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The usefulness of serum procalcitonin, C-reactive protein, soluble triggering receptor expressed on myeloid cells 1 and Clinical Pulmonary Infection Score for evaluation of severity and prognosis of community-acquired pneumonia in elderly patients

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ABSTRACT

Aims: To comparatively analyze the usefulness of serum procalcitonin (PCT), C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) and Clinical Pulmonary Infection Score (CPIS) for assessing the severity and prognosis of community-acquired pneumonia (CAP) in the elderly.

Methods: A total of 214 elderly patients with CAP and 106 healthy persons were enrolled in this prospective study. On the admission day, serum inflammatory markers, including CRP, PCT, sTREM-1, and CPIS were analyzed. By severity, the CAP patients were subdivided into non-severe CAP group and severe CAP group. By outcome, the patients were classified into survival group and death group. The efficiency of three inflammatory markers and CPIS on predicting prognosis of pneumonia patients was then analyzed.

Results: The serum inflammatory markers and CPIS were significantly higher in CAP patients than in healthy controls. These biomarkers and CPIS were significantly higher in patients with severe CAP than in patients with non-severe CAP. Compared with patients who would survive, these markers and CPIS were significantly higher in patients who would die. Receiver operating characteristic curve analysis showed that the area under the curve and sensitivity were higher for serum sTREM-1 than for other indicators, while the specificity of serum PCT was the highest.

Conclusions: Serum CRP, PCT, and sTREM-1 and CPIS determined on the admission day are effective indicators to evaluate the severity and prognosis of CAP in the elderly. The prognostic value of PCT and sTREM-1 is better than that of CRP and CPIS.

1. Introduction

Community-acquired pneumonia (CAP) is a common disease among elderly population, with substantial morbidity and mortality (Faverio et al., 2014; Thiem, Heppner, & Pientka, 2011). Compared with the younger population (aged < 65 years), CAP in elderly patients (aged > 65 years) has a higher incidence, is always accompanied by comorbidities, and shows higher short- and long-term mortality (Klapdor et al., 2012). CAP is becoming an increasing public health problem among elderly people owing to their waning immunity, decreased mucociliary function, impaired gag reflex, and various degrees of cardiopulmonary dysfunction (Fernández-Sabé et al., 2003; Kaplan & Angus, 2003). Due to the atypical clinical presentation, different epidemiology, and age-related modifications in drug metabolism, CAP in the elderly represents a major challenge for physicians (Petrosillo, Cataldo, & Pea, 2015). In addition, incorrect evaluation of CAP may cause a patient to miss the best treatment opportunity and can even influence the recovery and prognosis. Therefore, how to timely and accurately assess the progression and prognosis of CAP in elderly patients is of paramount importance.

In clinic, the commonly used indicators for assessment of the severity of CAP are confusion, respiratory rate, blood pressure, ≥65 years of age (CURB-65) and its modifications (CRB-65), and the pneumonia severity index (PSI) (Fine et al., 1997; Lim et al., 2003). Recently, the Clinical Pulmonary Infection Score (CPIS), composed of the severity of infiltrate, tracheal secretions, body temperature, chest x-ray infiltrates, oxygenation derangement, white blood cell response, and positivity of endotracheal aspirate cultures, has gained popularity for evaluating the prognosis of elderly patients with CAP (Han & Zhu, 2014; Zhou, Xing, Zhou, & Geriatrics, 2016). In addition, many biomarkers, such as a

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leukocyte count, albumin, procalcitonin (PCT), C-reactive protein (CRP), and soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) play crucial roles in the early diagnosis and prognosis of pneumonia, including CAP in elderly patients (Lee et al., 2011; Menendez & Martinez, 2009; Mira, 2008; Xie, Zhang, & Zhu, 2015). Nonetheless, the usefulness of CPIS and biomarkers for evaluation of the severity and prognosis has not been comparatively analyzed among elderly patients with CAP.

In this study, we compared CPIS and serum inflammatory markers, including CRP, PCT, and sTREM-1 between patients with non-severe CAP and patients with severe CAP, as well as between patients with different prognosis. Moreover, receiver operating characteristic (ROC) curve analysis was performed to verify the efficacy of CPIS and three inflammatory markers at assessing the prognosis of the patients with CAP. The aim of this study was to evaluate the utility of CRP, PCT, sTREM-1, and CPIS determined on the admission day for assessing the severity and prognosis of CAP in elderly patients.

