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Prediction of outcome in patients with sepsis using C - reactive protein & APACHE II scoring system

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Abstract:
Background: *Sepsis is one of the most common causes for mortality in the intensive care unit. Several biochemical markers and clinical scoring systems have been used to assess the severity and outcome of sepsis.* ***Objective:*** *To correlate the extent of C - reactive protein (CRP) elevation with mortality; in addition we also try to find a correlation by combining CRP level and APACHE II score as a predictor of outcome in patients with sepsis.* ***Methods:*** *This prospective study included 50 patients. Serum CRP and variables to calculate the APACHE II score were collected at the time of admission .The values of CRP concentrations and APACHE II score were compared, in relation to the severity and outcome of the disease.* ***Results:*** *Mean CRP value in patients who recovered from the illness was 140.6 mg/dl and in patients who died was 191.1 mg/dl (p .177). CRP level of > 137 mg/dl, has sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant (p .157). Mean APACHE II score in patients who died was 24.2, compared to the patients who recovered was 18.5 (p .002). We observed APACHE II score of >21 have sensitivity of 76% and specificity of 60% in predicting mortality in patients with sepsis, which was statistically significant (p .010). When we take both CRP level of > 137 mg/dl and APACHE II score of > 21, we observed sensitivity 48% and specificity 84% in predicting the mortality, which was statistically significant (p 0.015).* ***Conclusion:*** *It is better to combine both CRP and APACHE II for predicting the mortality in sepsis patients, than using either of them.*
Keywords: *APACHE II, C - reactive protein (CRP), mortality, sepsis.*

I. Introduction

Sepsis is one of the most common causes for mortality in the intensive care unit (ICU). Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. There is a continuum of severity ranging from sepsis to severe sepsis and septic shock. Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and are increasing in incidence [1].

Several biochemical markers and clinical scoring systems have been used to assess the severity and outcome of sepsis. An ideal prognostic method would be simple, inexpensive, easily and rapidly available with good sensitivity and specificity. Such a method is not available till date to predict the prognosis in sepsis [2]. The aim of this study is to determine the value of C-reactive protein (CRP) and Acute Physiologic and Chronic Health Evaluation (APACHE) II score in early stages (within 24hours) of sepsis for the prediction of patient outcome in the form of mortality.

Acute phase reactants (APR) comprise a major pathophysiologic phenomenon that accompanies infection, inflammation and tissue injury. They are elevated in the wide variety of disorders, including infection, inflammation, trauma, and neoplasms. Serum APR level measurements are useful because they frequently reflect the presence and intensity of an infection and/or inflammatory process [2]. C-reactive protein (CRP) is one of the most widely used acute phase reactants to predict the mortality in patients with sepsis. C - reactive protein of > 10 mg/L is a marker of acute inflammation and excludes etiologies of chronic inflammation [3].

Markedly elevated levels of CRP are strongly associated with infection. Studies have reported higher CRP values in patients with bacterial infection as compared to those with viral infection, autoimmune disorders, or other nonbacterial infection - related inflammatory disease. Bacterial infection was found in approximately 80 percent of patients with values in excess of 100 mg/L [4]. CRP level on admission is a useful marker for early infection and high CRP level at admission have been reported to correlate with an increased risk of organ failure and death [5].

Predictive scoring systems have been developed to measure the severity of disease and the prognosis of patients in the ICU. These scoring systems derive a score from a variety of clinical variables, to quantify the severity of disease and to predict the outcome, usually in terms of mortality. Several scoring systems have been developed, like Acute Physiologic and Chronic Health Evaluation (APACHE) system, Simplified Acute Physiologic Score

(SAPS), Mortality Prediction Model (MPM), and Sequential Organ Failure Assessment score (SOFA). The APACHE II scoring system is widely used and to be calculated within 24 hours of ICU admission [6].

