Biomarkers and clinical scoring systems in community-acquired pneumonia

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Abstract:

Community-acquired pneumonia (CAP) is the third most common cause of death globally. Due to the complexity of CAP, it is widely accepted that, currently, clinical prognosis and diagnosis is inadequate for the assessment of the severity of the disease. With the aim to determining the initial treatment and the appropriate level of intervention, several clinical scores of severity and biomarkers have been developed. Both biomarkers and clinical scoring systems are expected to determine the different aspects of the host factor and the response to therapy, in order for physicians to be able to make an accurate benefit/risk assessment that will lead to proper diagnosis and correct prescription of antibiotics. This review aims to highlight the prognostic and diagnostic accuracy of various laboratory and clinical parameters in CAP and discuss the perspectives for the reduction of CAP mortality.

Keywords:

Biomarkers, community-acquired pneumonia, clinical scoring systems

Community-acquired pneumonia (CAP) is the third most common cause of death globally, the major infection-related cause of death in developed countries, and accounts for between 5% and 12% of all cases of adult lower respiratory tract infection (LRTI) managed by primary care physicians.[1-4] The annual cost for treating CAP in the United States exceeded $9 billion throughout the mid-1990s[5] and mid-2000s.[6,7] Approximately 10% of CAP patients require lung ventilation support or are admitted to an intensive care unit (ICU) due to septic shock. The mortality rate among those patients ranges from 19% to 50%, and their survival depends on the genome, age, comorbidities, and immunity defense of the patient, as well as the pathogens and the therapy being administered.[8] Due to this complexity, it is widely accepted that clinical judgment can be inadequate to assess the severity of the disease.[8]

A definite diagnosis of pneumonia can be made based on chest radiography, when a new infiltrate appears on the chest radiograph, together with the presence of recently acquired respiratory symptoms, such as cough, increased production of sputum, dyspnea, fever, and abnormal auscultatory findings.[3,9-11] However, a chest radiograph may not be feasible in all cases, while clinical findings do not always reliably predict radiologically confirmed pneumonia.[12] Diagnosis can be problematic in the elderly (who present with atypical symptoms and without fever) and in patients with cardiac or respiratory comorbidity.[1,13] Moreover, primary care physicians rely more on taking the patient's history and on physical examination, rather than performing radiography.[14]

Most cases of pneumonia result from bacterial infection, which is treated with the prescription of antibiotics.[1] Overprescribing of antibiotics includes many risks, such as unnecessarily exposing patients to side

effects of antibiotics without achieving a more rapid recovery;[15] increasing the probability of infection with antibiotic-resistant organisms;[16,17] and increasing patient recovery time, costs, and workload.[18,19] On the other hand, underprescription of antibiotics may lead to an increased risk of severe pneumonia.[20,21]

Some noninfectious causes, such as pulmonary embolism, malignancy, and congestive heart failure, may lead to a wrong diagnosis of CAP.[22] In this case, the erroneous diagnosis is suspected after the failure of antibiotic therapy, increasing the potentially life-threatening risks that are related to the above untreated nonbacterial disease.[23] On the other hand, a more than 4 h delay of antibiotic treatment after hospital admission of a patient with CAP is significantly associated with increased mortality rates.[24] Thus, both a rapid diagnosis of CAP and an accurate differentiation from viral and noninfectious causes are necessary.[25]

With the aim of determining the initial site of treatment and the appropriate level of intervention, several severity clinical scores, such as "Pneumonia Severity Index (PSI)," "confusion, urea, respiratory rate and blood pressure (CURB-65)" or CURB-65 with urea measurements omitted (CRB-65), and "systolic blood pressure, multilobar chest radiography, albumin level, respiratory rate, tachycardia, confusion, oxygenation and arterial pH (SMART-COP)," have been developed and are recommended widely for clinical decision-making when evaluating CAP patients.[8,26] These scores, however, have many weaknesses, particularly regarding their positive predictive values.[27]