2. Methods

2.1. Subjects

This prospective study enrolled 214 elderly patients with CAP (males 127, females 87, age: 65–94 years) who were hospitalized in the Fifth People's Hospital of Shanghai, Fudan University, between January 2015 and June 2016. Meanwhile, 106 healthy persons (males 59, females 47, age: 65–89 years) who underwent a physical examination during the same period were selected as a control group. CAP in the elderly patients was confirmed in accordance with the diagnostic criteria in "Guidelines for the diagnosis and treatment of CAP" issued by the respiratory branch of Chinese Medical Association in 2006 (He, 2006), as follows: the chest X-ray examination of patients showed patchy infiltrate shadows or an interstitial change, and the patients developed any of the following symptoms: 1) symptoms of the original respiratory diseases worsened or cough and sputum newly emerged, and purulent sputum presented with or without chest pain; 2) a fever; 3) signs of lung consolidation and (or) moist rales; 4) the white blood count (WBC) $> 10 \times 10^9$/L or $< 4 \times 10^9$/L, with or without a shift of nuclei to the left. On the admission day, elderly patients with CAP were subdivided into a severe CAP group and non-severe CAP group based on the 2007 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) guidelines for the management of CAP in adults. Severe pneumonia was diagnosed as follows: 1) disturbances of consciousness; 2) the breathing rate $\geq$30 times/min; 3) PaO2 < 60 mm Hg, PaO2/FiO2 < 300, and mechanical ventilation therapy is needed; 4) artery systolic blood pressure < 90 mm Hg; 5) concurrent septic shock; 6) X-ray imaging shows bilateral or greater lung dysfunction, or lung lesions $\geq$50% within 48 h of admission; 7) oliguria or simultaneous acute renal failure. Exclusion criteria for eligible patients were the following: 1) clinical symptoms improved significantly and lung lesions showed obvious absorption without antimicrobial therapy; 2) constant presence of severe heart, brain, kidney, vascular diseases, or a tumor; 3) autoimmune diseases; 4) concurrent infection at another site; 5) a history of special treatments within a month, such as radiation therapy, chemotherapy, surgery, biological therapy, or immunosuppressive therapy. This study's protocol was approved by the Ethics Committee of the Fifth People's Hospital of Shanghai, Fudan University and conforms to the provisions of the Declaration of Helsinki (as revised in Brazil 2013). All the patients or their relatives provided written informed consent.

2.2. Data collection

On the admission day, clinical characteristic details such as age, gender, and body temperature were noted. Routine blood examination, blood gas analysis, X-ray imaging, and CPIS analysis were performed within 24 h of admission. The serum PCT was detected by a semi-quantitative solid-phase immunoassay, serum CRP was quantified by an immunoturbidimetric method, and sTREM-1 was measured by a solid-phase ELISA.

2.3. Prognosis follow-up

To evaluate the prognosis (survival or death), follow-up was performed until a patients' discharge or death. The survival group meant that the symptoms such as cough, expectoration, fever, fatigue, and anorexia were controlled; the complications were corrected, pulmonary rales decreased, and the total number of WBCs remained normal or slightly elevated until the patients' discharge from the hospital. The death group meant that the symptoms, such as cough, expectoration, fever, fatigue, and anorexia were not controlled, resulting in severe complications, multiple organ failure, or death.

2.4. Statistical analysis

Statistical analysis was performed by means of the SPSS 18.0 software (SPSS Inc., Chicago, IL). Quantitative data with a normal distribution were presented as mean ± standard deviation (SD), and the differences between groups were analyzed by a *t* test. Quantitative data with a non-normal distribution were expressed as the median (quartile range), and the differences between groups were determined by the Wilcoxon W method. The outcome of prognosis was evaluated by the Chi-squared (χ^2) test. In addition, to calculate the sample power, the median (quartile range) of quantitative data with a non-normal distribution were transformed to mean ± SD according to the previous described (Yang, Wang, Du, Ji, & Zheng, 2014), and then power calculations for testing the sample size were conducted with Power analysis and sample size (PASS) software package program (Utah, USA, version 11.0 for windows). The critical value and sensitivity of different indicators and sensitivity, specificity, and area under curve (AUC) of the three serum biomarkers and CPIS were subjected to ROC curve analysis. A value of $P < 0.05$ suggested statistical significance.