There are very few studies in the literature which have used both scoring systems and acute phase reactants together to predict the outcome in sepsis patients. The aim of our study is to correlate the extent of CRP elevation with mortality; in addition we also try to find a correlation by combining CRP level and APACHE II score as a predictor of outcome in patients with sepsis.

II. Materials And Methods

This was a prospective study conducted in the medical ICU at Father Muller Medical College hospital, after approval from the institute's ethical committee. The study was conducted over the period of 6 months (August 2013 – January 2014). A total of 50 patients of either sex in the age group of 20-80 years, who fulfilled the criteria for sepsis i.e., systemic inflammatory response syndrome (SIRS) with a presumed infectious etiology were included in the study. Systematic Inflammatory Response Syndrome is defined as a condition in which a patient having any two of the following abnormal vital signs: Body temperature > 38°C or < 36°C, heart rate > 90 beats/min, respiratory rate > 20 breath/min, white blood cell count > 12,000 cells/mm^3. A detailed history, clinical findings, and complications were noted. C-reactive protein and variables to calculate the APACHE II score were collected at the time of admission.

Exclusion Criteria: (1) Age <18years, (2) Patients referred from other hospitals or who have received antibiotics in the past 7 days, (3) Pregnant women, and (4) Collagen vascular diseases and malignancy possibly causing high CRP value.

III. Results

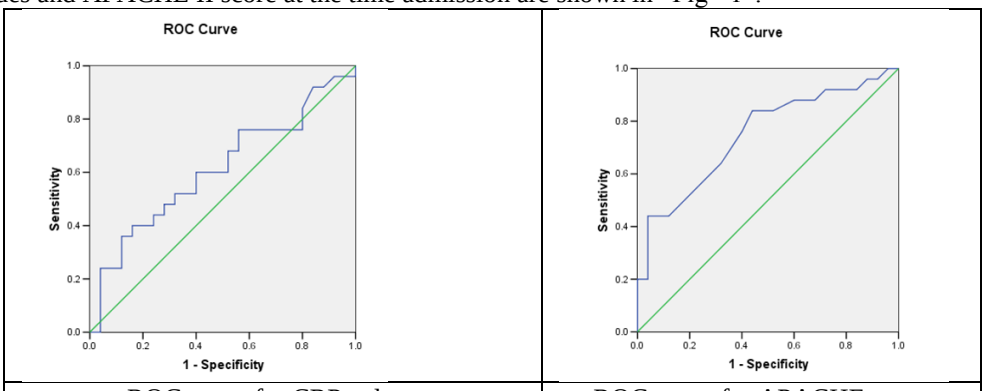
A total of 50 patients, 34 (68%) males and 16 (32%) females, in the age group of 20-80 years, with the predominant age group of 40-60 years were included in the study. Fifty percent mortality was noted in our study.

Normal C - reactive protein (CRP) value of our lab is < 5 mg/dl and the mean CRP value observed in our study was 166 mg/dl (range: 15.9 - 502 mg/dl). C-reactive protein was significantly elevated in elderly and in patients with ≥ 3 organ system involvement. Mean CRP value in patients who recovered from the illness was 140.6 mg/dl and mean CRP value in patients who died was 191.1 mg/dl (p value 0.177). We observed CRP level of > 137 mg/dl, has sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant (p .157).

The mean admission APACHE II score in our patients was 21.4. Mean APACHE II score in patients who died was 24.2, compared to the patients who recovered from the illness was 18.5 (p value 0.002). The derived predicted mortality estimate was 48% and the actual mortality observed in our study was 50%. The admission APACHE II predicted mortality and the mortality observed in our study group was almost similar. We observed APACHE II score of >21 have sensitivity of 76% and specificity of 60% in predicting mortality in patients with sepsis, which was statistically significant (p .010)

When we take both CRP level of > 137 mg/dl and APACHE II score of > 21 to predict the mortality in patients with sepsis, we observed sensitivity 48% and specificity 84% in predicting the mortality, which was statistically significant (p 0.015).

