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Role of biomarkers in community-acquired pneumonia management

Bahaeddin Onur[1,2]✉, Hakan Barış Demirbas[3], Arif Gulmez[4]

[1]*Department of Emergency Medicine, Istanbul Health and Technology University, Istanbul, Turkey*

[2]*Department of Emergency, PHCC, Al Karaana Health Center, Doha, Qatar*

[3]*Department of Emergency, PHCC, Umm Slala Health Center, Doha, Qatar*

[4]*Department of Family Medicine, PHCC, Al Thumama Health Center, Doha, Qatar*

ABSTRACT

Community-acquired pneumonia (CAP) poses a significant global health threat, particularly affecting vulnerable populations. Biomarkers and scoring systems play a crucial role in diagnosing, assessing severity, and guiding treatment decisions for CAP patients. Biomarkers like C reactive protein, procalcitonin, and the neutrophil-to-lymphocyte ratio aid in diagnosis and severity assessment, while scoring systems such as CURB-65 and Pneumonia Severity Index classify patients into risk categories. Emerging biomarkers (uremia, elevated respiratory rate, hypotension, and age ≥ 65) like serum amyloid A and S100 proteins show promise in predicting disease severity and prognosis. However, further research is needed to determine their precise roles and clinical utility in CAP management.

KEYWORDS: CURB-65; Community-acquired pneumonia; Procalcitonin; Alpha-1 antitrypsin; Serum amyloid A

1. Introduction

Pneumonia, an acute respiratory infection, is characterized by inflammation of the lung's air sacs, often caused by bacteria, viruses, fungi, or aspiration of foreign substances. It poses a significant global health threat, particularly affecting vulnerable populations such as children, the elderly, and individuals with underlying health conditions[1-3]. Prompt diagnosis and treatment are crucial to prevent complications such as respiratory failure and sepsis, highlighting the importance of early recognition and appropriate management strategies. Community-acquired pneumonia (CAP) remains a significant cause of morbidity and mortality worldwide, particularly among vulnerable populations such as the elderly, young children, and individuals with comorbidities. CAP is defined as pneumonia acquired outside of healthcare facilities, including cases diagnosed in the community, outpatient settings, and within 48 hours of hospital admission[4]. Despite advancements in medical care, CAP continues to pose substantial challenges due to its potential for rapid progression, complications, and associated mortality rates, especially when diagnosis and treatment are delayed. CAP-related mortality rates vary depending on factors such as age, underlying health conditions, microbial etiology, and timely access to appropriate healthcare services[5,6]. Understanding the severity and prognosis of CAP is paramount for effective management and reducing mortality rates. Consequently, the identification and utilization of reliable biomarkers and scoring systems play a crucial role in risk stratification, prognosis prediction, and guiding therapeutic interventions in patients with CAP[7,8].

✉To whom correspondence may be addressed. E-mail: bahaeddin.onur@istun.edu.tr

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CAP scoring systems play a crucial role in assessing the severity and prognosis of the disease. These systems are used to classify patients at risk, determine appropriate treatment options, and support the clinical decision-making process. There are several CAP scoring systems available, which typically include clinical findings, laboratory test results, and imaging findings. The goal of these systems is to predict the severity of the disease and categorize patients into low, moderate, or high-risk categories[8-10].

2. CAP scoring systems

Some commonly used CAP scoring systems include:

2.1. CURB-65 Score

This scoring system is used to assess the risk of severe illness and death and consists of five main components: Consciousness status, urea level, respiratory rate, blood pressure, and age. Each component is evaluated on a scale of 0-1, and an increase in the total score increases the likelihood of the patient having a poor prognosis.

2.2. Pneumonia severity index (PSI) or PORT score

This scoring system is used to assess the severity of CAP and includes over 20 variables such as age, comorbidity, vital signs, and laboratory results. PSI categorizes patients into five risk classes and is used to determine if they are at low, moderate, or high risk[11,12].

CAP scoring systems have both advantages and limitations in clinical use. These systems provide a valuable tool for classifying patients at risk and identifying high-risk patients requiring aggressive treatment. However, scoring systems may not be suitable for every patient, and in some cases, they may lead to false-positive or false-negative results. Additionally, the complexity and time-consuming nature of scoring systems can limit their clinical utility. Therefore, careful evaluation and appropriate use of CAP scoring systems in the clinical context are essential[7,13].

