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Review article ■

New Markers in Prognosis of Severe Community - Acquired Pneumonia

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SUMMARY

Community-acquired pneumonia (CAP) is the most common cause of death among infectious diseases.

During the management of pneumonia, it is often uncertain when the disease may turn into severe form. The first definition of severe CAP was provided by the ATS Guidelines. Definition was built up around simple clinical and radiographic criteria reflecting the actual illness. The assessment of disease severity is valuable for clinicians caring for patients with severe CAP. The Pneumonia Severity Index (PSI) and CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years) are usually employed to predict the prognosis of CAP. However, the accuracy of PSI and CURB-65 for predicting outcomes has been challenged. New biomarkers may be useful for improving the outcome prediction in PSI classes I-V and high-risk CURB-65 score categories. Patients with severe form of the disease have benefit from admission to the intensive care unit. We must recognize the right moment for admission.

Elevated concentrations of cytokines and markers reflect the complex changes in the immune response to microorganisms, and are associated with alterations of the neuroendocrine and vascular systems. Physicians must understand the problems associated with the pathogenesis of severe pneumonia and to apply the basic principles to guide the effective management.

A lot of biomarker tests demonstrate independent prognostic factors for either 30-day or in-hospital mortality, including procalcitonin, triggering receptor expressed on myeloid cells-1 (TREM-1), proadrenomedullin, CRP, pro-atrial natriuretic peptide and pro-vasopressin. Further study of these remarkable plasma proteins is necessary, aiming to treat CAP more efficiently.

Key words: **severe pneumonia, biomarkers, scoring of pneumonia**

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INTRODUCTION

Pneumonia remains a major public health problem. It is the number one cause of death from infectious diseases and it rises both in the hospital and in outpatient setting. The mortality rate due to pneumonia is 2.7-3.25% of all deaths, most of them occurring in the population aged over 65. More than one million patients with CAP require hospitalization annually, 10% of whom will be admitted to an ICU (1). Among ICU patients, especially in those who require mechanical ventilation or vasopressors, mortality rate increases to approximately 50% (2).

Community-acquired pneumonia (CAP) is the most important clinical infection with a high long-term mortality rate. Guidelines recommendation is that all hospitalized patients should have checked: full blood count, value of CRP, urea and electrolytes, liver function tests, chest radiograph, pulse oxymetry measured oxygenation saturations (and if necessary, arterial blood gases analyses) (3).

To optimally manage patients with CAP, it is necessary use the prognostic scoring systems. The use of these scoring systems help to identify the level of risk factors for death. Severe community-acquired pneumonia is an entity first described in patients with CAP admitted to the ICU, but there is no uniformly accepted definition of severe CAP. ATS guidelines identified nine criteria for severe illness, but this definition was overly sensitive, and not specific (4). Later, nine criteria for severe CAP were divided into five "minor" criteria (respiratory rate ≥30/min; Pa_{02} / Fl_{02} <250; bilateral or multilobular pneumonia; systolic BP≤90 mmHg; diastolic BP≤60 mmHg;) and four "major" criteria (need for mechanical ventilation; an increase in the size of infiltrates by >50% within 48 h; need for vasopressors for >4 h; acute renal failure;). The need for ICU admission requires the presence of two minor criteria or one major criterion (5).

The Pneumonia Severity Index (PSI) uses a two-step algorithm to divide patients into five classes based on the risk of death within 30 days (6). CURB-65 score (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥65 years) is a scoring system, an easily measured alternative to the PSI and is widely used in Europe (7). However, the accuracy of PSI and CURB -65 for predicting outcomes has been challenged, as it potentially overemphasizes the importance of age.

Several biomarkers, proinflammatory cytokines and adrenocortical hormones have been implicated with the outcomes and disease severity. They may be useful for improving outcome prediction in PSI classes I-V and high-risk CURB-65 score categories (8). It is important to recognize that the inflammatory response is a dynamic event (9). The time point of the initial clinical evaluation may not adequately reflect the true severity of the disease that is developing. Biomarkers for CAP are often compared with global measures of disease severity using clinical scoring systems.

Patients with elevated levels of both IL-6 and IL-10 had 20 times higher risk of death than patients with low levels of both cytokines (10). Interleukins are present in very low concentrations (picomolar levels) in most infectious disease and they are therefore difficult to measure.