3. Results

3.1. Baseline characteristics of patients with CAP and healthy controls

The characteristics of patients were shown in Table 1. The results revealed that no significant difference in age and gender existed between the CAP group and healthy control group (t = −1.51, χ^2 =

Table 1
The clinical features of patients and healthy controls.

Groups	Case	Age (years)	Gender (male/female)	Hospitalization days (days)	Survival (case, %)	Death (case, %)
Healthy control	106	78.18 ± 6.84	59/47	–	–	–
CAP	214	79.43 ± 7.05	127/87	12.65 ± 4.52	132(61.68)	82(38.32)
Non-severe CAP	112	78.60 ± 6.09	68/44	9.54 ± 3.71	85(75.89)	27(24.11)
Severe CAP	102	80.34 ± 6.33	59/43	16.03 ± 6.37[a]	47(46.08)	55(53.92)

[a] $P < 0.05$ compared with non-severe CAP group. CAP: community acquired pneumonia.

Table 2
The serum CRP, PCT, sTREM-1 and CPIS scores in patients of different groups.

Groups	CRP (mg/L)	PCT (μg /L)	sTREM-1 (ng/L)	CPIS scores
Healthy control	5.14(3.24–8.57)	0.05(0.02–0.09)	5.00(3.00–9.50)	1(0-1)
CAP	75.89(46.23–109.63)[a]	2.34(1.09–5.76)[a]	81.50(41.00–105.50)[a]	4(2.5–4)[a]
Non-severe CAP	47.68(25.79–64.27)	1.24(0.67–1.86)	41.50(28.50–59.50)	2 (2–3)
Severe CAP	109.46(94.37–136.82)[b]	5.38(3.27–9.14)[b]	126.00(94.00–152.00)[b]	4(3–5)[b]

CAP: community acquired pneumonia; CRP: C-reactive protein (CRP); PCT: procalcitonin; sTREM-1: soluble triggering receptor expressed on myeloid cells 1; CPIS: Clinical Pulmonary Infection Score.
[a] $P < 0.05$ compared with healthy control group.
[b] $P < 0.05$ compared with non-severe CAP group.

0.40, $P > 0.05$). In addition, among 214 CAP patients, there were 112 patients with non-severe CAP and 102 patients with severe CAP. The hospital stay of patients with severe CAP was significantly longer than that of patients with non-severe CAP (t = 9.20, $P < 0.05$). Moreover, the percentage of survival of patients in the non-severe CAP group (75.89%) was significantly higher than that of patients with severe CAP (46.08%; $\chi^2 = 20.08$, $P < 0.05$).

3.2. Comparison of three serum inflammatory markers and CPIS between CAP patients and healthy controls

As shown in Table 2, the serum levels of inflammatory markers, including CRP, PCT, and sTREM-1, as well as CPIS were significantly higher in CAP patients than in healthy controls (Z = −10.45, −8.67, −9.78, and −8.94, respectively, $P < 0.05$). In addition, these clinical markers and CPIS in patients with severe CAP were significantly higher than in the non-severe CAP group (Z = −8.56, −10.42, −8.06, and −5.62, respectively, $P < 0.05$). The sample power for testing CRP, PCT, sTREM-1, and CPIS between CAP patients and healthy controls, as well as between patients with severe CAP and patients with non-severe CAP, was all 1.000. Besides, the serum CRP, PCT, and sTREM-1 levels and CPIS were analyzed among CAP patients with different prognoses. As shown in Table 3, the serum CRP, PCT, and sTREM-1 and CPIS in CAP patients who would die were significantly higher than those among CAP patients who would survive (Z = −6.45, −7.24, −9.23, and −6.49, respectively, $P < 0.05$). Notably, the sample power for testing CRP, PCT, sTREM-1, and CPIS between CAP patients with different prognoses was also 1.000.