Both the PSI and CURB-65 scores consist of clinical rules that identify a subset of patients at low risk of death and thus, classify all the remaining patients as "high risk," recommending for them hospital admission, despite the fact that a significant percentage of these patients can be treated safely at home.[27] Most sensitive tests (low false-negative rate), such as the PSI, require from physicians the collection of data on twenty parameters (including detailed medical history, physical examination, arterial blood gas measurements, and chest radiograph), prohibiting their applicability in a busy emergency department setting.[28] The CORB-65 test does not require the evaluation of so many parameters; however, due to the fact that it does not address comorbidities, it underestimates the mortality risk in the elderly with other underlying diseases.[8] PSI and CURB-65 have both good discriminatory power for mortality, but low ability to predict ICU admission.[8] SMART-COP performs better than both CURB-65 and PSI, but fails to identify younger patients (<50 years of age) requiring mechanical ventilation and inotropic support due to CAP.[29]

Biomarkers are laboratory tests, which are easily measured, objective, and dynamic, reflecting a disease process.[8] They could potentially be very useful in the diagnosis of CAP as they can provide information for the identification of a pathology and thus, help physicians avoid further invasive or expensive diagnostic tests. Moreover, biomarkers can allocate CAP patients in the proper severity category and also determine the initiation and duration of CAP therapy.

Both biomarkers and clinical scoring systems are expected to capture the different aspects of the host factor and the response to therapy.[8] Therefore, there is a growing interest in the usage of biomarkers both as stand-alone tests and in combination with clinical risk scores for an enhanced risk assessment, proper diagnosis, and correct antibiotic prescription.

The recent advances in the fields of metabolomics, genomics, and microbiomics could further allow us to stratify patients into different severity groups, as personalized and precision medicine, focused on individual phenotypes, can be a great tool for determining a most accurate clinical outcome.[30]

Biomarkers in the Diagnosis of Lower Respiratory Tract Infection/ Community-Acquired Pneumonia

Biomarkers and the use of prognostic scores, such as CURB-65 and PSI, are indicated to support clinical judgment.[31] The usefulness of biomarkers for diagnosing LRTIs is unclear; however, when high-sensitivity C-reactive protein (CRP) and procalcitonin (PCT) are used, the specificity of pneumonia diagnosis is high. Some biomarkers that can reliably predict LRTIs mortality are PCT, CRP, mid-regional pro-atrial natriuretic peptide (MR-pro-ANP), and C-terminal pro-atrial vasopressin (CT-pro-AVP); however, these biomarkers do not significantly improve the severity score of predictive values [Table 1].[32]

Data from two randomized prospective studies with a total of 545 patients with suspected LRTI were combined in a *post hoc* analysis, and a significant relationship between PCT levels and PSI category was shown. PCT was distinctly elevated in the highest PSI Class V, indicating that it could be a useful tool in the assessment of CAP severity. Moreover, it had the highest diagnostic accuracy in differentiating radiographically confirmed CAP from other differential diagnoses and best predictive power for bacteremia.[36]

In a large multicentric, prospective observational cohort study, including 1651 patients admitted for CAP, for most patients, PCT levels did not provide prognostic

Table 1: Diagnostic and prognostic value of biomarkers and clinical scores in lower respiratory tract infections and community-acquired pneumonia

Biomarkers and clinical scores	Diagnosis	Prognosis
CRP	LRTIs, CAP	CAP caused by *Streptococcus pneumoniae* or *Legionella pneumophila*[33]
		Absence of severe CAP complications[34]
		Bacterial infection[35]
		Hospitalization[35]
PCT	LRTIs	CAP severity[34,36]
		Differentiation of radiographically confirmed CAP from other differential diagnoses[36]
		Bacteremia,[36] bacterial infection[35]
		Hospitalization[35]
		Initiation and duration of antibiotic treatment[32,37,38]
		28-day mortality[39]
MR-pro-ANP	LRTIs	28- and 180-day mortality[40,41]
		CAP severity[40,41]
CT-pro-AVP	LRTIs	28- and 180-day mortality[40,41]
		CAP severity[40]
Pro-ADM	LRTIs	Severity and outcome of CAP[42,43]
		28- and 180-day survival[44]
		CAP complications and mortality[45]
Platelets	CAP	CAP severity and mortality[46]
PSI	CAP	High-risk patients, need of hospital admission[27]
		Mortality[8]
		Pneumonia with low risk of death[28]
CURB-65	CAP	High-risk patients, need of hospital admission[27]
		Mortality[8]
		Pneumonia with low risk of death[28]
SMART-COP	CAP	ICU admission[8,29]