A number of biomarker tests have been demonstrated on univariante and multivariante analyses to be independent prognostic factors for either 30-day or in-hospital mortality. These include procalcitonin, triggering receptor expressed on myeloid cells-1 (TREM-1), proadrenomedullin, CRP, pro-atrial natriuretic peptide and pro-vasopressin (4). Biomarkers for CAP are often compared with global measures of disease severity using clinical scoring systems. The determination of the majority of these biomarkers is not widely or routinely available at present.

C-reactive protein

Measurement of CRP on admission may be helpful in distinguishing pneumonia from other acute respiratory diseases (4). Raised CRP level on admission is a relatively more sensitive marker of pneumonia than elevated temperature, erythrocyte sedimentation rate, fibrinogen or raised white cell count (11, 12). CRP in more than 75% of patients had levels ≥100 mg/l, and CRP level ≥100 mg/l in the diagnosis of CAP shows specificity of 96% (13). Chalmers et al. have reported an association of a low CRP level of ≤100 mg/l at the time of hospital admission with a reduced risk for 30-day mortality, need for mechanical ventilation and/or inotropic support, and complicated pneumonia (14). Some studies have not found an association of admission CRP level with prognosis (15). Patients in risk classes III-V had a higher median PCT value compared to those in classes I and II, whereas no significant difference was observed in the CRP concentrations between those groups classified as Pneumonia Severity Index (PSI) I-II or PSI III-V (Figure 1) (16).

The acute phase reactant CRP is a sensitive marker of progress in pneumonia (17). Repeated measurement of CRP at day 3 or 4 is helpful in identifying patients with treatment failure (18). If CRP is high, the chest radiograph should be repeated in patients who are not progressing satisfactorily after three days of treatment (3). A failure of CRP to fall less than 50% is associated with increased 30-day mortality rate, increased need for mechanical ventilation and/or inotropic support and increased incidence of complicated pneumonia such as empyema (14).

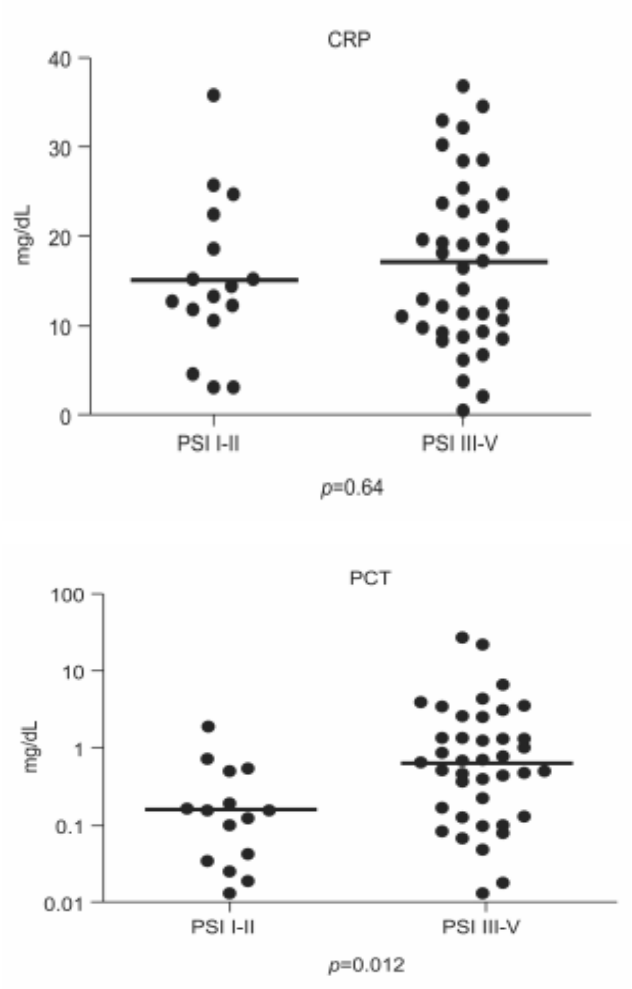


Figure 1. *CRP and procalcitonin (PCT) concentration according to the PSI in bacterial CAP (16)*

Procalcitonine

Procalcitonine (PCT) is produced by the c-cells in the thyroid. Circulating levels of the precursor hormone PCT, derived primarily from non-thyroidal tissues, can rise several thousand times above normal in various inflammatory conditions, especially in bacterial infection (19). PCT compared with CRP is more sensitive in differentiating between bacterial and viral infections.