3.3. The value of serum CRP, PCT, sTREM-1 and CPIS for assessment of prognosis of elderly patients with CAP

The efficacy of serum inflammatory markers at assessing the prognosis of pneumonia in the patients was determined by the ROC curve analysis. As shown in Table 4, the AUC, sensitivity, and specificity of each marker in terms of prognosis of CAP in the elderly were as follows: 0.704, 73.64%, and 68.45% for CRP > 78.62 mg/L; 0.814, 74.51%, and 82.02% for PCT > 2.96 g/L; 0.858, 88.24%, and 78.65% for sTREM-1 > 96 ng/L, and 0.808, 72.55% and 80.40% for CPIS > 3. The AUC and sensitivity of serum sTREM-1 were higher than those of serum CRP, PCT and CPIS, while the specificity of serum PCT and CPIS was higher than sTREM-1 and CRP, indicating that a combination of sTREM-1 and PCT or CPIS may be effective in the evaluation of the prognosis of elderly patients with CAP. Thus, with the combination of PCT > 2.85 μg/L and sTREM-1 > 95 ng/L to assess the prognosis of elderly patients with CAP, the AUC, sensitivity, and specificity reached 0.882, 78.65%, and 84.31%, respectively; with the combination of CPIS > 3 and sTREM-1 > 96 ng/L to predict the prognosis, the AUC, sensitivity and specificity reached 0.864, 72.55% and 87.64%. These data indicated the usefulness of combination of sTREM-1 and PCT or CPIS for predicting prognosis of CAP in elderly patients.

Table 4
The value of serum CRP, PCT, sTREM-1 and CPIS for the prognosis of elderly patients with CAP.

Markers	Critical value	AUC (95%CI)	Sensitivity (%)	Specificity (%)
CRP (mg/L)	78.62	0.704(0.621–0.796)	73.64	68.45
PCT(μg/L)	2.96	0.814 (0.738–0.891)	74.51	82.02
sTREM-1(ng/L)	96	0.858(0.796–0.921)	88.24	78.65
CPIS scores	3	0.808(0.729–0.888)	72.55	80.40

CAP: community acquired pneumonia; CRP: C-reactive protein (CRP); PCT: procalcitonin; sTREM-1: soluble triggering receptor expressed on myeloid cells 1; CPIS: Clinical Pulmonary Infection Score.

4. Discussion

In the present study, higher levels of serum CRP, PCT, and sTREM-1 as well as greater CPIS were observed in CAP patients, especially patients with severe CAP or CAP patients with poor diagnosis. Moreover, serum sTREM-1 had the largest AUC and highest sensitivity among these indicators, whereas serum PCT had the highest specificity. Moreover, the AUC of the combination of PCT and sTREM-1 for assessing the prognosis of elderly patients with CAP was higher than that of the combination of CPIS and sTREM-1. These data indicated that these indicators determined on the admission day, especially PCT and sTREM-1, could be used to evaluate the severity and prognosis of CAP in the elderly.

CRP is an acute-phase reactant associated with the severity of inflammation. High level of CRP is considered as an independent risk factor of 30-day mortality in patients with CAP (Park et al., 2015). A

Table 3
The serum CRP, PCT, sTREM-1 and CPIS scores in CAP patients with different prognosis.

Prognosis	CRP (mg/L)	PCT (μg /L)	sTREM-1 (ng/L)	CPIS scores
Survival group (n = 132)	53.61(30.24–78.45)	1.17(0.86–2.45)	57.50(46.50–80.50)	2(2–3)
Death group (n = 82)	106.27(91.87–138.56)	5.63(3.86–9.25)	134.00(105.75–158.75)	4(4–5)
Z	−6.45	−7.24	−9.23	−6.49
P	$1.12*10^{-10}$	$4.49*10^{-13}$	$< 1.00*10^{-16}$	$8.58*10^{-11}$

CAP: community acquired pneumonia; CRP: C-reactive protein (CRP); PCT: procalcitonin; sTREM-1: soluble triggering receptor expressed on myeloid cells 1; CPIS: Clinical Pulmonary Infection Score.

