Diagnostic markers for community-acquired pneumonia

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Abstract: Community-acquired pneumonia (CAP) is one of the respiratory infectious diseases caused by not only bacteria, but also viruses. Antibiotic agents are needed to treat only bacterial but not viral CAP. In addition, there are some non-infectious respiratory diseases in the differential diagnosis of CAP, such as malignant diseases, interstitial lung diseases, pulmonary edema, and pulmonary hemorrhage. We usually diagnose patients having CAP by comprehensive evaluation of symptoms, vital signs, laboratory examinations, and radiographic examinations. However, symptoms and vital signs are not specific for the diagnosis of CAP; therefore, we also use inflammatory biomarkers for differentiating bacterial from viral CAP and non-infectious respiratory diseases. We have used the white blood cell count, C-reactive protein (CRP), and erythrocyte sedimentation rate as common inflammatory biomarkers, but they are not specific for bacterial infection because they could be increased by malignant diseases and collagen diseases. Recently, some inflammatory biomarkers such as procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), pro-adrenomedullin (proADM), and presepsin have been developed as relatively specific biomarkers for bacterial infection. Many reports have evaluated the usefulness of PCT for diagnosing CAP. In this review, the characteristics of each biomarker are discussed based on previous studies.

Keywords: Biomarker; community-acquired pneumonia (CAP); C-reactive protein (CRP); diagnosis; procalcitonin (PCT)

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Introduction

Of infectious diseases worldwide, community-acquired pneumonia (CAP) is one of the most common and important causes of hospitalization and death (1-3). CAP is an infection of the lung parenchyma that is acquired in a community, not a hospital or a long-term care facility (4). CAP is defined as the presence of a lung infiltration shadow on chest radiography and any symptoms such as cough, sputum, fever, dyspnea, and chest pain (1). The diagnosis of CAP is sometimes difficult because viruses, fungi, and mycobacteria may cause the pneumonia, although the main causative pathogens are bacteria. In addition, there are many non-infectious diseases in the differential diagnosis of CAP, such as pulmonary edema, lung cancer, acute respiratory distress syndrome, and many interstitial lung diseases [cryptogenic organizing pneumonia (COP), eosinophilic pneumonia, drug-induced pneumonia, and vasculitis] (5).

We usually differentiate pneumonia from other non-infectious respiratory diseases by comprehensive evaluation including symptoms, laboratory examinations, and the properties of lung infiltrative shadows. However, some CAP patients, especially elderly patients, do not have cough, sputum, fever, and an elevated white blood cell count (6-8). Therefore, we usually perform blood tests for biomarkers to differentiate CAP from other non-infectious respiratory diseases. Currently, there are no biomarkers that could alone diagnose CAP, but the search for the ideal biomarker

Table 1 Common inflammatory biomarkers used in the diagnosis of CAP

White blood cell count
CRP
PCT
sTREM-1
proADM
Presepsin

CAP, community-acquired pneumonia; CRP, C-reactive protein; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; proADM, pro-adrenomedullin.

for pneumonia is ongoing, and multiple molecules are undergoing rigorous investigation (9). This article reviews some of the biomarkers for diagnosing CAP.

Inflammatory biomarkers in CAP

Biomarkers have been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (10). An ideal diagnostic biomarker for CAP should be elevated only when bacterial infection has occurred and not in other infections, such as viral infections and fungal infections, to determine the need for antibiotic therapy. Furthermore, an ideal biomarker is expected to be simple to test, have the results available quickly, and not be expensive (11).

Overprescribing of antibiotics would lead to an increase in the probability of infection with antibiotic-resistant organisms (12,13). Therefore, it would be beneficial to have either rapid detection of the causative pathogens or the availability of biomarkers that would signify a bacterial infection that requires antibiotic therapy (14). Many biomarkers have been developed and used for diagnosing CAP so far (*Table 1*). However, some biomarkers cannot be examined in daily clinical practice. Therefore, we usually use some biomarkers such as the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), and so on. Of these biomarkers, less reliance has come to be placed on the WBC count and ESR because they have lower sensitivity and specificity compared with CRP and PCT (15). In addition, PCT is specific to bacterial infection, and there is more evidence to support its use for adjunctive diagnosis in CAP than for other biomarkers. The characteristics and usefulness of each biomarker in the diagnosis of CAP are reviewed below.

CRP

CRP is a 118-kDa pentameric protein synthesized in hepatic cells through induction by interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α (TNF-α) whenever infection or tissue inflammation occurs (16). CRP was first identified in pneumococcal pneumonia patients in 1930 (17). In healthy adults, the normal CRP concentration is usually less than 5 mg/L (18). The secretion of CRP starts within 4–6 hours, and its level doubles every 8 hours; it then reaches its maximum level within 36–50 hours. After the stimulation is removed, the CRP level falls relatively quickly, with a half-life of 19 hours (19).

