International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 14, No. 1, 2026

The Value of Cytokines in Assessing the Severity of CAP

Zehua Li, Changli Yu *

North China University of Science and Technology Affiliated Hospital, Tangshan Hebei, 063000, China
*** Corresponding author:** Changli Yu

Abstract: Community-Acquired Pneumonia (CAP) is a common clinical infectious disease. Once it progresses to severe illness, the risk of mortality significantly increases. Therefore, early and accurate assessment of disease severity is of great significance for improving prognosis. In recent years, research on cytokines has gradually emerged. This article focuses on elucidating the value of cytokines in evaluating the severity of CAP. Cytokines have high value in determining the severity of CAP. Clinically, they can guide physicians in their judgment and have certain value in improving patient prognosis.

Keywords: Cytokines; Interleukin; CAP.

1. Clinical Manifestations of CAP

After infection with CAP, the clinical manifestations often vary significantly among different individuals. Most patients present with relatively mild symptoms, which are largely related to the body's own defense mechanisms, while a small number of patients exhibit more pronounced clinical features. Nasal catarrhal symptoms such as sneezing, nasal congestion, and rhinorrhea are the main clinical manifestations of CAP. A more distinctive clinical feature is fever, which is also the primary reason patients seek medical attention. CAP patients often present with cough and sputum production, or occasionally hemoptysis, dizziness, headache, generalized muscle aches, fatigue, and joint pain. Skin rashes may also be observed occasionally. CAP is more likely to occur and progress in the elderly, children, and patients with compromised immunity due to other underlying diseases. Clinical manifestations in these populations include persistent high fever unresponsive to treatment, chest tightness, wheezing, shortness of breath, difficulty with expiratory and/or inspiratory function, and cyanosis of the lips. In severe cases, patients may develop altered mental status, heart failure, respiratory failure, or even septic shock due to severe sepsis. Furthermore, viruses can easily trigger viral myocarditis in the human body, while also causing damage to liver and kidney function, leading to systemic diseases. Additionally, elderly patients may have other underlying comorbidities that adversely affect their prognosis.

2. Cytokines

Cytokines are a class of small molecular proteins produced and secreted by immune and tissue cells. They play important regulatory roles in both the innate and adaptive immune systems and are considered one of the key mediators linking infection and systemic inflammatory responses. When a pulmonary infection occurs, alveolar macrophages, monocytes, and neutrophils are rapidly stimulated by pathogen-associated molecular patterns to produce large amounts of pro-inflammatory and anti-inflammatory cytokines, initiating a systemic inflammatory cascade. When inflammation becomes uncontrolled, it can trigger a "cytokine storm," leading to diffuse damage to the alveolar epithelium and vascular endothelium, resulting in acute respiratory distress syndrome and septic shock—this is one of the important mechanisms underlying the progression of CAP to severe disease. Therefore, serum levels of cytokines can directly reflect the degree of inflammatory activation and are associated with the severity of CAP.

As signaling proteins, cytokines play important roles at all stages of the immune response[1]. There are many types of cytokines, with interferon being the first discovered. Among them, the most common cytokines and those most frequently used clinically are interleukins (IL). Various tissue cells in the human body, when induced and activated, can synthesize and secrete numerous small molecular peptides or glycoproteins [2], which can promote certain mutual interactions between cells and fulfill various human biological functions. With the advancement and development of hematological testing techniques, it is now widely accepted from a microscopic perspective that white blood cells are the main cells producing cytokines, and based on their sites and mechanisms of production, they have been named interleukins. With the deepening and progress of clinical research, ILs can be applied in various aspects of clinical practice, becoming an important component of patient admission examination and treatment. The first discovered IL was named IL-1, which is a central mediator of innate immunity and inflammation. The IL-1 family includes seven ligands with agonist activity (IL-1α and β, IL-18, IL-33, IL-36α, β, γ), three receptor antagonists (IL-1Ra, IL-36Ra, IL-38), and one anti-inflammatory cytokine (IL-37). IL-1 affects nearly all cells and organs and is a major pathogenic mediator of inflammatory responses, infections, and autoimmune diseases[3].