CRP level at admission < 169.502 mg/L is also shown to predict a fatal outcome in patients with *S. pneumoniae* CAP (Que et al., 2015). It has also been confirmed that serum CRP has a diagnostic value in elderly patients with CAP (Zheng, Xu, Sun, & Wu, 2014). In addition, accumulating evidences have indicated that serum PCT is useful for predicting severity of the disease in elderly patients with CAP (Lei, Cao, & Tan, 2014; Wang, Qian, Luo, & Department, 2014). The high serum concentrations of PCT indicate a poor prognosis in elderly patients with CAP (Li and Wang, 2013). The dynamic monitoring of PCT is also shown to have a prognostic value for 28-day survival in elderly patients with severe CAP (Deng, Zhang, & Liu, 2015). Besides, the sTREM-1 levels can also serve as guide indicators reflecting the severity, treatment, and prognosis of CAP (Lin, Guo, Weina, & Wencheng, 2015). Dynamic monitoring of sTREM-1 is useful for predicting the outcome of treatment in elderly patients with CAP (Zhao, Qin, Wang, & Sun, 2013). In our study, high serum concentrations of CRP, PCT, and sTREM-1 were detected in patients with severe CAP or with poor prognosis, indicating that CRP, PCT, and sTREM-1 have a diagnostic and prognostic value for analysis of disease severity and treatment effects in elderly patients with CAP.

The ROC curve shows a trade-off between sensitivity and specificity, and thus can help to select the best cutoff for clinical use (Florkowski, 2008). It has been reported that the ROC curve is used to assess the diagnostic value of CRP, PCT, and sTREM-1 for patients with multiple injury and early infection; those researchers found that serum sTREM-1 is a better diagnostic marker of early infection than PCT and CRP are for patients with severe multiple injury because of higher sensitivity and specificity (Xu et al., 2011). ROC curve analysis is also used to evaluate the usefulness of several biomarkers, including CRP, PCT, presepsin, and mid-regional pro-adrenomedullin in the management of patients with sepsis (Enguixarmada, Escobarconesa, La Torre, & Mv, 2015). In children admitted to a hospital with CAP, PCT is found to be more sensitive and specific than CRP according to ROC curve analysis (Moulin et al., 2001).

As for the ROC curve in the diagnosis of CAP, the sensitivity and specificity were 63.30% and 83.30% when the cut-off value of sTREM-1 was set to 15.79 ng/L, indicating that serum sTREM-1 may help with the diagnosis of CAP (Zhi, Li, & Ling, 2013). Moreover, CPIS score can be used for the early diagnosis of pulmonary infection and evaluation of the severity and prognosis in patients with pneumonia (Niederman & Craven, 2005). In our study, the sensitivity and specificity of each marker in terms of the prognosis of CAP in the elderly were 73.64% and 68.45% for CRP > 78.62 mg/L, 74.51% and 82.02% for PCT > 2.96 g/L, 88.24% and 78.65% for sTREM-1 > 96 ng/L, and 72.55% and 80.40% for CPIS > 3. The sensitivity of serum sTREM-1 was higher than that of other indicators, whereas serum PCT and CPIS had higher specificity. We further used the combination of indicators to predict the prognosis, the results showed that combination of sTREM-1 and PCT had the best efficiency and the AUC reached 0.882, which was more than the AUC of combination of sTREM-1 and CPIS. A combination of sTREM-1 and PCT may be a useful approach to prognosis of CAP in elderly patients.

Nonetheless, we did not evaluate the percentage of aspiration pneumonia in each group in this study. Given that patients with aspiration pneumonia have a more severe disease, frequent recurrence, and higher mortality than patients with nonaspiration pneumonia (Hayashi et al., 2014), evaluation of the percentage of aspiration pneumonia in each group will help to better understand the value serum CRP, PCT, and sTREM-1 and CPIS for prognosis of CAP. Moreover, we did not compare the prognostic value of these biomarkers with biomarkers, such as CURB-65, for assessing the severity and prognosis of CAP in elderly patients. Lastly, we did not perform statistical analyses to determine the confounding factors such as comorbidities for prognosis. Thus, more studies are still needed to verify our results in the future.

In conclusion, our findings indicate that serum CRP, PCT, and sTREM-1 as well as CPIS determined on the admission day are effective indicators of the severity and prognosis of CAP in the elderly. The prognostic value of PCT and sTREM-1 is better than that of CRP and CPIS.

Disclosure statement

The authors declare no conflict of interest.

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