CRP=C-reactive protein, PCT=Procalcitonin, MR-pro-ANP=Mid-regional pro-atrial natriuretic peptide, CT-pro-AVP=C-terminal pro-atrial vasopressin, PSI=Pneumonia Severity Index, CURB-65=Confusion, urea, respiratory rate and blood pressure, Pro-ADM=Pro-adrenomedullin, SMART-COP=Systolic blood pressure, multilobar chest radiography, albumin level, respiratory rate, tachycardia, confusion, oxygenation and arterial pH, CAP=Community-acquired pneumonia, LRTIs=Lower respiratory tract infections, ICU=Intensive care unit

information beyond the PSI and CURB-65 scores. Among high-risk groups, however, low PCT levels reliably predicted lower mortality.[47]

Moreover, it has been shown that PCT levels at admission is a better biomarker for CAP severity and outcome, when compared to leukocyte count (white blood cell [WBC]) and CRP levels in a study including 1671 patients with proven CAP, tested for PCT, CRP, WBC, and CRB-65 followed up for 28 days. Additionally, a PCT threshold of <0.228 ng/mL classifies low-risk patients within all CRB-65 risk groups.[48]

In a multivariate Cox proportional hazard regression analysis in 589 patients with CAP, high levels of MR-pro-ANP and CT-pro-AVP were the strongest predictors of mortality when compared to PCT and CRP. MR-pro-ANP and CT-pro-AVP were shown to be better predictors for CAP severity and 28-day mortality, than the CRB-65 score.[40] Furthermore, in 302 consecutively admitted adults with CAP, pro-adrenomedullin (pro-ADM) levels on admission predicted the severity and outcome of CAP with similar prognostic accuracy as the PSI. However, many patients with high PSI (Class V) had low pro-ADM levels.[42] In a

multicentric prospective cohort study including a total of 1653 patients, pro-ADM was indicated as superior to PCT, but only in high-risk patients, it was superior to PSI.[43]

Looking at the role of consecutive CRP measurement in the follow-up of CAP in a prospective, multicentric study including 289 hospitalized patients with severe CAP, delayed normalization of CRP was not significantly related to mortality, but to inappropriate treatment (steroids and pneumonia etiology).[49] When CRP was evaluated for its diagnostic accuracy in detecting radiologically proven pneumonia, it was shown neither sufficiently sensitive to rule out pneumonia nor sufficiently specific to rule in an infiltrate on chest radiograph and bacterial (rather than viral) etiology of LRTI. Thus, it was concluded that CRP cannot be widely introduced as a rapid test to guide the prescription of antibiotics.[46]

The inflammatory response at the time of CAP diagnosis is influenced by the time elapsed from the onset of symptoms. CRP levels measured were significantly lower in patients presenting <3 days since the onset of symptoms, whereas PCT, interleukin (IL)-6, and IL-8 were already elevated. Moreover, PCT, IL-6, and IL-8

were significantly reduced after 3 days of symptoms, but CRP was still high.[50] In a case–control study, CRP was shown to be significantly higher in confirmed CAP, compared to healthy controls and suspected CAP. CR*P* values were especially high in patients with pneumonia caused by *Streptococcus pneumoniae* or *Legionella pneumophila*.[51]

In a prospective, observational study including a total of 364 patients with LRTI enrolled from 42 general practices both PCT >0.06 ng/mL and CRP ≥20 mg/L were associated with radiographic pneumonia, bacterial infection, and subsequent hospitalization. However, positive predictive values were too low for any of the two markers to be of use in clinical practice, and there was no indication that PCT is superior to CRP in identifying patients with CAP, bacterial etiology, or adverse outcome.[33] A CRP level ≥100 mg/L, however, was indicated to be an indicator for CAP (specificity 91%) when the diagnosis of pneumonia is in doubt.[35]

CRP and PCT increase partially in parallel. In the setting of LRTI, it is especially important not to miss possible severe complications, such as sepsis.[52,53] The downside of CRP is not sensitivity, but specificity, because CRP is an inflammatory marker and PCT is a biomarker for infection. The increase in CRP is delayed, when compared to an increase in PCT.

