

DISCUSSION

Community-acquired pneumonia (CAP) accounts for 1.3 million hospitalizations each year in the USA.⁽¹⁵¹⁾ The average duration of hospitalization for CAP managed on the ward is 6 days, If intensive care unit (ICU) admission (for severe CAP) is required, then the stay increases to 23 days.^(151, 152) Although CAP is very common, it remains a common cause of death. Hence, severe CAP has been reported to be the largest single cause of mortality from infectious diseases in industrialized countries.⁽¹⁵²⁾ The factors that underlie the poor short-term and long-term survival rates in patients with CAP and severe CAP are not yet completely understood. However, aspects of the pathophysiology of the disease, reflected in some of the recently described biomarkers and genomic markers, may contribute to increased understanding.⁽¹⁵³⁾

The challenges of diagnosing and treating pneumonia only seem more difficult as incidence increases, patients become older and sicker, and pathogenic organisms evolve.^(154, 155) Early recognition of infection is not always straightforward and clinical signs themselves can be misleading especially in patients with several co-morbidities or variable demographic characteristics. Evidence supports early diagnosis and intervention⁽¹⁵⁶⁾ in sepsis and that the failure to intervene results in significant morbidity and mortality.⁽¹⁵⁷⁾ Blood and sputum cultures are frequently used as the “gold standard” diagnostic method for sepsis. However, it usually takes 3 to 7 days to obtain the results, frequently yields low positive results,⁽¹⁵⁸⁾ and may be influenced by several factors including previous antibiotic usage.⁽¹⁵⁹⁾ Early and appropriate antibiotic therapy is critical.⁽¹⁶⁰⁾ Likewise, limiting exposure when infection is absent will become exceedingly important as drug resistance increases.⁽¹³⁴⁾

These complexities have led to the search for a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for adverse outcomes, and reliably guiding treatment. Although an enormous numbers of different inflammatory markers have been suggested as promising candidate, only a few of them have been tested rigorously in clinical outcome studies and have found their way into clinical practice. Among different molecules that have been suggested as sepsis biomarkers in last years is procalcitonin (PCT).⁽¹⁶¹⁾

Owing its specificity to bacterial infections, PCT has been proposed as a pertinent marker in the rapid diagnosis of bacterial infections, especially for use in hospital emergency departments^(161, 162).

Therefore, the current study was carried out to assess the prognostic value of procalcitonin, CRP in adult patients with community acquired pneumonia (CAP).

We conducted a prospective observational study during the period from May 2014 to November 2014 on 20 adult patients of both sex, diagnosed as CAP. Patients were divided according to outcome into two groups; Survivors=Group I (n= 14) and Non-survivors=Group II (n=6).The patients are those who were presented to the emergency causality in Alexandria Main University Hospital and fulfilled the diagnostic criteria for CAP.

In the present study, Group I and Group II were homogeneous in terms of demographic characteristics with no statistically significant difference between them regarding age and gender ($p=0.067$, and $p=0.642$, respectively).

In Group I, the age ranged from 48.0 – 75.0 years with a mean age of 62.21 ± 8.84 years, In Group II, the age ranged from 63.0 – 78.0 years with a mean age of 69.83 ± 5.34 years.

In agreement with the present study, Luís Coelho et al reported that the mean age of patients with CAP was 59.4 ± 14.8 years in Survivors, and was 61.1 ± 12.1 years in Non-Survivors.⁽¹⁶³⁾

Martinelli LMB et al reported that the mean age CAP was 59 ± 19 years. The incidence of pneumonia among patients aged > 75 years was 7.8 times higher than among those aged 15-44 years.⁽¹⁶⁴⁾

In accordance to the present study, Jorge IF Salluh et al found that the mean age group in non-survivors was higher compared to those who survived.⁽¹⁶⁵⁾

Similar to the present study, Christophe Marti et al found that 78.3% of the non-survivors are over 70 years old.⁽¹⁶⁶⁾

Consistent with the present findings, Tobias Welte et al found that CAP is predominantly a disease of the elderly, with incidence rising steeply over the age of 70 years. The impact of CAP is also greater in older individuals since they are more likely to be hospitalized than younger patients and have a higher risk of mortality, with the mortality rate increasing with every decade until the eighth decade. Mortality from CAP has been shown to be independently associated with age, even when comorbidity and severity of illness are taken into account. Indeed, CAP appears to be a clinically distinct entity in older patients above the age of 65 years, being associated with more severe disease and presenting with fewer classical symptoms (e.g. fever and chest pain) than in younger individuals.⁽¹⁶⁷⁾

The importance of age in patients with CAP is well recognised in current severity assessment tools, being a highly influential factor in both the Pneumonia Severity Score (PSI) and CURB-65 index.⁽¹⁶⁷⁾

On the contrary, Márcio Soares et al found that there is a direct relationship between advanced age and the incidence of severe CAP. The present study found that 83.3% of the non-survivors in the study are over 65 years old. Increased severity of CAP in the elderly is explained by the aging of organ systems (in particular the respiratory system and the immune system).⁽¹⁶⁸⁾

In the present study, In Group I, males accounted for (50%), while females accounted for (50%). In Group II, males accounted for (66.7%), while females accounted for (33.3%).