3. Biomarkers

Biomarkers used in CAP encompass a range of hematological, biochemical, and immunological parameters that aid in the diagnosis, severity assessment, and prognosis of the condition. Some commonly employed biomarkers in CAP include C-reactive protein (CRP), procalcitonin, and the neutrophil-to-lymphocyte ratio (NLR). In clinical practice, these biomarkers are typically measured through routine laboratory tests on blood samples obtained from CAP patients upon presentation to healthcare facilities. Interpretation of biomarker levels in conjunction with clinical and radiological findings allows for a comprehensive assessment of CAP severity and informs treatment strategies, including the decision to initiate antibiotic therapy and the selection of appropriate antimicrobial agents[14,15].

3.1. NLR

NLR is considered an indicator of inflammatory response, expressing the ratio of neutrophil to lymphocyte counts. This ratio serves as a biomarker widely used in the diagnosis and assessment of the severity of various inflammatory conditions and infections[16,17]. The applications of NLR are extensive. Particularly, in conditions such as infections, inflammatory diseases, cancer, cardiovascular diseases, and chronic kidney disease, the evaluation of NLR is commonly performed. Elevated NLR values may reflect the presence or severity of an inflammatory or infectious condition and can be used as a marker in assessing prognosis[16-19].

In infections like CAP, the use of NLR is particularly significant. High NLR values may be associated with increased severity of pneumonia, higher risk of complications, and worsening prognosis for the patient. Therefore, the utilization of NLR as an indicator in the diagnosis and management of CAP is crucial for assessing the clinical course of patients and making treatment-related decisions[18,19].

3.2. CRP

CRP is an acute-phase reactant produced by the liver in response to inflammation, infection, or tissue injury. It is a non-specific marker of inflammation and plays a crucial role in the body's immune response. CRP levels rise rapidly in the bloodstream following the onset of inflammation, making it a valuable biomarker in various clinical settings.

CRP is widely used in medical practice for several purposes due to its versatility as a marker of inflammation[20-22]. CRP levels are measured to aid in the diagnosis and monitoring of inflammatory conditions such as infections, autoimmune diseases, and cardiovascular diseases. Elevated CRP levels indicate the presence and severity of inflammation in the body[20]. In conditions like pneumonia, CRP levels can provide valuable information about the severity of the infection. Higher CRP levels are often associated with more severe cases of pneumonia and may help clinicians in risk stratification and treatment decision-making[23]. In the management of infections, including CAP, CRP levels can assist clinicians in deciding whether to initiate antibiotic therapy and in monitoring the response to treatment. Lowering CRP levels over time may indicate a favorable response to antibiotic treatment[24].

In the context of CAP, CRP can be utilized as a biomarker

to support diagnosis, assess severity, and monitor response to treatment[25-27].

Elevated CRP levels in patients with suspected CAP can support the diagnosis of the condition, particularly when used in conjunction with clinical symptoms and imaging findings[25-27]. Secondly, CRP levels can help clinicians assess the severity of CAP, guiding decisions regarding hospitalization and the need for more aggressive management strategies. Besides, serial measurements of CRP levels during treatment can provide valuable information about the patient's response to therapy. A decline in CRP levels may indicate resolution of inflammation and improvement in the patient's condition.

3.3. Procalcitonin

Procalcitonin is a precursor peptide of calcitonin, primarily synthesized by the C cells of the thyroid gland. Under normal physiological conditions, procalcitonin is rapidly cleaved into calcitonin, a hormone involved in calcium homeostasis. However, in response to bacterial infections and systemic inflammation, procalcitonin levels rise significantly, making it a valuable biomarker for various clinical applications[28,29].

Procalcitonin measurement can aid in diagnosis, severity assessment, and guiding antibiotic therapy in CAP patients. Elevated procalcitonin levels in patients with suspected CAP may indicate a bacterial etiology, supporting the diagnosis of bacterial pneumonia over viral or other causes. This information can help guide initial treatment decisions, including the choice of antibiotics[30]. Procalcitonin levels can also provide insight into the severity of CAP, with higher levels correlating with more severe cases of bacterial pneumonia. This information may help clinicians in risk stratification and determining the need for hospitalization or intensive care management[31]. Serial measurements of procalcitonin levels during antibiotic therapy can help assess the response to treatment and guide decisions regarding the duration of antibiotic therapy. A decline in procalcitonin levels over time may indicate a favorable response to treatment and support the decision to discontinue antibiotics[32,33].