Platelets, as they play a very crucial role in antimicrobial host defenses and the coagulation mechanism, are another possible biomarker for CAP severity.[32] Thrombocytopenia and thrombocytosis have been significantly associated with mortality in CAP patients. When compared to abnormalities in WBC, abnormalities in platelet count are a better predictor of the severity and outcome of CAP.[54]

Prescription of Antibiotics in Community-Acquired Pneumonia

Unnecessary prescription of antibiotics is associated with an increased risk of patients' exposure to side effects of antibiotics without achieving a more rapid recovery. On the other hand, underprescription of antibiotics may lead to an increased risk of severe pneumonia. When exploring the influence of general practitioners' (GPs) examination findings in the prescription of antibiotics, auscultation abnormalities (crackles) and diarrhea were found to be the stronger predictors for GPs to prescribe an antibiotic. This, however, leads to inappropriate or unnecessary prescription of antibiotics to 86% of the patients (positive predictive value = 14%).[55]

In a 13-country, prospective, observational primary care study, including 1776 patients, clinicians reported

pneumonia in only 4.3% of the cases and an antibiotic was prescribed in 52.7% patients with acute cough/LRTI. However, after further cautious analysis, an estimated 70.8% of the patients could have been considered to have suspected or definite pneumonia, and according to the ERS/ESCMID guidelines, clinicians could have justified an antibiotic prescription for 71.2% of the patients.[56] In an observational study in the United Kingdom that included 346 primary care practices and 151,088 LRTI cases, antibiotic prescribing on the day of LRTI diagnosis was associated with reductions in hospital admissions and respiratory infection-related mortality, thus helping to prevent adverse outcomes in patients with LRTI.[20]

From the above evidence, it is clear that there is a great need for biomarkers that could be used for a more rationalistic antibiotic prescription in CAP. In this respect, it has been shown that PCT can be used as an indicator for the duration of antibiotic treatment in pneumonia.[32] A systematic review with individual patient data from 14 randomized controlled trials with a total of 4211 participants indicated that the use of PCT to guide the initiation and the duration of antibiotic treatment in patients with acute respiratory infections is not associated with higher mortality rates or treatment failure.[57]

A recent meta-analysis of patient data from 26 randomized controlled trials including 6708 patients from 12 countries suggested that the use of PCT to guide treatment with antibiotics in patients with acute respiratory infections reduces exposure to antibiotics and their side effects and improves survival. Thus, the implementation of PCT testing in patients with acute respiratory infections could improve antibiotic management, tackle the current threat of the increasing antibiotic multiresistance, and at the same time have positive effects on clinical outcomes.[58]

In another study of 1337 patients with proven CAP, levels of PCT, CRP, and WBC were significantly higher in patients with typical bacterial CAP, compared to CAP of atypical or viral etiology. PCT, CRP, and WBC were similar in patients with atypical and viral etiologies of CAP. PCT, noticeably, increased with the severity of CAP (measured by CRB-65 score, $P < 0.001$), in contrast to CRP and WBC, and thus it could be useful in the assessment of the severity of CAP. However, CRP, PCT, and WBC could not predict the etiology of CAP.[37]

A meta-analysis of data from individual participants from 12 countries indicated that PCT can be used as a safe tool to discontinue antibiotic therapy in patients with LRTI (including CAP, acute exacerbations of chronic obstructive pulmonary disease [AECOPD], and ventilator-associated pneumonia [VAP]). Therefore, PCT can be used to guide the initiation and duration

of antibiotic treatment, resulting in lower mortality risk and decrease in the consumption of antibiotics and antibiotic-related side effects.[59]