Flanders *et al.* reported that a bedside CRP test was useful for predicting CAP in adults with acute cough (20). In 173 adult patients with acute cough, if the CRP cut-off level was ≥40 mg/L, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for the diagnosis of pneumonia were 70%, 90%, 6.9, and 0.33, respectively. In addition, adding CRP to the clinical prediction rule of Heckerling (temperature >37.8 ℃, pulse >100 beats per minute, rales, decreased breath sounds, and absence of asthma) could improve the area under the curve (AUC) (0.93) for diagnosing pneumonia compared to Heckerling's score alone (AUC =0.88) (20).

Stolz *et al.* assessed the usefulness of CRP for predicting pneumonia in radiologically confirmed pneumonia patients (21). They showed that the specificity for predicting pneumonia was 91.2% when the CRP cut-off value was 100 mg/L (21).

As described above, some studies have reported that CRP was useful for diagnosing CAP, but CRP is not a specific biomarker of bacterial infection because it can be increased in malignant diseases and collagen vascular diseases (22,23). In addition, CRP is apparently decreased by corticosteroid therapy (24). Therefore, it was stated that "testing for C-reactive protein is neither sufficiently sensitive to rule out nor sufficiently specific to rule in both an infiltrate on chest radiograph and bacterial etiology of lower respiratory infection" in BMJ in 2005 (25).

PCT

PCT is a 13-kDa, 116 amino acid precursor peptide of calcitonin and was first reported in the medical literature

Table 2 Characteristics of PCT and CRP

Biomarker	PCT	CRP
Molecular weight (kDa)	13	118
Factors stimulating production	Endotoxin, IL-6, TNF-α	IL-6
Production organs	Lung, liver, kidney, intestine, muscle, adipocyte	Liver
Production time from infection (h)	2–3	4–6
Half-life time (h)	20–24	19
Peak time from infection (h)	12–24	36–50

CRP, C-reactive protein; PCT, procalcitonin.

in 1975 (26). It is usually produced by the C-cells in the thyroid (27). The PCT level in healthy adults is very low (<0.1 ng/mL) (28). In 1993, Assicot first reported that PCT increased in septic patients in a study of burn pediatric patients (29). When bacterial infection occurs, lipopolysaccharide (LPS), IL-1β, IL-6, and TNF-α can promote CALC-I gene expression, and then release of PCT is increased from parenchymal tissues, such as the liver, kidney, lung, intestine, and muscle (30,31). PCT is released within 2–3 hours after bacterial infection, with a peak at 6 hours and a half-life of approximately 22–35 hours (32-34). PCT levels are attenuated by the interferon-γ released in response to viral infection; therefore, PCT levels are theoretically not increased in viral infections. PCT release is not affected by systemic steroids, unlike CRP (35). The characteristics of PCT and CRP are listed in *Table 2*.

Regarding the diagnosis of CAP, Müller *et al.* reported that the clinical signs and symptoms routinely used to diagnose CAP are of limited value (36). They also showed that PCT was the most useful biomarker for differentiating radiologically confirmed CAP (n=373) from other non-infectious lung diseases (n=44) among PCT, highly-sensitive CRP, leukocytes, and temperature. The AUC of PCT (0.88) was significantly higher than of highly-sensitive CRP (0.76, P<0.001), leukocytes (0.69, P<0.001), and temperature (0.55, P<0.001) (36).

COP is one of the interstitial lung diseases that is defined histopathologically by intra-alveolar buds of granulation tissue consisting of intermixed myofibroblasts, fibroblasts, and connective tissue (37,38). COP is sometimes similar in symptoms and radiologic findings to CAP; therefore, it can be difficult to differentiate CAP from COP in the early stages, and we often treat COP patients with antimicrobial agents. There are some studies assessing the utility of PCT for differentiating CAP from COP (39-41). Kolditz *et al.* showed that both PCT and CRP were significantly higher in CAP than in OP (median PCT 2.6 *vs.* 0.14 ng/mL, P<0.001; median CRP 266 *vs.* 140 mg/L, P=0.014). They also showed that the AUC value of PCT (0.90, 95% CI: 0.73–0.98) for diagnosis of OP was significantly higher than that of CRP (0.76, 95% CI: 0.57–0.90). Another study by Takeda *et al.* also reported that PCT and CRP levels were significantly higher in CAP than in COP patients (40). However, their studies included small numbers of OP patients (Kolditz's study, n=15) or COP patients (Takeda's study, n=16). Therefore, we investigated the usefulness of PCT for differentiating CAP from COP in 56 COP and 914 hospitalized CAP patients (41). The diagnostic accuracy was significantly higher for PCT (AUC 0.79) than for WBC (AUC 0.69, P=0.048) and CRP (AUC 0.60, P<0.001). When the cutoff value of PCT was 0.25 ng/mL, the sensitivity and specificity for discriminating CAP from COP were 83.9% and 61.1%, respectively (41).