PCT is a more powerful guide biomarker of prognosis in pneumonia than several more commonly used biomarkers. PCT levels increase with increasing severity of CAP, classified according to the PSI score. This increase was more pronounced as compared to total leukocyte count, C-reactive protein (20).

A high PCT and an increase for one day is an early indicator for mortality in ICU patients (21). Persistently high levels of PCT are associated with worse outcome (22). In contrast, a falling level of PCT, with a half life of 20-24h, suggests a favorable outcome, especially in ventilator associated pneumonia (23).

The use of PCT values according to the severity of pneumonia is different. In patients with low Pneumonia Severity Index (PSI classes I-II), PCT can predict microbial etiology of pneumonia. PCT level is higher in those with pneumonia of bacterial etiology. In patients with high PSI risk classes (classes III-V), PCT has proved to be a good prognostic marker rather than a diagnostic marker (24). Low levels (<0,1 mg/ml) of PCT at baseline are predictive of survival, even in PSI group IV and V patients. With increase of PCT in PSI class IV and V, the risk of mortality is higher (Figure 2) (25). Median PCT levels on admission of non-survivors are significantly higher compared with those in survivors (26).

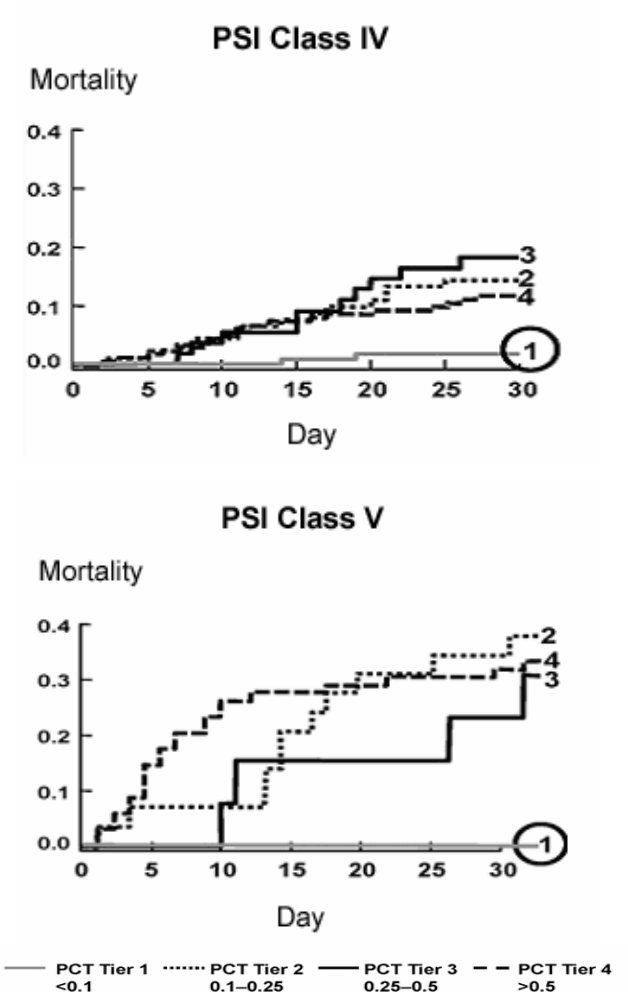


Figure 2. *Procacitonin (PCT) level and PSI prognostic value of mortality (25)*

PCT is a biomarker for sepsis and severe infection, with a high specificity and sensitivity; it is readily measurable, available in many hospitals. The use of PCT as a biomarker in Europe increases, not only in the diagnosis of sepsis, but also in less severe infections such as CAP.

D-dimer

D-dimer is a degradation product of cross-linked fibrin. This marker is mainly used in the diagnostic investigation of patients with suspected venous thromboembolism. However, there is an important interaction between inflammatory mechanisms and coagulopathy. Severe infection activates coagulations.