In accordance to the present study, Fine MJ et al found that men are more likely than women to develop severe CAP⁽¹⁶⁹⁾. However, it is not clear whether this difference could be due to a higher prevalence of comorbidities in men, or whether women are protected against the inflammatory changes that occur in severe infections.⁽¹⁷⁰⁾

Similar to the present study, Regina et al found that males accounted for (68%) patients of their non-survived population and females accounted for (32%) patients of their non-survived population.⁽¹⁶³⁾

In agreement with the current study, Wei Long et al found that the incidence of severe CAP is more common in males (59.2%).⁽¹⁶⁷⁾

In the present study, there was no statistically significant difference between Group I and Group II as regarding preexisting conditions. Patients with CAP frequently have underlying comorbidities which predispose them to infections and may have an additive contribution to mortality.⁽¹⁵⁵⁾

In the present study diabetes mellitus and hypertension were the most common preexisting conditions accounting for 12 (60%) and 11 (55.0%) of the studied patients, respectively. 7 (35.0%) patients with ischemic heart disease, 4 (20%) patients with COPD, 4 (20%) patients with heart failure, 3 (15%) patients with chronic kidney disease, and 2 (10%) patients with liver impairment.

Karlsson et al found during their prospective observational study to investigate the incidence, treatment, and outcome of severe CAP in ICU-treated adults in Finland that the most frequent preexisting conditions in patients with severe CAP were diabetes mellitus (34.9%) and hypertension (21.5%), which is in agreement of the present study.⁽¹⁷¹⁾

Considering the interrelation between infection and DM, Wang F et al reported that patients with DM are more prone to CAP.⁽¹⁷²⁾ This has been explained by that hyperglycemia impairs a wide range of functions of neutrophils and macrophages which are important in limiting invasion by pyogenic bacteria. Clinical investigations in diabetic patients and experimental studies in diabetic rats and mice clearly demonstrated consistent defects of neutrophil chemotactic, phagocytic and microbial activities. Lowering of blood glucose level by insulin treatment of diabetic patients has been reported to have significant correlation with improvement of neutrophil function.⁽¹⁷²⁾

Consistent with the present study, Ishigami et al studied the incidence of HAP among hypertensive patients and found that Pneumonia cases were higher among those with HTN. This is explained by that hypertension can lead to heart failure which causes fluid to collect in the lungs, this edema fluid impairs lymphatic drainage and increased incidence of pneumonia.⁽¹⁷³⁾

Jordi Rello et al found that chronic obstructive pulmonary disease play an important part in determining the risk for pneumonia and disease severity.⁽¹⁷⁴⁾

Josef et al reported that people with CKD are greater risk for adverse infectious events because of overwhelming uremia, which is associated with alteration in primary host defense mechanisms and increases the risk of bacterial infections. This is explained by hypocomplementaemia, impaired macrophage, neutrophil function and reduced humoral immunity observed in those patients.⁽¹⁷⁵⁾

Concerning the clinical findings encountered in our studied patients, cough was the most common symptoms representing 20 patients (100%), fever was the second common symptoms representing 18 patients (90%).

Supporting the present data, Lori et al in their study demonstrated that patients with pneumonia presented with cough, fever, and dyspnea (main symptoms).⁽¹⁷⁶⁾

Similar to the present results, Tobias Welte et al found that CAP should be suspected in patients presenting with evidence of clinical signs and symptoms: Cough, Fever, Sputum production, and Pleuritic chest pain.⁽¹⁶⁷⁾

Shapiro et al found that abnormal body temperature, i.e., fever or hypothermia, is a major clinical finding associated with systemic inflammation and is one of the criteria of SIRS. In patients with infection, abnormal body temperature and chills are common.⁽¹⁷⁷⁾

Similar to the present data, Jaimes et al. found that abnormal body temperature is included in the definition of systemic inflammatory response syndrome (SIRS). The SIRS criteria had proved to be sensitive but not specific to infection. The SIRS criteria alone was not prognostic for mortality.⁽¹⁶⁶⁾

On the contrary, Rotstein et al reported that the clinical manifestation of HAP are nonspecific and there are no pathognomonic sign or symptoms that are unique to this condition.⁽¹⁷⁸⁾ The symptoms constellations of cough, fever, chest pain, and dyspnea may be mimicked by other clinical entities such as congestive heart failure and pulmonary embolism.

