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Association of C - reactive protein with Degree of Septicemia in ICU Admitted Patients

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ABSTRACT

Background: CRP is a classical acute phase reactant discovered by Tillett and Francis in the 1930s. CRP belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins. CRP an acute phase protein involved in coagulation, acts as opsonin for gram positive bacteria to aid in their phagocytosis. CRP is synthesized by the liver in response to and as part of the inflammatory response. IL-6 is the major stimulus for production of CRP, along with IL-1 & TNF alpha. CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage. It has a half-life of 19 hours and may increase more than 1000-fold during an acute phase response. **Methods:** This study was carried out in the department of Microbiology and Immunology & intensive care units of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly. Blood samples from 70 patients meeting the inclusion and exclusion criteria was collected. Intensive care unit of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly. Adult patients (> 14 years of age) admitted to intensive cardiac unit of SRMS-IMS Hospital with suspicion of sepsis. **Results:** Diagnosis validity shows that CRP has sensitivity & specificity of 78.6% & 65.7% respectively. Further its Positive & Negative Predictive Value is 69.6% % 75.4%. This gives us a diagnostic accuracy of about 72.1%. **Conclusion:** This study concludes that, CRP could be very useful in resource-limited places, where newer biomarkers such as procalcitonin or interleukins are not available.

Keywords: C - reactive protein, Septicemia, ICU.

INTRODUCTION

Sepsis is a heavy burden on health services all over the world, both from economic and social points of view. According to an epidemiological study of the USA, over the last 20 years, the incidence of sepsis increased from 82.7 to 240.4/100 thousand inhabitants, as did the deaths related to it, although the general mortality rate among patients with sepsis was reduced over the period.[1] The incidence of severe sepsis and septic shock is difficult to determine accurately. There are estimated 7, 50,000 cases of severe sepsis leading to 2, 15,000 deaths per year in US alone.[2]

Although the signs and symptoms of sepsis may be highly variable, it takes only little experience of acute care in order to recognize the usual clinical picture characterized by fever, chills, general malaise and signs of physiological strain. Still defining specific and useful diagnostic criteria for sepsis has remained a complicated issue ever since the modern usage of the term was introduced. In an attempt to resolve this problem, a consensus conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced new diagnostic definitions in the early 1990s, with the intention to provide criteria that were apt for both clinical practice and standardization of research protocols.[3] Central to the proposed definitions was the presence of a "systemic inflammatory response syndrome" (SIRS), a physiologic reaction commonly seen in intensive care patients in response to conditions like trauma, burns and infection. SIRS was defined by at least two of the following signs: an abnormal body temperature, tachycardia, tachypnea or an abnormal white blood cell count (WBC) [Box 1]. Sepsis was defined as SIRS caused by an infection [Figure 1]. It was also suggested that SIRS could progress into a more severe state of organ failure, coined "multiple organ dysfunction syndrome" (MODS).[3]

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BOX 1: SIRS-defining criteria. Data adapted from Bone et al.[3]

Two or more of the following:

- Temperature (Oral) >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >24/min or
- PaCO2 <4,3 kPa
- White blood cell count >12,000/µL or <4000/µL, or >10% immature forms

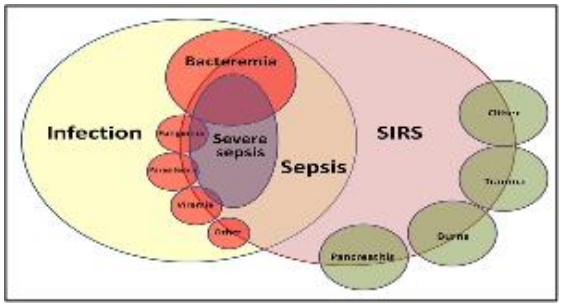


Figure 1: Interrelationship between infection, SIRS, sepsis & associated conditions. Adapted from Bone et al.[3]

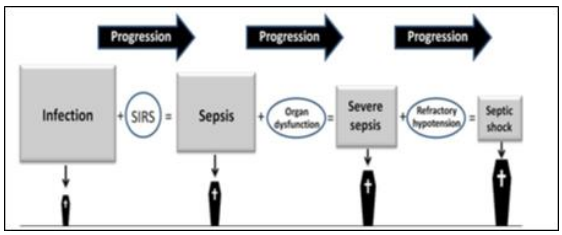


Figure 2: Progressive severity stages of sepsis. Increasing severity is characterized by lower incidence & increased case fatality rates.