Patients with severe CAP show abnormalities of coagulation, down regulation of anticoagulant systems and uncontrolled fibrinolysis. High D-dimer levels may represent micro vascular thrombosis or extracellular remodeling of fibrin in acute and chronic lung injuries. In lung parenchyma and pleural disease, a transitional fibrin neomatrix constitutes a part of the acute inflammatory response (27). An absence of high D-dimer level is a useful marker in ruling out clinical sepsis and 28-day mortality (28).

Plasma D-dimer levels correlate with PSI severity and outcomes in CAP patients. Baseline D-dimer as independent variable shows a strong relationship with probability of death in PSI IV and V patients (Figure 3). Elevated D-dimer levels are associated with radiologic pneumonia extension, mechanical ventilation needed, presents of major complications (3,629 ng/mL), respiratory distress syndrome (5,794 ng/mL), severe sepsis (2,860 ng/mL), and serious decomposition of their baseline disease (3,063 ng/mL) (29).

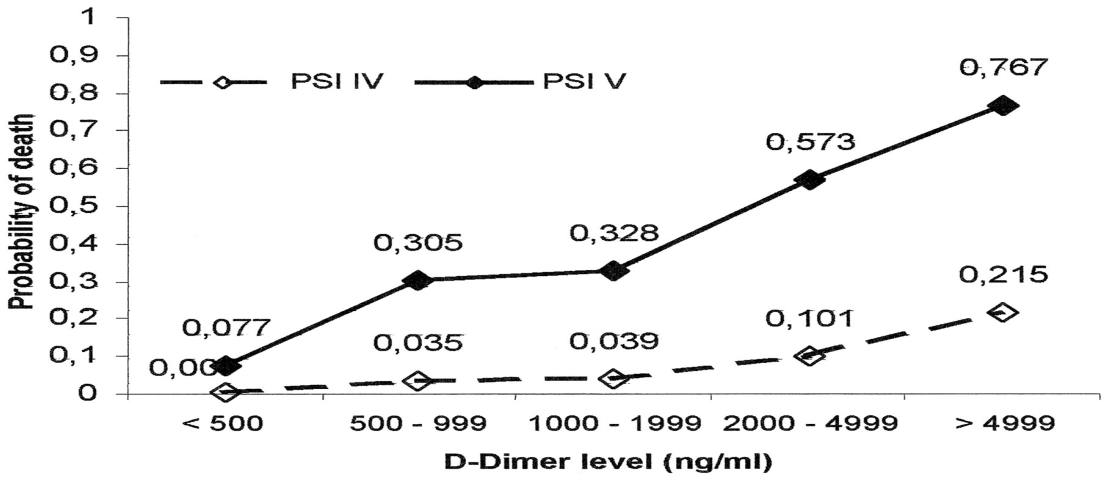


Figure 3. *Correlation of D-dimer with probability of death in CAP (PSI IV and V patients) (29)*

D-dimer correlates with the Pneumonia Patient Outcome Research Team (PORT) score, with length of hospital stay, number of organ failures and hospital mortality (30).

D-dimer is mainly used in the diagnostic investigation of patients with suspected venous thromboembolism. This marker on admission has also been reported to be an independent prognostic marker of outcomes in patients with severe CAP.

Triggering receptor expressed on myeloid cells 1 (TREM-1)

TREM-1 belongs to the immunoglobin super family and is involved in inflammatory response. It has the advantage of being increased during infectious processes, but not in noninfectious inflammatory conditions. TREM-1 is upregulated by microbial products, and is expressed on the surface of neutrophils, monocytes, and macrophages during acute inflammatory responses (31).

Exposure to infectious agents results in up-regulation of TREM-1 on blood neutrophils and a subset of monocytes, primary mediators of the host innate immune response. TREM-1 activation triggers pro-inflammatory cytokine and chemokine release, increased surface expression of cell activation markers, release of myeloperoxidase, and increased neutrophil and monocyte survival at the site of inflammation, thus amplifying the acute inflammatory response (32).

TREM-1 in bronchoalveolar lavage fluid accurately identifies bacterial or fungal pneumonia in mechanically ventilated patients, and is superior in this regard to clinical findings or other laboratory values. Such lavage is not appropriate, however, in the routine care of patients with severe CAP (33).

Serum sTREM-1 level is high in patients with CAP. The prognostic value of sTREM-1 is independent of age, other inflammatory markers such as IL-6, Pneumonia Severity Index, CURB-65, the severity of sepsis, and nutritional status. Patients who had increased sTREM-1 on admission had the worst prognosis (34).