Regarding vital signs of the studied population, the respiratory rate ranged between 16.0 – 44.0 breaths per minute with a mean of 29.40 ± 8.43 breath per minute. The heart rate ranged between 70.0 – 140.0 beats per minute with a mean of 103.75 ± 17.46 beats per minute. The systolic blood pressure ranged from 70.0 - 180.0 mmHg with a mean of 114.0 ± 25.83 mmHg. 3 patients (15%) were hypotensive.

Brendon et al showed that vital signs abnormality (including fever, hypotension, tachycardia, or tachypnea) were the only significant predictors of HAP regardless the age.⁽¹⁷⁹⁾

Aalto H et al found that the mean arterial pressure (mmHg) was higher among survivors (105) than non-survivors (94). Our findings coincide with that as the mean systolic blood pressure (mmHg) among survivors was 119.64 ± 24.61 , which was higher than non-survivors 100.83 ± 25.77 .⁽¹⁷⁷⁾

Concerning the hematologic profile of the studied patients, hemoglobin level (Hb) ranged between 6.70 g/dl - 16.10 g/dl with a mean of 11.59 ± 2.67 g/dl, white blood counts (WBCs) ranged between $3.70 - 32.80 \times 10^3/\text{ul}$ with a mean of $16.06 \pm 8.05 \times 10^3/\text{ul}$, platelets counts ranged between $80.0 - 420.0 \times 10^3/\text{ul}$ with a mean of $243.45 \pm 104.69 \times 10^3/\text{ul}$.

In accordance with the present data, Fabregas N et al described that the likelihood of bacterial pneumonia generally increases WBCs above $12 \times 10^3/\text{ul}$ and the differential count showed neutrophilia and left shift.⁽¹⁸⁰⁾

In agreement with the present study, Pettila et al studied 531 patients with pure community-acquired pneumonia (CAP). Various laboratory markers of systemic inflammation were evaluated in order to improve the prediction of positive blood culture

and diagnostics of hidden community-acquired infection on admission, and found that WBC count had no prognostic value.⁽¹⁸¹⁾

On the other hand, Raveh et al found that (21%) of patients with pneumonia presented with normal WBCs.⁽¹⁸²⁾

Valles et al found that Leukopenia, i.e., diminished WBC count, is associated with a greater susceptibility to severe infections and with a poor prognosis.⁽¹⁸¹⁾

Mirjam Christ-Crain et al assessed the diagnostic and prognostic accuracy of clinical signs and symptoms and a range of laboratory markers in a planned analysis of 545 patients with suspected lower respiratory tract infection admitted to the emergency department, and found that, 66% of patients with WBCs above 113×10^3 /ul and the differential count showed neutrophilia and left shift.⁽¹⁸³⁾

Similar to the present study, Lim WS et al found there is no significant difference between survived and non-survived as regard platelets counts.⁽²¹⁾

Carlo et al showed that acute infections may lead to reactive thrombocytosis and this was evident in 2 patients in our study.⁽¹⁸⁴⁾

Mirsaedi M et al found that thrombocytopenia was the main platelet disorder associated with worse outcome.⁽¹⁸⁵⁾

Michael C Reade et al utilized hemoglobin values obtained for clinical purposes, classifying subjects into categories consisting of no anemia (hemoglobin >13 g/dL), at least borderline (≤ 13 g/dL), at least mild (≤ 12 g/dL), at least moderate (≤ 10 g/dL), and severe (≤ 8 g/dL) anemia, stratified our results by gender, comorbidity, ICU admission, and development of severe sepsis, found that anemia was common in hospitalized CAP and independently associated with 90d mortality.⁽¹⁸⁶⁾

Regarding liver enzymes, alanine amino transferase (ALT) ranged between 20.0 – 300.0 U/L with a mean of 69.50 ± 73.57 U/L, aspartate amino transferase (AST) ranged between 20.0 – 392.0 U/L with a mean of 75.20 ± 88.80 U/L. Among the studied patients, 2 of them were proved to have hepatitis C virus.