CRP has also been suggested as a biomarker to guide the prescription of antibiotics in CAP. In a randomized controlled trial to assess whether CRP can be used to guide antibiotic prescription to patients with respiratory infections in GP offices (35 general practices, 812 patients with LRTI), the use of the CRP rapid test was not recommended (antibiotic prescription frequency: 43% in CRP group vs. 46% in control group, odds ratio = 0.9, nonsignificant, morbidity frequency: 12% in CRP group vs. 8% in control group, odds ratio = 1.6, $P = 0.05$).[60]

A cluster randomized trial of 431 patients recruited in twenty general practices in the Netherlands showed that both GP testing for CRP and training in enhanced communication skills significantly reduced antibiotic prescribing for LRTI, without compromising patient's recovery and satisfaction with care (GPs in CRP test group prescribed antibiotics to 31% of patients vs. 53% from GPs from no test group, $P = 0.02$, and trained GPs prescribed antibiotics to 27% of patients, vs. 54% from GPs from no training group, $P < 0.01$). This indicates that a combination of illness and disease approaches may be necessary to achieve reduction in the prescription of antibiotics for CAP in primary care.[38]

Use of Biomarkers in Lower Respiratory Tract Infection/Community-Acquired Pneumonia Prognosis

A summary of the biomarkers that can be used for the prognosis of LRTIs and CAP is shown in Table 1. A prospective cohort study in 394 hospitalized patients with CAP indicated that low levels of CRP and PCT after 72 h of treatment–in addition to clinical criteria–might improve the prediction of absence of severe complications, as they reflect stability. However, CRP and PCT levels at 72 h do not significantly improve the prediction of severe complications as compared to clinical criteria for clinical stability. Therefore, the addition of the biological information provided by CRP and PCT levels to clinical criteria of stability improves the safety of that prediction.[34]

In a meta-analysis of 23 studies, which aimed to predict mortality in patients with CAP (22,753 patients, average mortality 7.4%), the different scoring systems employed in the studies were compared. PSI had the highest sensitivity and the lowest specificity for mortality, CRB-65 was the most specific, but least sensitive, and CURB-65 was between the two. Negative predictive values ranged from 0.94 (CRB-65) to 0.98 (PSI), and positive predictive values ranged from 0.14 (PSI) to 0.28 (CRB-65). All four

prognostic scales had good negative predictive values in populations with low prevalence of death, but modest positive predictive values. This suggests that the PSI and CURB-65 scoring systems perform well at identifying patients with pneumonia who have a low risk of death. All the four scales, however, have limitations and should be used in combination with careful clinical judgment.[28]

Investigating the mortality predictive value of serum biomarkers and clinical risk scales in 125 CAP patients, serum PCT was found to be a valuable single predictor for 28-day mortality. The models combining PCT and/or CRP with PSI or IDAS/ATS guidelines demonstrated better performance than PSI or the IDAS/ATS guidelines alone.[39]

In another study of 1740 patients with proven CAP, MR-pro-ANP, CT-pro-AVP, PCT, CRP, WBC, and CRB-65 score were determined on admission and patients were followed up for 180 days. Both MR-pro-ANP and CT-pro-AVP levels increased with increasing severity of CAP (CRB-65 score classification). Median MR-pro-ANP and CT-pro-AVP levels were significantly higher in patients who died within 28 and 180 days, than in survivors. MR-pro-ANP and CT-pro-AVP were independent and the strongest predictors of short-term and long-term mortality in patients with CAP.[41]

In a multicentric CAP cohort study (28 hospitals, 1653 CAP patients), the prognostic role of MR-pro-ADM was investigated and its significance was compared to PCT. MR-pro-ADM levels correlated with increased severity of illness and death. High MR-pro-ADM levels do not alter PSI-based risk assessment in most CAP patients (PSI I–III) but offer additional risk stratification in high-risk CAP patients (PSI IV/V).[43]