IL-6 has a wide range of biological activities. Following tissue damage and pathogen invasion leading to infection, white blood cells are mostly released and increased within a short period, thereby producing large amounts of IL-6. This makes IL-6 an indicator for judging infection. Particularly during the COVID-19 pandemic, the use of IL to assess the condition of clinical patients became even more common. Clinically, elevated levels of IL-6 are associated with various diseases. Relevant studies have reported that the inflammatory pathway involving IL-6 is one of the important reasons for the progression of rheumatoid arthritis. The principle is that elevated IL-6 levels stimulate the further release of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, which are closely associated with rheumatoid arthritis[4], gradually worsening the condition of

rheumatoid arthritis and affecting patient prognosis. Therefore, IL-6 levels are crucial in the treatment of patients with rheumatoid arthritis.

IL-10 is an important multifunctional anti-inflammatory cytokine. It targets various innate and adaptive leukocytes, exerting negative inhibitory effects on these cells, reducing the exudation of inflammatory factors, protecting the human body from the effects of inflammatory responses, and maintaining tissue integrity. Currently, there are 18 known types of ILs, each with its unique functions, but most are related to the occurrence of inflammatory responses. In summary, ILs exhibit significant changes in serum levels during inflammatory responses and infections; therefore, they are considered useful for determining the severity of infections. Cytokines can be applied in patients with CAP. The generation of a cytokine storm can attack various organs of the human body. When vital organs are attacked, it may lead to further exacerbation of the primary disease, increase adverse prognosis of the disease, and raise the mortality rate. Some studies suggest that highly pathogenic viral infections often trigger the development of a cytokine storm[5]; therefore, clinical vigilance is required.

3. The Role and Clinical Value of Pro-Inflammatory Cytokines in CAP

In addition to the core pro-inflammatory cytokines mentioned earlier, IL-1β, IL-12, IL-18, Granulocyte Colony-Stimulating Factor (G-CSF), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) also play key regulatory roles in the inflammatory cascade of CAP. Abnormal serum levels of these factors are closely associated with the progression of CAP to severe disease.

As a core pro-inflammatory member of the IL-1 family, IL-1β, along with TNF-α, is considered an "initiating factor" of inflammation. It is released by activated mononuclear macrophages and alveolar epithelial cells upon pathogen stimulation through NLRP3 inflammasome activation. IL-1β induces airway and vascular endothelial cells to secrete adhesion molecules and chemokines, recruiting inflammatory cells and amplifying local inflammation. It also triggers fever and initiates systemic inflammatory responses. Clinical studies have shown that serum IL-1β levels are significantly higher in CAP patients than in healthy individuals, with even more pronounced elevations in severe cases, positively correlating with the extent of pulmonary lesions. Its excessive activation is a core mechanism of secondary ARDS in viral pneumonia and an independent risk factor for the need for mechanical ventilation and ICU admission. Its genetic polymorphisms may also provide a genetic reference for screening high-risk populations[6].

IL-12 and IL-18 synergistically regulate Th1-type immune responses. Secreted by macrophages and dendritic cells, they promote the secretion of IFN-γ by NK cells and T lymphocytes, thereby enhancing immunity against intracellular pathogens. IL-12 bridges innate and adaptive immunity. In mild CAP patients, its levels increase early and recover as infection is controlled, whereas in severe CAP patients, its levels are relatively insufficient, leading to immune deficiency and infection spread. IL-18 is excessively elevated in severe CAP, amplifying the inflammatory cascade and exacerbating lung tissue injury. It is an important mediator in the progression of CAP to ARDS, and elevated levels indicate an increased 30-day mortality risk[7]. Furthermore, the IL-12/IL-18 ratio reflects the balance between immunity and inflammation; a decreased ratio suggests an increased risk of disease severity, providing a potential target for immunomodulatory therapy.

G-CSF and GM-CSF are both hematopoietic growth factors and important pro-inflammatory cytokines, playing central roles in innate immunity during pulmonary infection. G-CSF promotes the production and release of neutrophils from the bone marrow and enhances their bactericidal capacity. GM-CSF activates myeloid cells and dendritic cells, promotes the clearance of alveolar exudates, and accelerates lung repair. Serum levels of both factors are significantly higher in patients with bacterial CAP than in those with viral CAP, positively correlating with procalcitonin (PCT) and neutrophil counts, which can aid in differentiating the type of infection[8-9]. However, overexpression of GM-CSF can exacerbate lung injury. In patients with severe CAP complicated by sepsis, persistently elevated GM-CSF levels are closely associated with multiple organ dysfunction.