Kung CM et al demonstrates high prevalence of pneumonia in HCV infected patients and this was a factor exacerbating liver dysfunction⁽¹⁸⁷⁾

Whereas, Steven et al reported that elevated ALT and AST indicates acute hepatocellular injury caused by hypoperfusion and these were considered indicators of severe sepsis.⁽¹⁸⁸⁾ This is not likely the underlying cause of observed high liver enzymes level, since patients with septic shock were excluded from this study.

Regarding renal functions, blood urea ranged between 16.0 – 44.0 mg/dl with a mean of 78.90 ± 45.21 mg/dl, serum creatinine ranged between 0.60 – 3.10 mg/dl with a mean of 1.37 ± 0.68 mg/dl. Among the studied patients, 3 of them were proved to have chronic kidney disease (CKD).

In accordance to these findings, Naqvi A et al demonstrated that compared with Non-CKD population, the rates of pneumonia are 3 times greater in CKD population.⁽¹⁸⁹⁾

Kalin M et al found that there is no significant difference between non-survived (0.78 (0.62–1.46) mg/dl), and survived (0.77 (0.65–1.02)mg/dl) as regards serum creatinine.⁽¹⁹⁰⁾ In the present study, the mean serum creatinine was (1.38 ± 0.75) in survived, and (1.35 ± 0.54) in non-survived.

Kruger S et al found that serum urea nitrogen and history of renal disease were independently associated with mortality in CAP. They concluded that in future studies of patients with CAP renal function measurements, including serum creatinine and urea, should be included in the database because they may allow a more sophisticated interpretation of biomarkers for prognosis or therapeutic management.⁽¹⁹¹⁾

On the other hand, Steven et al reported that elevated urea and creatinine (doubling level) indicates acute kidney injury caused by hypoperfusion and these laboratory indicators of severe sepsis.⁽¹⁸⁸⁾

On the contrary, W S Lim et al found that serum urea level play an important role in prognosis of CAP as it is included in CURB-65 score.⁽¹⁹²⁾

In conclusion, findings of this study and those of others, pointed out that on one hand, hepatic and renal dysfunction are risk factors for development of CAP and severe CAP could be an augmenting factors for renal and hepatic dysfunctions on the other hand.

Concerning the bacteriological examination in the current study, sputum cultures revealed that *Streptococcus pneumoniae* was the commonest isolated gram-positive organism representing 12 patients (60%). *Pseudomonas aeruginosa* was detected in 2 patients (20%).

In agreement with the present study, Jordi Rello et al found that some specific pathogens carry an increased risk for severe CAP. The most common organisms observed in patients with CAP are *Streptococcus pneumoniae*. The most common lethal pathogens are *S. pneumoniae*, *Pseudomonas aeruginosa*. The most prevalent pathogen associated with severe CAP, namely *S. pneumoniae*, is responsible for two-thirds of CAP-related deaths. Although the worst outcome is associated with infection with Gram negative organisms, such infections are relatively infrequent.⁽¹⁶⁸⁾

Similar results were reported by Elisa G et al who found that *Streptococcus pneumoniae* was the microorganism cultured in 133 (81%) of the 164 patients studied.⁽²⁸⁾

In agreement of the present study, S. Kashyap et al found that of the 70 patients studied, etiological diagnosis could be established in 53 (75%). Twelve patients had evidence of mixed infections. The most common pathogen was *Streptococcus pneumoniae* (n=19; 35.8%) followed by *Klebsiella pneumoniae* (n=12; 22.6%). Of the 23 patients in whom Gram negative bacilli were the etiological cause, 17 patients (74%) were more than 40 years of age, 16 (70%) were smokers; 18 (78%) were having one or more underlying co-morbid conditions with COPD being the most common among them.

Kulpati and Khastgir in a survey of CAP in India reported that *Streptococcus pneumoniae* is the most common isolated pathogen responsible for 40-60% of cases. The second commonest isolated in this study was *Klebsiella pneumoniae* (n=12; 22.6%). Studies reported during the last two decades from India have also reported a higher prevalence of *Klebsiella pneumoniae* among culture positive pneumonias.⁽¹⁹³⁾

Tobias W et al found that a microbiological diagnosis cannot be made in around 50% of patients, possibly due in part to difficulties associated with collecting valid sputum samples in elderly patients. Nevertheless, a wide range of pathogens have been found to cause CAP, with the most common being *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella* spp., *Staphylococcus aureus* and *Enterobacteriaceae*.⁽¹⁹⁴⁾