Receiver operating characteristic (ROC) curves and the respective areas under the curves (AUC) calculated for CRP values and APACHE II score at the time admission are shown in "Fig - 1".



ROC curve for CRP values | ROC curve for APACHE score

Figure 1: Receiver operating characteristic (ROC) curves and the respective areas under the curves (AUC) for CRP values and APACHE II score at the time admission.

IV. Discussion

The acute phase reactants and scoring systems are widely used for the assessment of severity, prognosis, and outcome in patients with sepsis. Several biomarkers used to monitor the patients with sepsis includes procalcitonin, C-reactive protein, various interleukins, eosinophil count, adrenomedullin and pro-ADM, atrial natriuretic peptide and pro-ANP, pro-vasopressin (copeptin), interferon-gamma, triggering receptor expressed on myeloid cells 1 (TREM-1), and resistin. Of these, procalcitonin and C-reactive protein has been studied extensively and is now being used routinely in clinical practice. They are also useful in diagnosis of infection and to assess the response to antibiotic therapy in patients with sepsis [2, 7].

In healthy young adults, the median CRP concentration is 0.8 mg/l, the 90^{th} centile is < 3.0 mg/l, and the 99th centile is < 10 mg/l [8], but, following bacterial infection, trauma, tissue necrosis, and any forms of inflammation, CRP levels rise rapidly and may exceed 300 mg/l within 48 hours of an acute event [9]. In our study, CRP was elevated in all patients with sepsis at the time of admission; however there was no statistically significant variation in CRP level between the patients who died and the patients who recovered (p value 0.177). We observed CRP level of > 137 mg/dl, has sensitivity of 60% and specificity of 60% in predicting mortality in patients with sepsis and was not statistically significant (p .157).

Study done by Jeschke et al [10], Silvestre et al [11], and Pettilä et al [12] have also found that CRP level does not vary significantly in patients with sepsis who die compared to those patients who recovered from the illness, and have also concluded that the CRP is a poor prognostic marker for the prediction of outcome of patients with sepsis. The result of our study and the above mentioned studies, differed from the work done by Lobo et al [5], Ho et al [6], Hogarth et al [13], and Cox et al [14], who have noticed that the admission CRP value was significantly elevated in patients with sepsis who died and have concluded that high CRP level is a good predictor of poor outcome in patients with sepsis.

Admission CRP was not a good mortality predictor in our study; which is similar to the study done by Devran et al [15], who have also noticed that the initial CRP level is not a good predictor for mortality in sepsis patients, however 3rd day CRP levels was better than initial CRP values in predicting the mortality. A serial daily CRP measurement was not done in our study and is one of the limitations of our study. Daily measurement of CRP is better for monitoring the sepsis patients, and may be used to guide the successful treatment and change of antibiotics [16].

In our study, when we take both CRP level of > 137 mg/dl and APACHE II score of > 21 to predict the mortality in patients with sepsis, we observed sensitivity 48% and specificity 84% in predicting the mortality, which was statistically significant (p 0.015). Study done by *Agarwal et al* [17] have observed an elevated CRP levels on admission in patients with sepsis, but also there was a significant and serial increase in the CRP levels in patients, who later deteriorated and expired. Whereas, the patients who recovered and got shifted out of ICU to their wards showed a maximum rise until D2-D3, after which the values showed a decreasing trend though they still often remained elevated over normal values for several days. They have also observed that APACHE II scoring system underestimates the mortality. So, it can be assumed that isolated APACHE II score is a poor predictor of mortality when used alone and it would be better if combined with other parameters, such as CRP levels.

V. Conclusion

There are very few studies in the literature which have used both scoring systems and acute phase reactants together to predict the outcome in sepsis patients. In conclusion, it is better to combine both the acute phase reactants such as CRP and predictive scoring systems such as APACHE II for predicting the mortality in sepsis patients, than using either of them.

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