4. The Immunomodulatory Role of Anti-Inflammatory Cytokines in CAP

Anti-inflammatory cytokines are at the core of the negative regulation of inflammation and maintain the homeostasis of the internal environment. In addition to the aforementioned IL-10, IL-4, and TGF-β, the roles of emerging anti-inflammatory factors such as IL-13, IL-35, and IL-37 in CAP are gradually becoming clearer, providing new directions for the discovery of therapeutic targets.

IL-13 is a core anti-inflammatory cytokine secreted by Th2 cells. It is homologous to IL-4 and shares its receptor. IL-13 can inhibit Th1-type pro-inflammatory responses, reduce the secretion of pro-inflammatory cytokines, promote the polarization of macrophages toward a reparative phenotype, alleviate lung injury, and repair the alveolar barrier. Animal experiments have shown that exogenous supplementation with IL-13 can reduce the mortality rate of mice with pneumonia. Clinically, IL-13 levels increase early in mild CAP patients but are significantly reduced in severe cases. IL-13 levels are positively correlated with the oxygenation index and negatively correlated with pneumonia severity. Reduced IL-13 levels are an independent risk factor for the progression of CAP to severe disease. IL-13 can also improve airway obstruction, and its abnormal reduction is associated with an increased risk of acute exacerbation in CAP patients with concurrent airway diseases[10].

IL-35 is secreted by regulatory T cells and belongs to the IL-12 family. It is a key molecule in immune tolerance and the negative regulation of inflammation. IL-35 can promote the proliferation of regulatory T cells, inhibit the activation of pro-inflammatory cells, and reduce the release of inflammatory mediators. Serum IL-35 levels in CAP patients are significantly lower than those in healthy individuals, with even more pronounced reductions in severe cases. IL-35 levels are negatively correlated with pro-inflammatory cytokines and positively correlated with prognosis. Levels below the critical value indicate an increased risk of severe disease and death. Dynamic changes in IL-35 levels can reflect treatment response, and persistently low levels indicate a poor prognosis.

IL-37 is the only anti-inflammatory cytokine in the IL-1 family. It is widely expressed in various cell types. By

inhibiting classical pro-inflammatory signaling pathways, IL-37 reduces the secretion of pro-inflammatory cytokines and enhances the expression of anti-inflammatory cytokines. Animal experiments have confirmed that IL-37 overexpression can alleviate pulmonary inflammation and improve the survival rate of mice with pneumonia. Clinically, IL-37 levels are higher in patients with severe CAP than in those with mild CAP, representing a compensatory protective mechanism of the body, though it is insufficient to suppress uncontrolled inflammation[11-12]. The IL-37/IL-6 ratio can more accurately assess the inflammatory balance; a lower ratio indicates a higher risk of disease severity. The predictive efficacy of this ratio for poor prognosis is superior to that of IL-6 testing alone. Genetic polymorphisms of IL-37 may also provide new biomarkers for screening high-risk populations.

5. Current Status and Limitations of Cytokine Testing in The Clinical Diagnosis and Treatment of CAP

The rapid development of cytokine detection technology has provided new perspectives and tools for the clinical diagnosis and treatment of CAP. It has gradually transitioned from basic research to clinical application, playing an increasingly important role in the early diagnosis, severity stratification, treatment guidance, and prognosis assessment of CAP.

In terms of early diagnosis and pathogen identification, cytokine profiling can compensate for the shortcomings of traditional etiological diagnostic methods. Traditional etiological diagnosis of CAP mainly relies on sputum culture, blood culture, nucleic acid testing, and similar methods. Sputum and blood cultures are time-consuming and have low positivity rates, making it difficult to meet the needs of early diagnosis. Although nucleic acid testing is rapid and accurate, its high cost limits widespread use in primary hospitals, and it cannot distinguish between colonization and infection. In contrast, cytokine profiling can yield results within a short time after hospital admission. CAP caused by different pathogens exhibits characteristic cytokine profile changes: bacterial CAP is characterized by a significant elevation of IL-6, TNF-α, and IL-8 as core features; viral CAP predominantly shows elevations of IFN-γ, IL-18, and IL-10; and atypical pathogen infection is characterized by elevated IL-17 and IL-5[13]. By combining the detection of multiple cytokines and establishing pathogen identification models, it is possible to rapidly distinguish between bacterial, viral, and atypical pathogens early in the infection. This provides an important reference for selecting early empirical anti-infection regimens and reduces inappropriate antibiotic use.