Similar to the present study, Welte T et al found that *S. pneumoniae* is the most frequently isolated, both in outpatients and hospitalised patients, including those in the intensive care unit (ICU). *S. pneumoniae* is also reported to be common in patients with severe sepsis and has been found to trigger bacteraemia and sepsis in mouse lung infection models. *H. influenzae* is the second most frequently isolated pathogen, being found in 5 patients 14% of elderly CAP patients.⁽¹⁹⁵⁾

The incidence of CAP due to *Enterobacteriaceae* is generally reported to be below 10%, though associated mortality is high, and may reach 20% in confirmed cases and 22% in bacteraemia cases. This high mortality rate is likely to be due to the fact that infections with Gram negative bacteria are often related to comorbid illness and are more likely to occur in more vulnerable, elderly patients. Indeed, cardiac and cerebrovascular disease, age >65 years and nursing home residency have been shown to be independent risk factors for *Enterobacteriaceae*.^(195, 196)

C-reactive protein (CRP) is a protein found in the blood, and considered as an acute-phase protein that is released from hepatic cells after stimulation by inflammatory mediators like interleukin (IL)-6 and IL-8. CRP has both pro- and anti-inflammatory properties. It activates the complement system after binding to bacterial polysaccharides or fragments of cell membranes. CRP prevents the adhesion of granulocytes on endothelial cells and the synthesis of superoxides. It stimulates the production of IL-1 receptor antagonists.⁽¹⁹⁷⁾

Levels of CRP increase within 4-6 hours of acute insult, reaching a peak at 48 hours. Its half-life is constant, and therefore its level is mainly determined by the rate of production and hence the severity of the precipitating cause.⁽⁹¹⁾

Normal concentration in healthy human serum is usually lower than 10mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10-40 mg/L), active inflammation, bacterial infection (40-200 mg/L), severe bacterial infections (> 200 mg/L).⁽¹⁹⁸⁾

In the present study, CRP levels were measured on admission and after 2 weeks of antibiotic therapy. On admission, the mean levels of CRP concentrations in plasma were 82.29 ± 55.19 mg/dl in Group I and 53.17 ± 31.28 mg/dl in Group II. After two weeks, the mean levels of CRP concentrations in plasma were 79.07 ± 57.11 mg/dl in Group I and 75.67 ± 42.34 mg/dl in Group II.

According to the above data, CRP is of poor predictive value for the assessment of pneumonia severity ($p=0.282$). This may be due to plasma levels of CRP reach their peak not before 48 hours⁽¹⁹⁹⁾. Circulating CRP increases during minor infections, does not correlate with the severity of host response, and does not differentiate between survivors and non-survivors of sepsis. CRP plasma levels may remain elevated up to several days

even after elimination of the infectious focus. CRP is found in many noninfectious conditions such as acute coronary syndrome, pulmonary embolism, and congestive heart failure.⁽²⁰⁰⁾

In agreement with the present study, Konrad Reinhart et al found that CRP is of poor predictive value for the diagnosis of sepsis and its power to assess severity of disease is still unproved. Nevertheless, CRP plays an important role in the guidance of antibiotic therapy in localized infection.⁽¹¹⁵⁾

In accordance to these findings, Mirjam Christ-Crain et al found that the routine laboratory tests for CRP and the white cell count lack specificity for bacterial infection; a high CRP could be due to numerous other inflammatory conditions or ischemic injury including myocardial infarction.⁽²⁰¹⁾

Robin P et al studied Twenty-eight consecutive patients (mean age, 60 years) admitted to the hospital with community-acquired pneumonia. Serial daily plasma samples were taken and assayed for CRP, tumor necrosis factor- α (TNF- α), and interleukin 6 (IL-6). Clinical parameters, laboratory data, and response to treatment were recorded. Of those who survived, mean ($\pm$ SD) CRP values for days 1, 2, 3, 4, and 5 were as follows: 136 $\pm$ 43, 96 $\pm$ 44, 53 $\pm$ 36, 54 $\pm$ 43, and 44 $\pm$ 31 mg/L. CRP levels on day 1 in patients who had received antibiotics prior to hospital admission were significantly lower than those who had not, 107 $\pm$ 42 and 152 $\pm$ 44 mg/L, concluded that CRP is a sensitive marker but its power to assess severity of disease is still unproved.⁽²⁰²⁾

In accordance to these findings, Takala et al found that numerous other illnesses affect the level of CRP, often increasing it, CRP not being a specific marker for sepsis, and so CRP is not associated with patient outcome.⁽²⁰³⁾

In agreement with the present study, S. Kruger et al found that regarding the accuracy of CRP, PCT, CRB-65 predict death at 28 days according to ROC curves, the AUC (95% CI) was highest for PCT which was not significantly different compared with CRB-65 score. However, the AUC for CRP was significantly lower compared with PCT and CRB-65 score.⁽²⁰⁴⁾

