Review Article

The significance of clinical scores and biological markers in disease severity, mortality prediction, and justifying hospital admissions in patients with community-acquired pneumonia

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ABSTRACT

There is a higher prevalence of community-acquired pneumonia (CAP) worldwide. The stratification of the severity and prognosis of CAP is a vital feature as it is one of the most common causes of mortality among other infectious diseases in the developed countries. The mortality rate of patients with CAP depends on the severity of the disease, treatment failure along with the requirement of hospitalization and/or Intensive Care Unit (ICU) management which is quite cost-effective. To improve the outcomes in the management of CAP, there has recently been a significant attention paid to focus on the use and implication of evidence-based scoring systems and biological markers to justify hospital admission in either acute medical settings or ICU, also to classify the disease severity which will help in predicting the mortality rate. We have reviewed the significance of established and newly developed clinical scores, biological markers, and cytokines whether used alone or in conjunction with the clinical severity scores to assess the severity of the disease, prediction of early or late treatment failure, justify the acute in-hospital or ICU admission, and for the identification of short- and long-term mortality. In conclusion, the incorporation of the biological markers in the prognostic scales of the clinical scoring systems may improve the mortality prediction value of patients with CAP requiring acute hospitalization or ICU care and further studies at a larger scale are needed to corroborate the additive value of biological markers.

Key words: Biomarkers, clinical scores, community-acquired pneumonia, disease severity, mortality prediction

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INTRODUCTION

The stratification of the severity and prognosis of community-acquired pneumonia (CAP) is a vital feature as it is one of the most common causes of mortality among other infectious diseases in the developed countries.[1] CAP is globally the second biggest cause of death,[2] 1.2 and 11.6 cases/1000 population/year in Europe,[3,4] approximately 4 million adults each year in the United States with over 600,000 being hospitalized[5,6] and worldwide between 1.5 and 14.0 cases/1000 persons/year.[7-9]

The mortality rate is <1% for those individuals who do not require hospitalization.[10,11] The 30-day mortality rate among hospitalized ranges from 4% to 18%;[9,12,13] however, for Intensive Care Unit (ICU) patients, this rate can reach up to or >50%.[14] The hospitalization of patients with CAP is quite cost-effective,[15] and there have been few recommendations to reduce their hospital length of stay with effective hospital outreach programs, provision of community parental antibiotics, appropriate and adequate antibiotics usage, and the introduction of vaccines in the community.[16,17]

To improve the outcomes in the management of CAP, there has recently been a significant attention paid to focus on the use and implication of evidence-based scoring systems and biological markers to predict treatment failure, justify hospital admission in either acute medical settings or ICU, also to classify the disease severity which will help in predicting the mortality rate.

The recent literature concerning the significance of clinical scores, biological markers, and cytokines whether used alone or with other clinical severity scores has been reviewed for the prediction of early or late treatment failure, justification of acute in-hospital or ICU admission, and identification of short- and long-term mortality among these patients cohort. A comprehensive search has been conducted in PubMed, Wikipedia, and Google Scholar database searching the following terminologies: CAP, clinical scores, biomarker, prognosis, ICU, and mortality.

CLINICAL SCORES IN PREDICTING MORTALITY AND JUSTIFYING ADMISSIONS

There are numerous clinical tools for prediction of the severity of CAP, indications of in-hospital and ICU admissions, treatment failure and progression of the disease, few examples are CURB-65,[18-20] pneumonia severity index (PSI),[10] and SMART-COP.[21] There are few severity assessment scores to predict mortality in CAP in ICU including predisposition, insult, response, and organ dysfunction (PIRO),[22] Acute Physiology and Chronic Health Education (APACHE) II,[23] sequential organ failure assessment score (SOFA),[24] and the American Thoracic Society/Infection Disease Society of America (ATS/IDSA) criteria as a prognostic index in CAP patients requiring ICU admission.[25]

CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30/min, blood pressure ≤90/60 mmHg, and age ≥65 years) predicts mortality with an overall sensitivity and specificity of about 80%[18-20] and helps in the stratification of patients in three management groups with CURB-65 score of 0–1, 2, and >2 as low risk (mortality <2%) for outpatient management, intermediate risk (mortality 9%) for hospital supervised treatment, and high risk (mortality >19%) treated initially in an intensive care or high dependency unit, respectively.[26]

The expanded version of CURB-65 with eight parameters is more effective score for CAP to predict disease severity, mortality, and mode of treatment, called expanded CURB-65 (standard CURB-65 with lactate dehydrogenase (LDH) >230 μL, platelets $<10^5$/mL, and albumin <3.5 g/dL).[27] It is categorized into three classes with 0–2 as low risk, 3–4 intermediate risk, and 5–8 high risk should be treated either as outpatient or inpatients in hospital ward or ICU, respectively. The thrombocytopenia, raised LDH, and hypoalbuminaemia are considered as independent mortality risk factors at multivariate analysis.[27]

