the CURB-65 (confusion of new onset [defined as an Abbreviated Mental Test Score of ≤8], blood urea nitrogen level > 7 mmol/L [19 mg/dL], respiratory rate of ≥30 breaths/min, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, age 65 y or older) index (**B**). The analysis revealed that, compared with PCT and CRP, presepsin was a superior marker for differentiation between the 2 risk groups.

report, presepsin levels were an independent predictor of severity, and when combined with the usual severity scoring systems, presepsin levels improved their ability to detect more-severe disease status and mortality, including in patients with CAP.[8,15] In the results of another study,[16] presepsin and PCT were significantly higher in patients with sepsis than those without sepsis, but the diagnostic accuracy of presepsin was not superior to that of PCT (AUC, 0.75 vs 0.80). However, the capability of presepsin to diagnose severe CAP was significantly better than that of PCT, and presepsin levels were predictive of ICU mortality in sepsis and in patients with severe CAP. The present study confirmed these results by revealing the correlation between severe CAP and significantly increased presepsin values.

The results of a French study[17] suggested that presepsin levels could increase with age, especially after age 70 years. Also, because presepsin is filtered by the glomerulus and

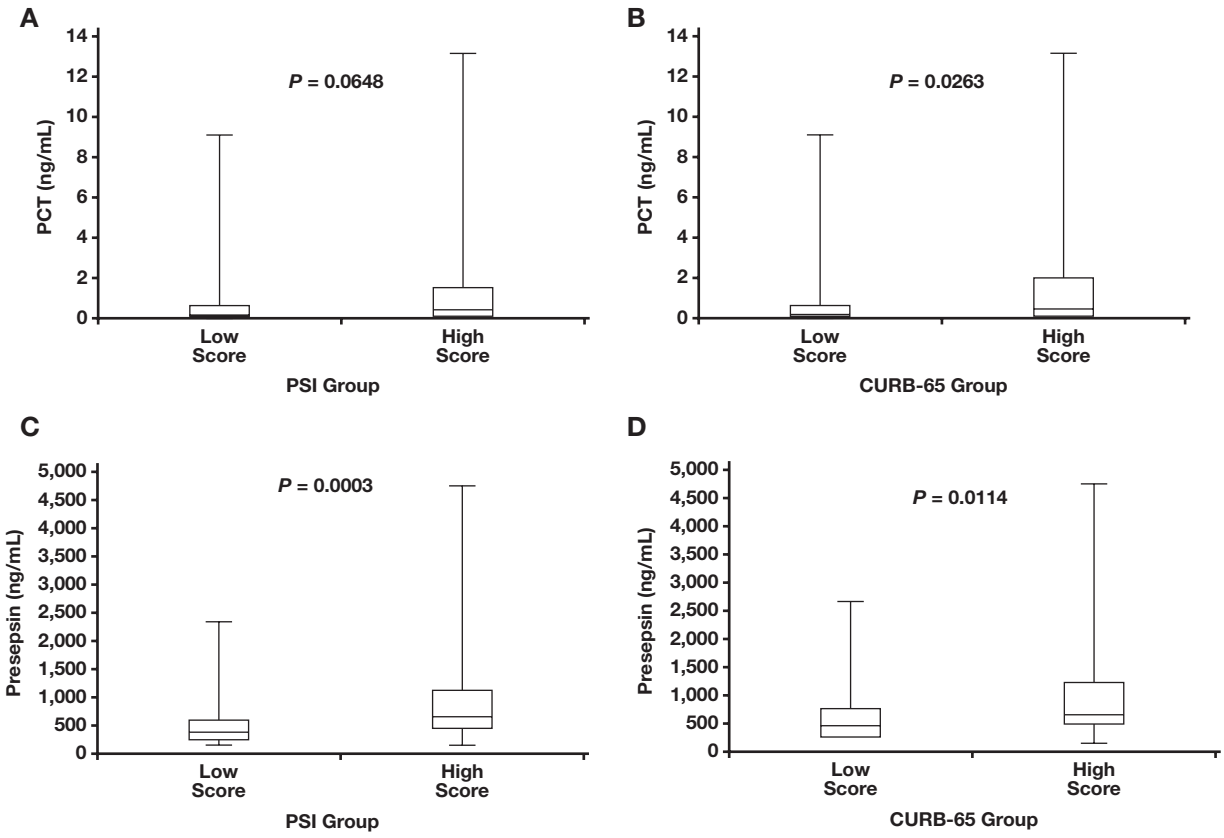

Figure 2

Procalcitonin (PCT) and presepsin levels according to the 2 studied indices. **A**, PCT levels according to the Pneumonia Severity Index (PSI) risk groups. **B**, PCT levels according to the CURB-65 (confusion of new onset [defined as an Abbreviated Mental Test Score of ≤8], blood urea nitrogen level > 7 mmol/L [19 mg/dL], respiratory rate of ≥30 breaths/min, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, age 65 y or older) risk groups. **C**, Presepsin levels according to the PSI groups. **D**, Presepsin levels according to the CURB-65 risk groups.

mostly is reabsorbed by the proximal tubules, kidney dysfunction (defined as eGFR <60 mL/min/1.73 m^2) can increase presepsin levels in the absence of any infectious focus or acute illness. In the present study, patient age and eGFR were significantly different between the low-score group and the high-score group, according to PSI and CURB-65 (**Table 1**), and Spearman correlation results showed significant coefficient *r* values of 0.247 and –0.257 for each factor. However, measuring cystatin C is optimal for the calculation of eGFR in older patients because the classical formulas for eGFR do not yield accurate results in this population.[18] Moreover, our multivariate analysis indicated that neither older age nor lower eGFR were independent predictors of an increase in presepsin, whereas the results of a previous study[17] revealed that only age and not eGFR was an independent predictor on logistic regression analysis. Therefore, significant differences in the presepsin levels between the 2 groups according to the 2 studied severity indices were unlikely to occur due to those factors. Although larger controlled studies are needed to identify the variability of presepsin levels due to such factors, our data indicate that patient age and kidney function should be considered when interpreting presepsin levels.

Conclusions

Presepsin levels were significantly different in 2 severity groups according to PSI and CURB-65 indices. Thus, presepsin could be a valuable biomarker for the rapid

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prediction of CAP severity in patients, with better performance than previously used biomarkers, such as PCT. Further, its rapidity and simplicity of measurement make presepsin a useful marker to enable effective and rapid decision-making for early goal-oriented therapies in EDs. **LM**

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