In another study of 728 patients with CAP, some new biomarkers were compared for the prediction of short- and long-term all-cause mortality in CAP. MR-pro-ADM had the best performance for 28 days (hazard ratio = 3.67) and 180 days (hazard ratio = 2.84) survival, when compared to MR-pro-ANP, copeptin, pro-ET-1 (pro-endothelin-1), PCT, CRP, and WBC. Moreover, MR-pro-ADM was independent of CRB-65, and a combination of MR-pro-ADM with CRB-65 was indicated to be the best predictor for mortality, as the addition of MR-pro-ADM significantly improved the prognostic value of CRB-65 score for 28- and 180-day outcome.[44]

Additionally, the prognostic value of prohormones in CAP was investigated in 925 CAP patients (CURB-65 and PSI vs. MR-pro-ADM, pro-ET1, CT-pro-ANP, copeptin, and PCT), and the results indicated that both PSI and CURB-65 overestimated the observed mortality and that MP-pro-ADM or pro-ET1 alone was significantly better

than the PSI or CURB-65 score to predict complications. The inclusion of MR-pro-ADM alone in addition to the PSI and CURB-65 scores significantly increased the area under the curve (for PSI from 0.69 to 0.75 and for CURB-65 from 0.66 to 0.73) for the prediction of serious complications.[61]

A meta-analysis of eight studies and 4119 patients demonstrated that MR-pro-ADM is predictive of increased complications and higher mortality rates in patients suffering from CAP, as an elevated MR-pro-ADM level is associated with increased risk of death from CAP (relative risk = 6.16; 95% confidence interval = 4.71–8.06, mean cutoff = 1.416 ng/ml, positive likelihood ratio = 2.8; 95% confidence interval = 2.3–3.3, negative likelihood ratio = 0.36; 95% confidence interval = 0.29–0.45).[45]

From the abovementioned studies, we can conclude that CRP-point of care and training in communication skills can decrease antibiotic prescription in LRTI at the GP office. Moreover, procalcitonin can be used as a safe tool to discontinue antibiotic therapy in patients with LRTI (including CAP, AECOPD, and VAP). CRP, PCT, or WBC cannot predict the etiology of CAP. All prohormones, however, provide prognostic information in CAP and are superior than the prognostic scores alone. MP-pro-ADM seems to be the best predictor in CAP, providing additional information than the scores alone, particularly in patients with PSI Class IV–V.

Perspectives for the Reduction of Community-Acquired Pneumonia Mortality

Recent advances in the field of severe infections indicate the crucial role of interindividual genetic variability. CAP development and its treatment depend on many different characteristics of the host, such as susceptibility to specific organisms, inflammatory responses to invasion of pathogens, and response to antibiotics.[30] Not all CAP episodes are similar. In other words, successful CAP treatment strategies require to take individual variability into consideration.[8] Even with low bacterial burden, some patients can be susceptible to morbidity. An explanation to this fact was provided by a genome-wide association study of survivors of sepsis due to CAP. The study indicated that some common variants in the FER gene are significantly associated with survival.[62]

Current guidelines take into account only macroscopic differences in immunosuppression and comorbidities, such as neutropenia, hematologic cancers, HIV, diabetes, and chronic obstructive pulmonary disease. Research on genetics, microbiomics, proteomics, and metabolomics has demonstrated that individual characteristics (such as genetic variability, metabolic composition of the host, and specific patterns of saprophytic flora colonizing the lower airways) can have a great impact on the final outcome of prognostic and diagnostic procedures and also contribute significantly to the progression of CAP.[30] Therefore, at the moment, the most important unmet clinical need in CAP medicine is the creation of novel designs, in order to test and evaluate the contribution of personalized and precision medicine in the management of CAP.[30]

The implementation of new rapid microbiologic and nonmicrobiologic molecular testing, that is the new fast multiplex real-time polymerase chain reaction and the study of integrated host gene expression in the context of an inflammatory process in order to distinguish an infection from an inflammatory process, or even discriminate a viral or a bacterial cause of infection, together with the application of personalized medicine, will contribute to the reduction of CAP mortality rates[30] and will lead to the reduction of unnecessary administration of antibiotics.[63,64]

Conflicts of interest
There are no conflicts of interest.

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