PSI is an extensive scoring index including demographic characteristics, comorbidities, physical examinations, laboratory parameters, and pleural effusion.[10] It stratifies patients of CAP into five classes on the basis of the severity of the disease. It predicts the short-term mortality and also identifies patients with low-risk mortality at presentation. The 30-day mortality in Class I is 0.4%, Class II (PSI score ≤70) is 0.7%, Class III (PSI score 71–90) is 2.8%, Class IV (PSI score 91–130) is 8.5%, Class V (PSI score >130) is 31.1%, and all classes' 30-day mortality is 10.2%.[10]

CURB-65 (74.6%) has a higher specificity than PSI (52.2%) and lower sensitivity in predicting ICU admission.[28] PSI better identifies low probability of death as compared to CURB65, also later score system does not adequately evaluate patients' comorbidities as compared to PSI.[29]

SMART-COP (low systolic blood pressure, multilobar involvement, low albumin, high respiratory rate, tachycardia, confusion, poor oxygenation, and low arterial pH), a clinical tool, helps predict 30-day mortality rate, and the need for ICU admission for intensive respiratory or vasopressor support (IRVS). The SMART-COP scores of 0–2, 3–4, 5–6, and ≥7 suggests low, moderate, high, and very high risk of mortality requiring ICU or HDU admission for IRVS, respectively.[21]

PIRO is another clinical severity assessment tool designed to predict 28-day mortality rate in CAP patients in ICU and associated with increased healthcare resource utilization in

these patients.[22] It comprises eight variables with one point each including comorbidities; age >70 years; multilobar opacities in chest radiograph; shock, severe hypoxemia; acute renal failure; bacteremia; and acute respiratory distress syndrome. The score within first 24 h from ICU admission with 0–2 as low risk, 3 as mild, 4 as high, and 5–8 as very high mortality risks with longer ICU stay and prolonged mechanical ventilation.[22]

APACHE II is a computer-based ICU scoring system points from 0 to 71 based on patient's age, oxygen partial pressure (PaO_2), body temperature, mean arterial pressure, arterial pH, heart rate, respiratory rate, serum sodium, serum potassium, creatinine, hematocrit, white blood cell count (WCC), and Glasgow Coma Scale (GCS).[23] It is applied within 24 h of admission to ICU to describe patients' morbidity, assess the disease severity, and mortality risk. The higher APACHE II score reflects disease severity and increased mortality in ICU patients with CAP.[30,31]

SOFA is an ICU sepsis assessment score based on six variables including PaO_2/FiO_2, mean arterial pressure, bilirubin, platelets, creatinine, and GCS. It is used to determine the extent of a person's organ function and rate of failure[24,32] during ICU stay. It has been shown that the SOFA scores help in predicting survival in patients with CAP-associated sepsis.[33]

The ATS and IDSA have convened a joint committee to develop unified ATS/IDSA criteria to improve the care of adult patients with CAP by assessing the severity of illness and site of care decisions.[25] In relation to the decision regarding hospital admission, objective scores such as CURB-65 and PSI must be tampered by the physicians' clinical judgment. ATS/IDSA has setup criteria for ICU admission for patients with CAP. It comprises two major (invasive mechanical ventilation, septic shock requiring vasopressors) and nine minor criteria (respiratory rate >30/min, PaO_2/FiO_2 <250, multilobar pneumonia, confusion, urea >20 mg/dL, WCC <4000 cells/mm^3, platelet count <100,000 cells/mm^3, temperature <36°C, and hypotension).[25] If the patients fulfill any of the major criteria and/or at least three minor criteria require ICU admission.

Although these assessment tools help in identification of high-risk CAP patients with poor outcome and may impact on hospital resource consumption[25,34] and prognosis, these scores have some limitations such as low-risk patients as defined by these scores may require hospital admissions and high-risk have good response with short hospital stay and parental antimicrobials.[35] Furthermore, low sensitivity of these scores has been demonstrated in the prediction of ICU admissions too.[36] There are few more facts which limit the utilization of these scores such as misapplication or failure to remember the score by doctors, over- or under-estimation of acute medical or ICU admission, or mortality risks under certain circumstances, which further emphasize that these scores should cautiously be used in conjunction with thorough systemic clinical assessment of the patients.