On the contrary, Luís Coelho assessed the value of different patterns of CRP ratio response to antibiotic therapy in patients with severe CAP requiring ICU admission as an early marker of outcome. Total of 191 patients with severe CAP were prospectively included and CRP was sampled every other day from D1 to D7 of antibiotic prescription. CRP-ratio was calculated in relation to D1 CRP concentration. Patients were classified according to an individual pattern of CRP-ratio response with the following criteria: fast response, when D5 CRP was less than or equal to 0.4 of D1 CRP concentration; slow response when D5 CRP was more than 0.4 of D1 CRP concentration. They concluded that in severe CAP, sequential evaluation of CRP-ratio was useful in early identification of patients with poor outcome.⁽²⁰⁵⁾

Concerning CURB-65 score on admission, the mean values were 2.21 $\pm$ 1.05 in Group I and 3.67 $\pm$ 1.0 in Group II. The mean values of CURB-65 score were 2.89 $\pm$ 1.02 in Admitted patients and 0.50 $\pm$ 0.71 in Non-admitted patients.

In agreement with the present study, S. Kruger et al found that increasing CURB-65 scores were associated with increasing death rates. Moreover, and similar to the present study, they found that the decision for hospitalization was highly associated with an increasing CURB-65 score.⁽⁷⁹⁾

Jean-Paul Mira et al conducted a recent retrospective study of specificity and sensitivity in 419 patients with CAP showed that the CURB-65 score outperformed the Standardized Early Warning Score and the systemic inflammatory response syndrome criteria as a predictor of mortality. The authors concluded that CURB-65 may be preferred over systemic inflammatory response syndrome criteria and Standardized Early Warning Score in the initial prognostic assessment of patients with CAP.⁽²⁰⁶⁾

Similar to the present study, David T. Huang et al found that 30 day mortality generally increased with increasing CURB-65 score in patients with CAP.⁽²⁰⁷⁾

Barlow G et al have shown effectively that CURB-65 outperforms early warning scores in the prediction of 30-day mortality from community acquired pneumonia (CAP). CURB-65 was as good as the PSI in predicting mortality and also appeared usefully to stratify the need for mechanical ventilation and hospital admission in a mixed cohort of outpatients and inpatients with CAP.⁽²⁰⁸⁾

Motoi U et al found that CURB-65 score is a simple and widely used severity scoring systems for CAP. Similar to the present study, this simple severity score was capable of predicting mortality and severity of disease in subjects with CAP.⁽²⁰⁹⁾

Severity assessment and site-of-care decisions for patients with community-acquired pneumonia (CAP) are pivotal for patients' safety and adequate allocation of resources. Late admission to the intensive care unit (ICU) has been associated with increased mortality in CAP. Christophe M et al systematically searched Medline, Embase, and the Cochrane Controlled Trials registry for clinical trials evaluating the performance of CURB-65 to predict the need for ICU admission, intensive treatment, or the occurrence of early mortality in patients with CAP. CURB-65 was studied in nine cohorts including a total of 5,773 patients and 479 ICU admissions (8.3%). At the usual cut-off value of 3 or more, pooled sensitivity was 66%, and specificity, 74%. The global performance of CURB-65 to predict ICU admission was similar to PSI with an AUC of 0.69.⁽²¹⁰⁾

Capelastegui et al studied the CURB-65 score, and has been proposed as a tool for augmenting clinical judgment for stratifying patients with community-acquired pneumonia (CAP) into different management groups. The six-point CURB-65 score was retrospectively applied in a prospective, consecutive cohort of adult patients with a diagnosis of CAP. A total of 1,100 inpatients and 676 outpatients were included. The 30-day mortality rate in the entire cohort increased directly with increasing CURB-65 score: 0, 1.1, 7.6, 21, 41.9 and 60% for CURB-65 scores of 0, 1, 2, 3, 4, and 5, respectively. The score was also significantly associated with the need for mechanical ventilation and rate of hospital admission in the entire cohort, and with duration of hospital stay among inpatients. The CURB-65, and a simpler CRB-65 score that omits the blood urea measurement, helps classify patients with community-acquired pneumonia into different groups according to the mortality risk and significantly correlates with community-acquired pneumonia management key points. The new score can also be used as a severity adjustment measure.⁽²¹¹⁾

Concerning procalcitonin (PCT), PCT levels, start to increase upon an infectious stimulus somewhat slowly after 2 hours and peak at 24 hours, provided no second infectious hit occurs. This response is considerably faster than that of CRP, whose levels increase slowly and only peak at 48 hours.⁽²¹²⁾