In terms of severity stratification and prognosis assessment, cytokine testing can accurately identify patients at high risk for severe disease. The commonly used clinical scoring systems, such as CURB-65 and PSI, primarily rely on patients' clinical symptoms, underlying diseases, and routine laboratory indicators. They inadequately assess the immune-inflammatory state and struggle to identify patients with rapid disease progression early. Cytokines, however, can reflect the state of uncontrolled inflammation before clinical symptoms worsen, providing an early warning signal for progression to severe illness. Clinical data confirm that CAP patients with admission IL-6 levels exceeding a certain threshold have a significantly increased risk of progressing to severe disease, consistent with the findings of this study. The combined detection of IL-6, TNF-α, and IL-10 is significantly more effective in predicting 30-day mortality in CAP patients than the traditional CURB-65 score[14]. Furthermore, cytokine profiling can stratify CAP patients according to their immune status, distinguishing between those with excessive inflammatory activation and those with immunosuppression, thereby providing precise guidance for immunomodulatory therapy. For patients with markedly elevated pro-inflammatory cytokines like IL-6 and TNF-α, suggesting a cytokine storm, early administration of immunosuppressive therapy such as glucocorticoids can significantly reduce the incidence of acute respiratory distress syndrome and mortality[15]. For patients with significantly elevated IL-10 and TGF-β, indicating immunosuppression, administering immunostimulatory therapy can enhance pathogen clearance and reduce the risk of secondary infections.

In terms of assessing treatment efficacy, dynamic monitoring of changes in cytokine levels can provide an early indication of the response to anti-infective therapy. Traditional indicators such as body temperature, white blood cell count, and CRP often show significant changes only 48-72 hours after treatment initiation, whereas cytokine levels can decrease significantly within 24 hours of effective treatment. Clinical observations show that after effective anti-infective therapy, serum IL-6 levels in CAP patients decrease by more than 30% within 24 hours, indicating effective treatment and a good prognosis. If the decrease is less than 20% or if levels continue to rise, it suggests that the anti-infective regimen is ineffective, or that a secondary infection or complication has occurred, necessitating timely adjustment of the treatment plan[16]. Moreover, dynamic monitoring of cytokines can guide the duration of antibiotic therapy. For patients whose cytokine levels rapidly return to normal, the antibiotic course can be appropriately shortened, reducing overuse and the risk of developing drug-resistant bacteria.

Although cytokine testing has significant advantages and broad application prospects in the diagnosis and treatment of CAP, there are still many limitations in its current clinical application. First, the specificity of testing needs improvement. In addition to pulmonary infection, various other pathological conditions such as trauma, acute myocardial infarction, autoimmune diseases, malignant tumors, and chronic liver disease can also cause abnormal changes in cytokine profiles. In elderly CAP patients with multiple underlying diseases, relying solely on cytokine levels to assess the condition is susceptible to confounding factors, which can lead to false-positive results. Second, there is significant heterogeneity in cytokine profile changes among CAP patients infected with different pathogens or at different stages of the disease. Currently, there are no unified cut-off values or reference standards for clinical diagnosis and disease assessment. Differences in detection methods, instruments and reagents, and enrolled populations across studies lead to poor comparability of results, limiting standardized application. Third, the cost of cytokine testing is relatively high, and the testing process is relatively complex. Most methods cannot achieve rapid point-of-care testing, which limits their use in emergency departments and primary hospitals[17-19]. Furthermore, the role of cytokines in CAP is bidirectional; the same cytokine may play completely different roles at different stages of the disease. A single test result is difficult to comprehensively assess the condition and must be interpreted in conjunction with dynamic monitoring and clinical data.

6. Conclusion

Cytokines have high value in determining the severity of CAP. Clinically, they can guide physicians in their judgment and have certain value in improving patient prognosis. However, they also have the limitations mentioned above and require further research for improvement.

