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Original Article

Evaluation of C-reactive protein and tumor necrosis factor- alpha as reliable laboratory markers for early diagnosis of sepsis.

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ABSTRACT

Background: Sepsis and septic shock are common causes of mortality in critically ill patients. The high mortality rate associated with the sepsis underlines the need for reliable laboratory marker for early identification of patients at high risk. Microbiological diagnosis of sepsis is usually difficult and time consuming. The demonstration of increase in the level of certain cytokines can be used as indirect evidence of sepsis. Objective: The present study was conducted with an aim to determine the relevance of C-reactive protein (CRP) and serum tumor necrosis factor α (TNF- α) and C-reactive protein (CRP) as diagnostic markers of sepsis. Materials and methods: One hundred and sixty two patients diagnosed as sepsis clinically were included as study, serum levels of CRP and TNF-α were estimated. Results: Serum CRP levels were found to be elevated in 91 (89.2%) sepsis patients. Serum TNF- α levels were elevated in 98 (96.1%) sepsis patients. Conclusion: Estimation of CRP and TNF- α can be useful for empiric management of sepsis cases.

1. Introduction

Sepsis is a common cause of critical illness, often complicated by the development of multiple organ dysfunction syndrome with poor outcomes [1]. Sepsis and septic shock are common causes of mortality in critically ill patients [2]. The mortality is up to 28% to 50%, and 60% to 90% of the patients die due to complications of sepsis [3]. The high mortality rate associated with the sepsis underlines the need for reliable laboratory marker for early identification of patients at high risk.

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The infective pathogen has no significant role in development of sepsis. The metabolic and immunologic host systemic inflammation is triggered by the bacteria and their endotoxin present in the blood of sepsis patients [4]. The cascade of endogenous mediators causing systemic inflammation can be initiated by various bacterial and fungal aetiological agents and their cellular components. Shock and ischemia leads to hypoperfusion and hypoxia of various vital organs, altering the permeability of cell membrane leading to multiple organ failure [5].

The diagnosis of sepsis remains as the challenge for the clinicians and laboratory professionals. Microbiological diagnosis of sepsis is usually difficult and time consuming. It is dependent on the blood culture which takes approximately three days at the earliest and seven days at the latest [6]. The demonstration of increase in the level of certain cytokines can be used as indirect

evidence of sepsis. A number of inflammatory cells and mediators involved in the inflammatory response have been assessed for their significance as potential markers of the presence and severity of inflammatory response and organ failure [7].

Serum levels of C-reactive protein (CRP), an acute-phase protein synthesized by the liver following stimulus by various cytokines including tumor necrosis factor and interleukin (IL-6), markedly increase within hours of infection or inflammation. The levels of cytokines can be detected by various simple and rapid laboratory investigative methods and the results of these are available on the same day in contrast diagnostic bacteriological methods. The rapidity in reporting of these markers will be of aid clinician for inducing prompt treatment.

The present study was conducted with an aim to determine the relevance of C-reactive protein (CRP) and serum tumor necrosis factor α (TNF- α) and C-reactive protein (CRP) as diagnostic markers of sepsis.

2.Materials and Methods

The present study was conducted at SRTR Medical College and Hospital, Ambejogai. A total of one hundred and sixty two patients diagnosed as sepsis clinically were included as study group. The criteria for selection of study group were (1) objective signs of acute infection. (2) > 3 recognized signs of systemic inflammatory response and (3) evidence of ≥2 organ dysfunctions [4]. The control group consisted of healthy individuals with age and sex matched to those in the study group. The control group was used to compare the CRP and serum TNF- α levels.

The blood sample was collected from the both study and control group. The blood sample was obtained in plain bulb by veni-puncture following aseptic procedure. The sample was allowed to clot for 30 minutes. The clot was then broken and the sample was centrifuged for the separation of the serum. The serum samples were used for the assay of CRP and TNF- α.

TNF- α levels were estimated by enzyme immunoassay using Titerzyme TNF- α. EIA kit (Perceptive Biosystems Inc., Framingham, MA 01701) following the manufacturer's instructions. Standard curve was prepared against which the sample reading were plotted. The lowest detectable value for TNF- α. Was 3.78 pg/ml and the highest detectable limit was 1658 pg/ml. CRP analysis was done by done by latex agglutination by using kit of Tulip diagnostics (Goa, India)P.