In addition, PCT has been evaluated in a number of clinical research studies and has been shown to be a more specific marker for bacterial infections compared with more traditional markers such as CRP and WBCs. The upregulation of PCT in multiple tissues in response to bacterial infections correlates with the severity and extent of bacterial infections. Conversely, interferon-, a cytokine released in response to viral infections, blocks the upregulation of PCT, resulting in a higher specificity of PCT toward bacterial infections.⁽²¹³⁾

Therefore, in the current study, Serum PCT levels were measured on admission for patients who met the diagnostic criteria of CAP and after two weeks of antibiotic therapy. On admission, the mean levels of PCT concentrations were 3.59 ± 3.96 ng/ml in Group I, and 9.33 ± 5.16 ng/ml in Group II. PCT concentrations were significantly higher in Group II ($P=0.020$) in comparison to Group I. The mean levels of PCT concentrations were 5.86 ± 4.98 ng/ml in Admitted patients and 0.40 ± 0.14 ng/ml in Non-admitted patients. PCT concentrations were significantly higher in Admitted patients ($P=0.037$) in comparison to Non-admitted patients.

In agreement with the present study, S. Kruger et al found that Median PCT levels on admission of non-survivors were significantly higher compared with those in survivors 0.88 (0.32–3.38) versus 0.13 (0.08–0.38) ng/mL ($p= 0.0001$). Moreover, and similar to the present study, patients who were hospitalized had significantly high levels of PCT.⁽²¹⁴⁾

In accordance to these findings, Robert et al demonstrated that PCT is associated with the severity of illness in patients with severe pneumonia and appears to be a prognostic marker of morbidity and mortality comparable to the APACHE II Score.⁽²¹⁵⁾

Cornado et al & Sergio et al corroborate that PCT is a good predictor of severity of pneumonia.⁽²¹⁶⁾ Patients with a higher PSI score or with complications or death had significantly higher PCT levels than those with an uncomplicated clinical course.

Seligman et al reported that initial and max PCT significantly correlate with mortality risk in patients with CAP requiring mechanical ventilation.⁽²¹⁷⁾

Simon et al reported that decreasing levels of PCT is a finding that shows improvement of infections, while increasing levels of PCT should be considered as a poor prognostic sign.⁽²¹⁸⁾

In accordance to the present study, P. Schuetz et al assessed the performance of PCT overall, stratified into four predefined procalcitonin tiers (, 0.1, 0.1–0.25, .0.25–0.5, .0.5 mg/L) and stratified by CURB-65 risk classes to predict all-cause mortality and adverse events within 30 days follow-up in 925 CAP patients, and found that non-survivors had significantly increased median PCT levels on admission compared to survivors. This was also true for patients with adverse events compared to patients without adverse events, the risk of any adverse event and ICU admission strongly increased with higher PCT level on admission.⁽²¹⁹⁾

David T. Huang et al found that the mean procalcitonin level at presentation was 3.4 ng/mL, but levels were broadly spread (SD 16.5), such that 542 subjects (32.8%) were in tier I, 356 (21.6%) in tier II, 169 (10.2%) in tier III, and 584 (35.4%) in tier IV. Higher procalcitonin tiers were associated with more clinical signs of infection and a worse course and outcome. Moreover, and similar to the present study, Lowest procalcitonin tier patients were also the most likely to be discharged from the ED.⁽²²⁰⁾

Concerning relationship between PCT, CURB-65, and CRP on admission, PCT level showed significant positive correlation with CURB-65. Whereas, PCT level showed insignificant correlation with CRP.

Similar findings have been demonstrated by Abedini et al who reported that PCT levels showed insignificant correlation with CRP.^(220, 221) S. Kruger et al found that PCT levels on admission predict the severity and outcome of CAP with a similar prognostic accuracy as the CURB-65 score.⁽¹⁹⁴⁾

Concerning follow up PCT measurement, after 2 weeks of therapy, the mean levels of PCT concentrations were 0.75 ± 0.51 ng/ml in Group I on day14 and 10.33 ± 6.09 ng/ml in Group II.