References

[1] PARTHASARATHI A, PADASHETTI V C, PADUKUDRU S, et al. Association of Serum Albumin and Copeptin with Early Clinical Deterioration and Instability in Community-Acquired Pneumonia[J]. Adv Respir Med, 2022, 90(4): 323-337.

[2] SAXTON R A, GLASSMAN C R, GARCIA K C. Emerging principles of cytokine pharmacology and therapeutics[J] . Nat Rev Drug Discov, 2023, 22(1): 21-37.

[3] FOSGERAU K, HOFFMANN T. Peptide therapeutics: current status and future directions [J]. Drug Discov Today, 2015, 20 (1): 122-128.

[4] GARLANDA C, DINARELLO C A, MANTOVANI A. The interleukin-1 family: back to the future[J] . Immunity, 2013, 39(6): 1003-1018.

[5] TANAKA T, NARAZAKI M, KISHIMOTO T. IL-6 in inflammation, immunity, and disease [J] . Cold Spring Harb Perspect Biol, 2014 , 6(10): a016295.

[6] YUAN S, JIANG S C, ZHANG Z W, et al. Quantification of Cytokine Storms During Virus Infections[J] . Front Immunol, 2021, 12: 659419.

[7] NING J, SHAO X , Ma Y ,et al.Valuable hematological indicators for the diagnosis and severity assessment of Chinese children with community-acquired pneumonia: Prealbumin[J]. Medicine, 2016, 95(47):e5452.

[8] PARDO E, JABAUDON M, GODET T ,et al.Dynamic assessment of prealbumin for nutrition support effectiveness in critically ill patients[J].Clinical nutrition, 2024, 43(6):10-18.

[9] ADEOSUN P O, FATUST O A, ADEDEJI T A. Assessment of Severity of Illness and Monitoring Response to Treatment of Odontogenic Space Infection Using Serum Prealbumin[J]. J Maxillofac Oral Surg, 2019, 18(1): 106-111.

[10] Sun Yaohong, Zhang Jun, Sun Xiaona, et al. Value of prealbumin in diagnosis and severity assessment of community-acquired pneumonia in children[J]. Chinese Journal of Nosocomiology, 2018, 28(1): 123-126.

[11] Sun Xin, Zhai Meng, Zhou Wen. Value of CRP/PA, PCT/ALB, MCP-1, sICAM-1 in evaluating the severity and prognosis of infectious pneumonia in neonates[J]. Journal of Hebei Medical University, 2025, 46(4): 412-417.

[12] Chen Yong, Chen Yu, Zhang Na, et al. Value of routine blood parameters in prognosis assessment of community-acquired pneumonia[J]. Chinese Journal of Nosocomiology, 2019, 29(12): 1801-1805.

[13] DUAN Z, LI C, LEUNG W T, et al. Alterations of Several Serum Parameters Are Associated with Preeclampsia and May Be Potential Markers for the Assessment of PE Severity[J]. Dis Markers, 2020, 2020: 7815214.

[14] MATTIUZZI C, LIPPI G. Serum prealbumin values predict the severity of coronavirus disease 2019 (COVID-19) [J]. J Med Virol, 2021, 93(2): 622-623.

[15] Huang Lingxiu, Feng Cangcang. Clinical significance of serum prealbumin in diagnosis and disease assessment of community-acquired pneumonia in children[J]. Chinese Journal of Ethnic and Folk Medicine, 2017, 29(20): 20-22.

[16] Qing-Kai G , Zhong-Liang W. Clinical Diagnostic Value of BNP, Serum Cystatin C and Serum Prealbumin for Severe Heart Failure[J].[2026-02-23].

[17] Huang Jianfeng, Zhang Xiaoqiong. Clinical significance of serum prealbumin detection in patients with chronic liver disease[J]. Journal of Clinical and Experimental Medicine, 2011, 10(4): 252-253.

[18] Hu Zhiling, Liu Fengcang. Clinical significance of serum prealbumin in diagnosis and severity assessment of community-acquired pneumonia in children[J]. Chinese Journal of Ethnic and Folk Medicine, 2017, 29(20): 20-22.

[19] Tu Yunyong, Zhang Yongqing, Luo Longjian. Clinical significance of dynamic changes of prealbumin in critically ill patients[J]. Jilin Medical Journal, 2018, 39(8): 1425-1427.