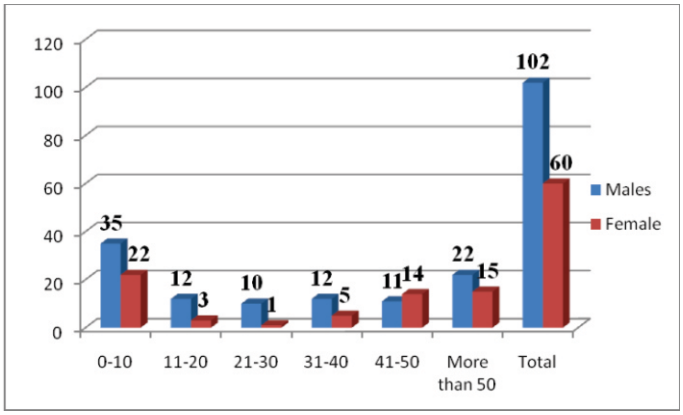
3.Results

As shown Table 1 out of total patients included in the study 102 (62.9%) were male whereas, 60 (37.1%) were female. Sepsis was more common in age group 0-10 years both in males and females, 34.3% of total male patients included in the study and 36.6% of females belonged to this age group. In our study the incidence of sepsis was low in age group 11-20 years in both male and female patients.

CRP was not detected in the serum samples of control group. Serum CRP levels were found to be elevated in 91 (89.2%) sepsis patients.

Levels of TNF- α (mean ± SD) in the sera were 20.8±6.7 in the control group, the range being 3.8 pg/ml to 27.1 pg/ml. Cut off value of positive TNF- α was 28 pg/ml. Serum TNF- α levels were elevated in 98 (96.1%) sepsis patients.

Figure 1. Age and sex distribution of sepsis patients.



4.Discussion

Several studies have been performed by different researchers to determine the relationship between cytokines and sepsis [8, 9, 10]. Cytokines are proteins that are produced by immune and non-immune cells and they act as mediators to facilitate cellular communication. The growing knowledge on the pathophysiological role of cytokines in septic shock stimulated efforts to control their synthesis and action pharmacologically in clinical situations [11]. In our study we estimated the serum CRP levels and TNF- α levels in the sepsis patients.

The results of the present study show that sepsis influences CRP and TNF- α levels of serum. CRP was discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide by the liver and adipocytes [12]. It is an acute-phase protein, and its levels are upregulated in viral, bacterial and fungal infections, as well as in non-infectious inflammatory conditions. In our study, serum CRP levels were found to be elevated in 89.2% patients with sepsis. Sahin et al [13] also reported the same finding and stated that increased CRP concentration along with other clinical parameters may be valuable to predict the risk of death in sepsis patients. They also concluded that CRP concentrations in critically ill patients may help to identify patients who may require more aggressive diagnostic and therapeutic interventions to avoid complications. Lobo et al [14] reported the relationship between CRP concentration and the severity and pattern of multiple organ dysfunction. They concluded that CRP levels are good early markers of morbidity and mortality. Kumar et al [6] reported CRP levels to be elevated in 67% patients with sepsis. In their study sensitivity of CRP was higher than that of blood culture. CRP is a currently widely

available biomarker used to discriminate the inflammatory response to infection [15]. In addition, serum levels of CRP reflect not only the presence of infection but also severity [16].

Studies by other workers have demonstrated the relationship between TNF- α and sepsis [8, 9]. Most of them have reported TNF- α levels to be significantly higher in patients with sepsis than in controls. Our study also documents the same finding. TNF- α serum levels were found to increased in 96.1% patients with sepsis. In the study conducted by Kumar et al [6] TNF- α levels were found to be elevated in 84.8% sepsis cases. They reported TNF- α to have the highest sensitivity for diagnosis of sepsis with 100% specificity. Similar observation has been reported by Kocabas et al [17] On the other hand; Harris et al [18] noted that plasma IL-6 level is more reliable indicator of bacterial sepsis and necrotizing enterocolitis than TNF- α. As TNF- α producing capacity is higher in septic patients than in healthy subjects, it has a pivotal role in the pathogenesis of sepsis and septic shock. TNF- α levels can be estimated on the very day of onset of sepsis [11].

From our study, it can be concluded that estimation of CRP and TNF- α can be useful for empiric management of sepsis cases. Since this study is a baseline study with smaller patient group, we think that more extensive and controlled research about this subject should performed.

5.References

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