Adrenomedullin (ADM), Atrial natriuretic peptide, Copeptin

Potentially useful prognostic markers of CAP patients are adrenomedullin (ADM), the natriuretic peptides (atrial natriuretic peptide and B-type natriuretic peptide) and copeptin.

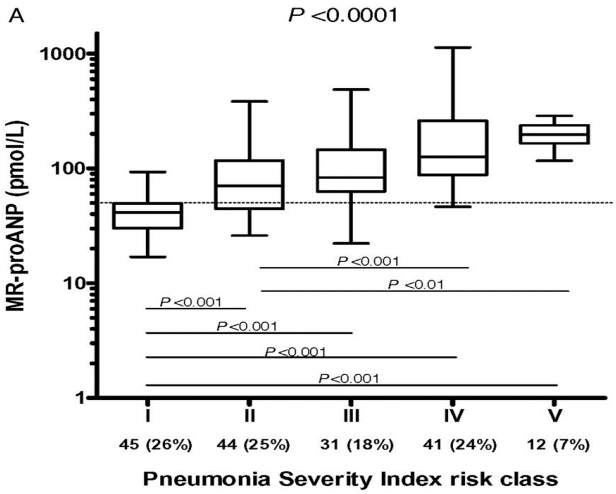
Adrenomedullin (ADM) is one of the most potent vasodilatation agents and has additional immune modulating. Levels of proADM increased with increasing disease severity, as reflected in the PSI score (35).

Arginine vasopressin (AVP) is a key hormone in maintaining fluid balance and vascular tone. Precursor protein, pre-pro-vasopressin, consists of a signal peptide, AVP, neurophysin II, and copeptin. Copeptin is the Carboxyl-terminal part of the AVP precursor (CT-proAVP) and it is a stable and sensitive surrogate marker for AVP release. Copeptin reflects individual stress at a higher (hypothalamic–pituitary) level (36).

Due to the positive association of copeptin with the severity of disease and outcome, copeptin has been proposed as a prognostic marker in acute disease. Copeptin levels have a tendency to increase as the severity of lower respiratory tract infection increases. Copeptin levels increased with increasing severity of CAP, as defined by the PSI (Pneumonia Severity Index (PSI) standard clinical score. In patients who died, copeptin levels on admission were significantly higher compared to levels in survivors (20).

Atrial natriuretic peptide, primarily produced in the cardiac atria, belongs to the natriuretic peptide family. The mid-region of the prohormone of ANP, known as MR-proANP (midregional pro-atrial natriuretic peptide) has been found to increase with severity of sepsis and may be used as a predictor of mortality, and a prognostic marker in pneumonia (37).

Both MR-proANP and CT-proAVP (Copeptin) can be used to predict severity of disease in patients with CAP. MR-proANP and CT-proAVP levels increased with increasing severity of CAP, classified according to CRB-65 score (38), and PSI risk class (Figure 4) (39).



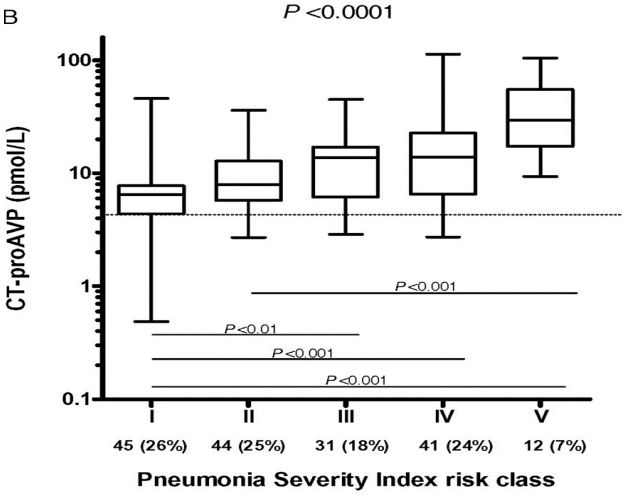


Figure 4. *MR-proANP (A) and CT-proAVP (B) in CAP patients according to PSI risk class (39)*

The levels of MR-proANP and CT-proAVP were significantly higher in non-survivors than the levels in survivors. Cut off values of >18.9 pmol/L for CT-pro-AVP and >227 pmol/L for MR-proANP showed the highest diagnostic accuracy to predict mortality (39).