BIOMARKERS – THEIR ROLE IN PREDICTION OF TREATMENT FAILURE, DISEASE SEVERITY, AND MORTALITY IN COMMUNITY-ACQUIRED PNEUMONIA

Biomarkers are cellular, biochemical, or molecular markers which are objectively measured in biological media such as human tissues, cells, or fluids. These biomarkers play vital role in assisting normal physiological processes, can also be used to indicate pathogenic processes or pharmacological responses to a therapeutic intervention.[37,38]

These biomarkers are useful in establishing diagnosis, identifying etiology, assessing severity and prognosis, and for therapeutic interventions in CAP. Recently, increased attention has, therefore, been paid in the research field of medicine on the biomarkers in resolving fundamental issues regarding prognostic prediction, disease severity, and aggressiveness that cannot be readily addressed using CAP-specific scores.

The multiple investigators have used several biomarkers to evaluate the alteration in immunological, cardiovascular, endocrine, and coagulation systems in patients with CAP knowing it as a multisystem disease.[39,40] The multivariate analysis has been conducted in several studies to establish a relationship among different biomarkers and mortality rates in patients with CAP, and to assess the predictive power of the study, area under receiver operating characteristic (AUROC) has been used.

The serum C-reactive protein (CRP) predicts mortality in hospitalized patients with CAP[41] with lesser mortality risk once CRP <100 mg/L, and an independent mortality predictor once it fails to fall <50%. Further mentioned that CRP in combination with interleukin-6 (IL-6), a potent host defense cytokine with ability to induce the acute phase response, has been independently associated with mortality risks in patients with CAP.[42]

There has been a strong association between treatment failure and risks of mortality in patients with CAP, ranges from 2.4% to 31% for early treatment failure (clinical deterioration within 72 h of the treatment) and 3.9–11% for late failure[43] (clinical deterioration between 72 and 96 h after starting the treatment),[44,45] developing shock, requiring invasive mechanical ventilation or death. It has been shown that serum markers including CRP, procalcitonin (PCT), IL-6, higher CURB-65 >3, with radiological presentation of pleural effusion and/or multilobar involvement are predictors of treatment failure in patients admitted with CAP.[46]

IL-6 and pleural effusion are independent risk factors for early treatment failure whereas CRP, PCT, and multilobar involvement are as late failure predictors.[46]

The biomarkers including proadrenomedullin, thrombin-antithrombin complexes, kallistatin, red blood cell distribution width, mid-regional proatrial natriuretic peptide, C-terminal proatrial vasopressin, D-dimers, and B-type natriuretic peptide have significant role in predicting long-term mortality in CAP,[47-53] which is helpful in identifying high-risk patients who need close observation posthospital discharge which can impact their long-term mortality rate.

The role of multiple biomarkers in predicting the mortality in patients with CAP admitting to ICU has been assessed in several studies.[47,54-57] A series of biomarkers including kallistatin (a serine proteinase inhibitor with significant role in ion transport, inflammation, and blood pressure regulation),[47] platelets,[54] D-dimers,[55] PCT,[56] and CRP[57] have been analyzed in different studies and found that they all are independently associated with the prediction of mortality in ICU patients with CAP. Further mentioned that the acute rise in the concentration of PCT and CRP[56,57] has significantly predicted mortality in ICU patients during the initial phase of admission.

Thrombocytopenia influences the outcome in patients admitted to ICU for severe CAP. A multicenter, observational, French study has classified patients into three categories on the basis of the degree of their thrombocytopenia and found significant increase in mortality rate in patients with CAP in ICU with lower platelet count.[54] Further, in non-ICU hospitalized patients with CAP, it has been shown that abnormal platelet count, either thrombocytopenia of <100,000/L or thrombocytosis of >400,000/L, is associated with increased mortality.[58]

A soluble urokinase-type plasminogen activator receptor (suPAR) positively correlates with the activation of immune system and is a marker of disease severity and aggressiveness.[59] suPAR possesses high sensitivity and specificity levels in terms of differential diagnosis. The higher levels of suPAR along with PCT and CRP can predict mortality in patients with pneumonia requiring ICU admission.[60] The concentration of suPAR helps in establishing the prognostication of patients with pneumonia.[61]

INTEGRATION OF CLINICAL SCORES AND BIOMARKERS IN MANAGING COMMUNITY-ACQUIRED PNEUMONIA

Visfatin, a pre-B-cell colony-enhancing factor 1 enzyme, promotes vascular smooth muscle cell maturation and inhibits the neutrophil apoptosis. There is a higher plasma concentration of visfatin in the patients with CAP.[62] It has a strong association with PSI, APACHE II, WCC, and CRP of these patients, further strengthens its correlation with disease severity and is considered as an independent 30-day mortality marker in patients with CAP.[62]

Endothelin-1 is a potent vasoconstrictor protein secreted by endothelial cells and contributes to vascular tone and regulates cell proliferation. It has been illustrated that the changes in endothelin-1 levels on day 3 since admission has significantly improved the patients' outcome by changing their PSI score classification from admission.[63] In another multicenter study, the prognostic significance of the panel of biomarkers including endothelin-1, atrial-natriuretic peptide, antidiuretic hormones, and PCT has been assessed in CAP and found that adding these prohormones has led to a significant improvement in the model for CURB-65.[64] A 6-year prospective study has shown that the addition of proadrenomedullin and proatrial natriuretic peptide has further improved the prognostic capabilities of the PSI and the CURB-65 score[65] in patients with CAP.