Regarding the correlation with causative pathogens of CAP and PCT, the PCT levels of classic bacterial pneumonia patients (n=27, median 1.41 μg/L) were reported to be higher than those of atypical pneumonia patients (n=9, median 0.05) (42). In this study, only one atypical patient (11.1%) had PCT levels ≥0.5 μg/L, whereas 21 of 27 bacterial pneumonia patients (77.8%) had PCT levels ≥0.5 μg/L (42). Thereafter, Krüger *et al.* compared the PCT levels among 5 groups (typical bacterial pathogens, atypical pathogens, virus, mixed infection, and unknown etiology) in 1,337 CAP patients (43). They reported that the PCT levels of typical bacterial pathogens were significantly higher than those of atypical pathogens (P<0.01) and viruses (P<0.01) (43). We also reported that the PCT levels of bacterial pneumonia patients (median 1.85 ng/mL) were significantly higher than those of atypical pneumonia patients, excluding *Legionella* pneumonia (median

Table 3 Causes of false-positive and false-negative PCT results

False-positive
Acute respiratory distress syndrome
Multiple organ failure
Systemic fungal infections
Part of viral infections
Severe trauma
Severe burns
Surgical trauma
Cardiac shock
Renal failure
Patients with medullary thyroid cancer, small cell lung cancer with paraneoplastic hormone production
Inflammation associated with cytokine storms
False-negative
Early course of infection
Localized infection
Subacute endocarditis

PCT, procalcitonin.

0.41 ng/mL) (44). In addition, we showed that the CRP values were not significantly different between bacterial and atypical pneumonia patients (44). Self *et al.* showed that the median PCT values (ng/mL) of viral, atypical bacterial, typical bacterial, mycobacterial/fungal, and unknown etiology patients were 0.09, 0.20, 2.5, 0.19, and 0.14, respectively, and the PCT values of typical bacterial etiology patients were significantly higher than those of viral etiology patients (P<0.01) (45). However, of the 169 patients with typical bacterial pneumonia, 39 (23.1%) had PCT <0.25 ng/mL, and 21 (12.4%) had PCT <0.1 ng/mL (45). Naturally, we cannot detect the etiologic pathogens based on the PCT levels and should treat with antibiotic agents if we suspect clinically that the patients have bacterial pneumonia, because there are some bacterial pneumonia patients who have PCT levels less than 0.25 ng/mL. However, based on the previous reports, we may be able to guess the etiologic pathogen group, such as bacterial pathogens or atypical pathogens and viruses.

As we stated above, there are many reports regarding the usefulness of PCT for differentiating CAP from other respiratory diseases and bacterial from atypical or viral pneumonia. However, there are some limitations of PCT use because of false-positive and false-negative results; the false-positive and false-negative situations are listed in *Table 3*. Specifically, the PCT values could be less than 0.25 ng/mL because of measurement soon after symptom onset. Therefore, it is important to measure PCT serially within 6–24 hours, as stated by PCT-guided algorithms (46).

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

Triggering receptor expressed on myeloid cell 1 (TREM-1) is a glycoprotein member of the immunoglobulin family (47) that was first identified on both human and murine myeloid cells, especially neutrophils, mature monocytes, and macrophages (48). TREM-1 is highly increased in skin, biological fluids, and tissues when bacterial and fungal infections occur, but it is not increased in non-infectious inflammatory conditions (49). TREM-1 exists in both a membranous and a soluble form (sTREM-1), and sTREM-1 is released and can be measured in several body fluids (48).

Richeldi *et al.* reported that TREM-1 expression at the surface of alveolar neutrophils and macrophages was increased in bacterial pneumonia compared with in non-infectious interstitial lung diseases, although the expression of TREM-1 in peripheral blood neutrophils was similar in these patients (50). In addition, Gibot *et al.* showed that alveolar sTREM-1 concentrations were highly predictive of lung infection and performed better than any other clinical or biological findings in both CAP patients who required mechanical ventilation (n=38) and ventilator-associated pneumonia patients (n=46) (51). The area under the receiver-operating characteristic curve of sTREM-1 for differentiating the presence from the absence of pneumonia was 0.93 (95% CI: 0.92 to 0.95) (51). When the cutoff value of sTREM-1 was 5 pg/mL, the sensitivity and specificity were 98% and 90%, respectively (51). Huh *et al.* also reported that sTREM-1 concentrations in bronchoalveolar lavage (BAL) fluid of patients with bilateral lung infiltrates were significantly higher in bacterial or fungal pneumonia patients (n=29, 521.2±94.7 pg/mL) than in viral or atypical pneumonia patients (n=14, 92.9±20.0 pg/mL, P<0.05) and non-infectious disease patients (n=37, 92.8±10.7 pg/mL, P<0.05) (52). On multiple logistic regression analysis, they showed that the sTREM-1 level (cutoff value ≥184 pg/mL) in BAL fluid is an independent predictor of bacterial or fungal pneumonia, with an odds ratio of 59.742 (52).