Pneumonia severity index, MR-proANP and CT-proAVP are independent and the strongest predictors of short-term and long-term mortality compared to PCT, CRP and leukocyte count. Non-survivors have significantly higher MR-proANP concentrations than patients who survived. CT-proAVP and MR-proANP may be used to predict prognosis in patients with CAP (40). Analysis of proADM, pro-atrial natriuretic peptide and B-type natriuretic peptide, copeptin have become available in Europe. Copeptin increases with increasing severity of the PSI and was an independent predictor of outcome, in contrast to other clinical symptoms and findings (20). Clinical experience with these peptide precursor molecules is limited, but presents a correlation with severity of disease.

CONCLUSION

What could these biomarkers in patients with severe CAP be used for in the future?

Severe CAP may be considered a systemic response to an initially local infection. Severe CAP is a progressive disease which may lead to rapid decompensation, multyorgan dysfunction and significant mortality. Current clinical practice involves determining the presence of infection, usually through cultures, Gram stain, urine antigen testing or serology, but it does not involve routine assessment of the patient's level of inflammatory response or for disorders of coagulation. Procalcitonin could be used for a better diagnosis of CAP and sepsis and for the guidance of antibiotic therapy. Cytokines are prognostic for the development of CAP, severe disease, sepsis and death in hospitalized patients. MR-proANP

could be used for the identification of patients with a high cardiovascular risk.

In fact, in the present study, as well as in the recent CAP studies, it could be shown that clinical scores and biomarkers can both be merged and result in superior predictions of mortality. Several biomarkers are good options for identifying patients who are likely to develop more severe CAP. None of these markers should ever be used in isolation to make clinical decisions. A combination of a clinical score, such as PSI and CURB 65, with these markers for risk assessment and PCT for guidance of antibiotic therapy is very usefully in the management of severe CAP.

At present, PSI IV or V disease with elevated PCT and/or D-dimer may be clinically useful tools for identifying CAP patients with high-risk of severe disease and risk of mortality.

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NOVIJI PROGNOSTIČKI MARKERI TEŠKE VANBOLNIČKI STEČENE PNEUMONIJE

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Sažetak

Vanbolnički stečena pneumonija (VSP) je i dalje vodeći uzrok smrtnosti među infektivnim bolestima. Tokom lečenja bolesnika sa pneumonijom često je neizvesno kada bolest može prerasti u tešku pneumoniju. Termin „teška pneumonija" je prvi put uveden od strane Američkog torakalnog društva. Definicija je bila bazirana na kliničkim i radiološkim parametrima bolesti. Pravovremena procena težine bolesti je jako bitna za kliničara. Najčešće korišćeni skoring sistemi za procenu težine pneumonija i rizika od mortaliteta su PSI (Pneumonia Severity Index) i CURB 65 (Confusion- konfuzija, Urea nitrogen- urea, Respiratory rate-frakfenca disanja, Blood pressure- krvni pritisak, age (starosna dob) ≥65 god). Ovi skoring sistemi, međutim, nisu u potpunosti usaglašeni i precizni. Dodatna primena nekih novijih markera nam može pomoći da izdvojimo bolesnike sa visokim rizikom za smrtni ishod i donesemo pravovremenu odluku o nihovom lečenju na odeljenju intenzivne nege.

Promene u koncentraciji citokina i novijih biomarkera, koji su udruženi sa neuroendokrinim i vaskularnim promenama, nastaju kao posledica aktivacije imunoloških mehanizama od strane nekih mikroorganizama. U cilju uspešnijeg lečenja bolesnika neophodno je shvatiti patofiziološke mehanizme teške pneumonije.

Novijim istraživanjima je utvrđeno da brojni biomarkeri mogu biti nezavisni predikotori povećanog rizika od smrti u prvih 30 dana lečenja pneumonija. Među njima se izdvajaju: prokalcitonim, TREM-1, proadrenomedulin, prekursori vazopresina. Detaljnija istraživanja i praktična klinička primena ovih biomarkera je opravdana u cilju efikasnijeg lečenja teških pneumonija.

Ključne reči: **teška pneumonija, biomarkeri, skoring sistem za procenu stepena težine pneumonija**