3.4. Serum amyloid A

Serum amyloid A (SAA), an acute-phase protein synthesized by the liver, serves as a marker of systemic inflammation. It is involved in various physiological processes, including the immune response and tissue repair. SAA levels increase rapidly in response to inflammatory stimuli, making it a valuable biomarker for assessing the severity and progression of infectious and inflammatory diseases[34,35]. In CAP patients, SAA levels may be elevated, reflecting the extent of systemic inflammation and tissue damage associated with the infection. In a study from China, conducted on patients with CAP, SAA showed a higher predictive value, with an AUC of 0.777 on the admission day, surpassing hs-CRP, which had an AUC of 0.729. Additionally, dynamic monitoring of ΔSAA demonstrated superior predictive performance compared to SAA alone, with an AUC of 0.979 for assessing disease trends[36].

Thus, monitoring SAA levels in CAP patients could aid in disease prognosis, treatment monitoring, and risk stratification for adverse outcomes. However, further research is needed to elucidate the specific role and utility of SAA as a biomarker in CAP management.

3.5. Alpha-1 antitrypsin

Alpha-1 antitrypsin (AAT), a protease inhibitor primarily produced by hepatocytes, plays a crucial role in regulating the activity of neutrophil elastase, thus protecting tissues from excessive proteolytic damage. In addition to its classical role in inhibiting proteases, AAT exhibits anti-inflammatory and immunomodulatory properties, implicating its involvement in various physiological and pathological processes beyond protease inhibition[37]. Clinically, AAT deficiency predisposes individuals to early-onset emphysema and liver disease. Moreover, emerging evidence suggests potential roles for AAT in modulating immune responses and tissue repair mechanisms, warranting further investigation into its therapeutic applications[38,39]. AAT's anti-inflammatory properties may offer insights into disease pathogenesis and prognosis of CAP, potentially informing therapeutic strategies aimed at mitigating excessive inflammatory responses and tissue damage associated with severe pneumonia. In a small simple-size study, Ogan *et al*. showed that ATT was elevated in exacerbations of chronic obstructive pulmonary disease and CAP[40]. Another study involved 210 patients diagnosed with CAP and identified sputum volume score and the AAT/IL-10 ratio as significant predictors of bacterial pneumonia. It showed that utilizing a decision tree based on these predictors could assist in predicting BP and guiding antibiotic use in CAP patients, offering a valuable tool for clinical decision-making[41]. However, the precise utility of AAT as a biomarker or therapeutic target in CAP requires comprehensive evaluation through clinical studies and mechanistic investigations.

3.6. S100 proteins

S100 proteins are small calcium-binding proteins that play various roles in cellular functions, predominantly found in the cytoplasm. They are involved in processes such as cell proliferation, differentiation, motility, and cell death. Additionally, they can be found at increased levels in pathological conditions such as inflammation, immune responses, thromboembolic events, and neurological diseases[42]. S100 proteins have numerous applications in the diagnosis and monitoring of various clinical conditions. Particularly, they are widely used in areas such as inflammation

detection, tissue damage assessment, and prognosis prediction. For instance, S100B protein, the best-known S100 protein, is known to be used as a biomarker for identifying neurological damage[43].

In CAP, the levels of S100 proteins are being investigated as potential markers for assessing the severity of infection. Elevated levels of S100 proteins may reflect the severity of lung damage associated with pneumonia and can help predict the prognosis of the disease. Wang *et al*. demonstrated that patients with elevated serum S100A12 levels exhibit more severe CAP, increased inflammatory response, and higher 30-day mortality rates compared to those with lower S100A12 levels[44]. Similarly, Liu *et al*. showed a positive correlation between S100A9 and the severity of CAP[45]. Zheng *et al*. reported that S100A8 demonstrated high discriminative ability with AUC values of 0.855 for CAP and 0.893 for CAP severity[46]. S100 proteins could serve as a potential tool in the diagnosis of CAP and in evaluating the response to treatment.

In conclusion, CAP remains a significant public health concern worldwide, particularly affecting vulnerable populations such as the elderly, children, and individuals with comorbidities. Prompt diagnosis and appropriate management are essential to mitigate complications and reduce mortality rates associated with CAP. Biomarkers and scoring systems play a crucial role in risk stratification, prognosis prediction, and guiding therapeutic interventions in CAP patients. While biomarkers like CRP, procalcitonin, and the NLR aid in diagnosis and severity assessment, scoring systems such as CURB-65 and PSI help classify patients into risk categories. Moreover, emerging biomarkers like SAA and S100 proteins show promise in predicting disease severity and prognosis. However, further research is warranted to elucidate their precise roles and clinical utility in CAP management.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Conception, supervision, literature review, writing, and critical review: BO, HBD, and AG.

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