However, all these studies indicated the usefulness of

sTREM-1 in BAL fluid for diagnosing pneumonia, and there were few reports showing the usefulness of serum sTREM-1 for diagnosing pneumonia patients. Indeed, Müller *et al.* showed that the sTREM-1 levels in plasma and serum of CAP patients at admission were not significantly different according to pneumonia severity [mild *vs.* severe (median, interquartile range), 93.3 (44.1–165.2) *vs.* 79.1 (45.8–154.1), P=0.31] (53). Another study by Esposito *et al.* found that plasma sTREM-1 levels had a poor ability to differentiate bacterial from viral CAP in 433 hospitalized pediatric patients (AUC 0.50, 95% CI: 0.45–0.56) (54).

Basically, we do not routinely perform BAL examinations for CAP patients, especially in mild to moderate cases, because it is a relatively invasive procedure. Therefore, we think that sTREM-1 is not a useful biomarker for diagnosing pneumonia.

Pro-adrenomedullin (proADM)

ADM is produced by physiologic stress and has vasodilatory activity, bactericidal activity, and anti-inflammatory properties. Hirata reported that ADM levels increased according to disease severity in adult sepsis patients (55). However, ADM is rapidly cleared from the circulation due to its rapid binding to receptors and its half-life of 22 minutes (56). Therefore, midregional-proADM (MR-proADM), a precursor of ADM, is used in daily clinical practice because of its stability (57).

Krüger *et al.* showed that MR-proADM was the best predictor for 28-day and 180-day mortality among WBC, CRP, PCT, copeptin, CT-proET-1, MR-proANP, and MR-proADM in 728 CAP patients (58). In addition, Bello *et al.* showed that MR-proADM was the only biomarker able to predict short and long-term mortality among MR-proADM, WBC, CRP, and PCT in 228 hospitalized CAP patients (59). However, in their study, MR-proADM levels were almost similar between bacterial [median (interquartile range), 0.909 nmol/L (0.669–1.506 nmol/L)] and viral or atypical pneumonia patients [median (interquartile range), 0.875 nmol/L (0.606–1.155 nmol/L)] (59). Therefore, we think that MR-proADM is not useful for differentiating bacterial from viral pneumonia to determine whether we need to treat by antibiotics.

Presepsin

Presepsin is a 13-kDa protein and a fragment of monocyte LPS receptor CD14 that is released in the blood circulation during the process of bacterial phagocytosis. Yaegashi *et al.* reported that presepsin levels in sepsis patients were significantly higher than those of SIRS patients and healthy controls (60). Furthermore, Endo *et al.* reported that presepsin had similar diagnostic accuracy to PCT for differentiating bacterial and nonbacterial infectious diseases in a multicenter, prospective study in Japan (AUC of presepsin was 0.908, and that of PCT was 0.825) (61).

In 72 ICU patients admitted for acute respiratory failure, Klouche *et al.* reported that presepsin was useful for differentiating severe CAP from non-infectious respiratory failure (AUC 0.85) (62). When the cutoff value of presepsin was 588 pg/mL, the sensitivity and specificity for the diagnosis of pneumonia were 81% and 80%, respectively (62). In another study by Qi *et al.*, presepsin levels in active pulmonary tuberculosis patients were reported to be slightly increased compared with those of healthy controls [median (interquartile range) pg/mL, 218.0 (146.0–368.0) *vs.* 128.0 (101.5–176.5)] (63). However, they also showed that presepsin was useful for discriminating bacterial CAP from active pulmonary tuberculosis (AUC 0.841) (63). Recently, Halıcı *et al.* reported that presepsin was useful for diagnosing pneumonia in chronic obstructive pulmonary disease patients with acute exacerbations (AUC 0.70) (64). However, the diagnostic accuracy of presepsin was not higher than of PCT (AUC 0.72) and CRP (AUC 0.75) (64).

There are only a few studies that have evaluated the usefulness of presepsin for diagnosing pneumonia. Therefore, whether presepsin is useful as a diagnostic biomarker in pneumonia patients in routine clinical practice is controversial, and further studies are needed.

Conclusions

Biomarkers are useful for differentiating CAP from other non-infectious respiratory diseases, but we should not rely only on biomarkers; they should be used adjunctively. The search for biomarkers that have higher sensitivity and specificity than the existing biomarkers for diagnosing CAP and could suggest the causative microorganisms continues, and it is hoped that they will be identified.

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