In agreement with the present study, P. Schuetz et al showed absolute PCT levels on admission and at days 3, 5 and 7, comparing survivors and non-survivors. Non-survivors had significantly increased PCT concentrations on each of the follow-up days compared with survivors. Moreover, in patients with adverse events, PCT was significantly increased on all follow-up days ($p=0.01$ for each comparison) compared to patients without adverse events (i.e. need for mechanical ventilation, ARDS, death).⁽²²²⁾

In conclusion, results of this study document that PCT is a more powerful guide to prognosis in pneumonia than several more commonly used biomarkers. Raised PCT was significantly related to increasing severity of CAP as assessed by the CURB-65. CRP did not show the same systematic relationship. The prognostic value of PCT can be markedly increased by serial measurement. Increasing PCT level or persistently elevated PCT value despite therapy, were always indicative of an unfavorable outcome.

SUMMARY

Community acquired pneumonia (CAP) is defined as acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) pneumonia. The overall rate of CAP in adults is approximately 5.16 to 6.11 cases per 1000 persons per year. CAP accounts for 1.3 million hospitalizations each year in the USA.

The average duration of hospitalization for CAP managed on the ward is 6 days, If intensive care unit (ICU) admission (for severe CAP) is required, then the stay increases to 23 days. Although CAP is very common, it remains a common cause of death. Hence, severe CAP has been reported to be the largest single cause of mortality from infectious diseases in industrialized countries.

The challenges of diagnosing and treating CAP only seem more difficult as incidence increases, patients become older and sicker, and pathogenic organisms evolve. Early recognition of infection is not always straightforward and clinical signs themselves can be misleading especially in patients with several co-morbidities or variable demographic characteristics. Evidence supports early diagnosis and intervention in sepsis and that the failure to intervene results in significant morbidity and mortality.

These complexities have led to the search for a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for untoward outcomes, and reliably guiding treatment. Among different molecules that have been suggested as sepsis biomarkers in last years, Procalcitonin appears quite promising due to its reported correlation with the septic process. A highly sensitive, and fully automated PCT assay system have been developed based on the Electrochemiluminescence immunoassay (ECLIA) for the quantitative determination of PCT in human serum.

PCT is a propeptide of calcitonin that is expressed as part of the host's inflammatory response to a variety of insults. PCT levels start to increase upon an infectious stimulus somewhat slowly after 2 hours and peak at 24 hours, provided no second infectious hit occurs. This response is considerably faster than that of CRP, whose levels increase slowly and only peak at 48 hours.

In the normal physiological condition, PCT is not released into the bloodstream and its concentration in the blood remains low (below 0.05 ng/mL); however, in severe infectious conditions, the concentration of PCT in the blood can rise above 100 ng/mL.

The aim of the work was to assess the role of CRP and procalcitonin as prognostic factors in adults with community acquired pneumonia.

We conducted a prospective observational study on 20 adult patients of both sex, who presented to the emergency casualty in Alexandria Main University hospital; diagnosed as community acquired pneumonia. . Patients were divided according to outcome into two groups; Survivors=Group I (n= 14) and Non-survivors=Group II (n=6).

Subjects' data including name, age, sex, past medical history, and data obtained from clinical examination were recorded at enrollment including CURB-65 Score. Laboratory investigations including complete blood count, blood chemistry, PCT level, CRP level, sputum cultures, were obtained on admission and after two weeks of therapy.

In the present study, CAP was more evident among males (66.7%) than females (33.3 %), most of them are old age (55.0 % above 65 years).

In the present study, Cough was the commonest complaint among the studied patients (100%) followed by fever, dyspnea, and chest pain (90%, 85%, 50%, respectively).

Patients with CAP frequently have underlying comorbidities which predispose them to infections and may have an additive contribution to mortality. In the present study diabetes mellitus and hypertension were the most common preexisting conditions accounting for 12 (60%) and 11 (55.0%) of the studied patients, respectively.

The present study revealed that *Streptococcus pneumoniae* was the commonest isolated gram-positive organism representing 12 patients (60%). *Pseudomonas aeruginosa* was detected in 2 patients (20%).

The present study found that CRP is of poor predictive value for the assessment of pneumonia severity, as compared with PCT.

The study on our hand showed that, increasing CURB-65 scores were associated with increasing death rates. Moreover, we found that the decision of hospitalization was highly associated with an increasing CURB-65 score.

In the present study, we found that PCT is a good predictor of severity of pneumonia. We also found that non-survivors had significantly increased median PCT levels on admission compared to survivors.

The present study showed that non-survivors had significantly increased PCT concentrations on compared with survivors after 2 weeks of therapy.

The study revealed that initial high levels of PCT were indicative of a more severe disease, and this was reflected to more in hospital death. PCT levels on admission predict the severity and outcome of CAP with a similar prognostic accuracy as the CURB-65 score, and is better than CRP. Increasing levels of PCT were associated with higher mortality rate, and hence, should be considered as a poor prognostic sign.