The soluble receptor for advanced glycation end products (sRAGEs) play an important role in inflammatory mechanism by cell adhesions, proliferations, and migrations.[66] sRAGEs have been analyzed along with other severity scores (CURB-65, PSI, APACHE II, and SOFA) in patients admitted with CAP and found that SOFA and sRAGEs are the two variables with ability to identify high-risk patients with poor outcome.[33]

Copeptin, a peptide secreted from hypothalamus responsible for folding of vasopressin, has a role in the pathophysiological pathways in which vasopressin is involved[67] such as diabetes insipidus, acute myocardial infarction, syndrome of inappropriate secretion of antidiuretic hormone, and septic shock. A Swiss study has demonstrated higher copeptin levels in patients with CAP which predict disease severity as classified in PSI score and also mortality rate. The AUROC for survivals are significantly higher for copeptin as compared to CRP, PCT, and leukocytes, which emphasizes that copeptin is a potent biomarker in the risk stratification of patients with CAP.[68]

A panel of proinflammatory cytokines including IL-6, IL-8, serum markers including CRP, and PCT has been analyzed at admission along with severity scores including PSI, CURB-65 in a Spanish study to predict mortality in patients admitted with CAP.[42] There are significantly increased concentrations of IL-6, IL-8, CRP, and PCT in patients who died with the severity of the disease, further it has shown that IL-6 and CRP are independent 30-day mortality predictive markers.[42]

PCT and CRP along with CURB-65 help in predicting the severity of CAP, admission criteria, and microbial etiology as bacterial pneumonia has a significantly higher PCT, and CRP levels as compared to CAP with atypical or viral etiology. Furthermore, PCT and CRP with CURB-65 may have a role

in predicting hospitalization or safe outpatient management in these patients.[69]

In ICU, the in-hospital mortality has been assessed using D-dimer along with SOFA and APACHE II scores and found higher levels of D-dimer in nonsurvivors than surviving CAP patients. Furthermore, the addition of D-dimer to APACHE II or SOFA score has increased the discriminative ability of both scores in predicting disease severity and mortality among these patients.[55]

Vitamin D has immunomodulatory properties and role in host defense against infections. Vitamin D and cortisol levels along with PSI and CURB-65 have been studied in ICU patients with CAP to predict 30 days mortality and ICU admission. It has been found that Vitamin D deficiency is associated with adverse outcome of CAP, higher rate of ICU admissions and considered as an independent 30 days mortality predictor. The Vitamin D deficiency has added prognostic value to serum cortisol, and measured clinical scores in particular PSI.[70]

Serum albumin level within 24 h of hospitalization is a good prognostic marker in CAP.[71] The levels of serum albumin, CRP, and PSI score have been analyzed in CAP patients requiring hospitalization and found increased prognostic performance when albumin and CRP are added with their respective PSI scores. Hypoalbuminemia with high PSI score is associated with prolonged hospital stay, ICU admission, disease severity, and mortality rate.[71,72]

DISCUSSION WITH FORWARD DIRECTIONS

The role of the mentioned biomarkers in predicting the severity of the CAP and mortality risks is commendable but those studies have some limitations as well. There is a need of further research with larger sample size such as PSI[10] and CURB-65[18] studies. The timing of biomarker analysis is critical in most of the studies as different time of measurements can significantly vary the severity classification.[73] As we know, there are multiple factors which can influence the concentrations, and bioavailabilty of these biological markers including aging,[74] medications such as steroids, antimicrobials, acute kidney injury, and the microorganisms causing CAP.[53]

The significance of biomarkers of CAP whether used alone or in conjunction with the above mentioned clinical severity of illness scores has been examined in this review. The identification of the short- and long-term mortality of patients with CAP and the prediction of both the need for ICU admission and the potential for treatment failure has also been emphasized here. Further validation of these biomarkers and invention of more advanced biomarkers are required in prospective trials to elucidate their application in clinical practice.

CONCLUSION

We can conclude on the basis of the available data that the incorporation of the biological markers in the prognostic scales of the clinical scoring systems may improve the mortality prediction value of patients with CAP requiring acute hospitalization or ICU care. These biomarkers may also improve or better evaluate the mortality prediction of the prognosis, based on the inflammatory response of each patient. The early prediction of treatment failure using clinical scores, with biomarkers, and cytokines plays a critical role in improving survival of these patients. Further studies are needed to corroborate the additive value of biological markers.

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Conflicts of interest
There are no conflicts of interest.

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