Sepsis: documented or suspected infection and some of the following:

General parameters

- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >120 mg/dl or 7.7 mmol/l) in the absence of diabetes

Inflammatory parameters

- Leukocytosis (white blood cell count >$12x10^9$/l)
- Leukopenia (white blood cell count <$4x10^9$/l)
- Normal white blood cell count with >10% immature forms
- Plasma C reactive protein>2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic parameters

- Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation >70%
- Cardiac index >3.5 l/min/m^2

Organ dysfunction parameters

- Arterial hypoxemia (PaO_2/FIO_2 <300 mmHg or <40 kPa)
- Acute oliguria (urine output <0.5 ml/kg/h for at least 2 h)
- Creatinine increase ≥0.5 mg/dl or ≥45 µmol/l
- Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 sec.)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/µl)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

Tissue perfusion parameters

- Hyperlactatemia (>3 mmol/l)
- Decreased capillary refill or mottling

Severe sepsis: sepsis with organ dysfunction, hypoperfusion or hypotension.

Septic shock: severe sepsis with hypotension refractory to intravenous fluid replacement.

2012 International sepsis definitions.[4]

CRP is a classical acute phase reactant discovered by Tillett and Francis in the 1930s.[5] CRP belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins. CRP an acute phase protein involved in coagulation, acts as opsonin for gram positive bacteria to aid in their phagocytosis.[6] CRP is synthesized by the liver in response to and as part of the inflammatory response. IL-6 is the major stimulus for production of CRP, along with IL-1 & TNF alpha.[7] CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage. It has a half-life of 19 hours and may increase more than 1000-fold during an acute phase response.[6]

CRP is particularly useful in managing late onset bacterial infection, since the concentration of CRP increase rather slowly in the initial phase. Serial measurements at 24 and 48 hours after the onset of illness considerably improve the sensitivity to 82% and 84% respectively.[8]

MATERIALS AND METHODS

This study was carried out in the department of Microbiology and Immunology & intensive care units of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Blood samples from 70 patients meeting the inclusion and exclusion criteria was collected.

Study Area

Intensive care unit of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Study Population

Adult patients (> 14 years of age) admitted to intensive cardiac unit of SRMS-IMS Hospital with suspicion of sepsis.

Inclusion criteria

Critically ill patient aged >14 years and admitted to ICU and further diagnosed and categorised into different stages of septicemia. Diagnosis was done using clinical findings, blood tests including procalcitonin. Only confirmed cases were included in the study.

Exclusion criteria

1. Patient age ≤ 14 years.
2. Patient who is empirically on antibiotic therapy.
3. The inability to acquire a written informed consent
4. Patients with severe infections due to viruses, parasites or tuberculosis
5. Patients entering the ICU for merely short-term post-operative observation
6. Patients with an estimated length of stay less than 24 hrs.
7. Severely immunocompromised patients such as patients with HIV and a CD4 count of less than 200 cells/mm, neutropenic patients (<500 neutrophils/mL)
8. Patients with solid organ transplantation
9. Moribund patients.

All patients admitted in SRMS-IMS hospital, meeting inclusion and exclusion criteria were included in the study. Informed oral and written consent were taken from the patients.

Blood sample was collected on day 1 of admission to the ICU of SRMS-IMS. General parameters like pulse, blood pressure, oral temperature, respiratory rate and urine output were recorded on the same day.

Blood sample was also collected from negative control group.

Blood sample was collected and sent for:-

1. Total Leukocyte count, Differential Leukocyte count and Platelet count
2. Procalcitonin
3. C-reactive protein

C-Reactive Protein

CRP analysis was done by Turbidimetric immunoassay (Quantia – CRP UV®) which is a quantitative method of analysing CRP levels.

Measuring range

Quantia – CRP UV® reagent measures CRP concentrations in the range of 0.6-10 mg/dl.

Detection limit: 0.6 mg/dl

Normal Range: < 0.6 mg/dl

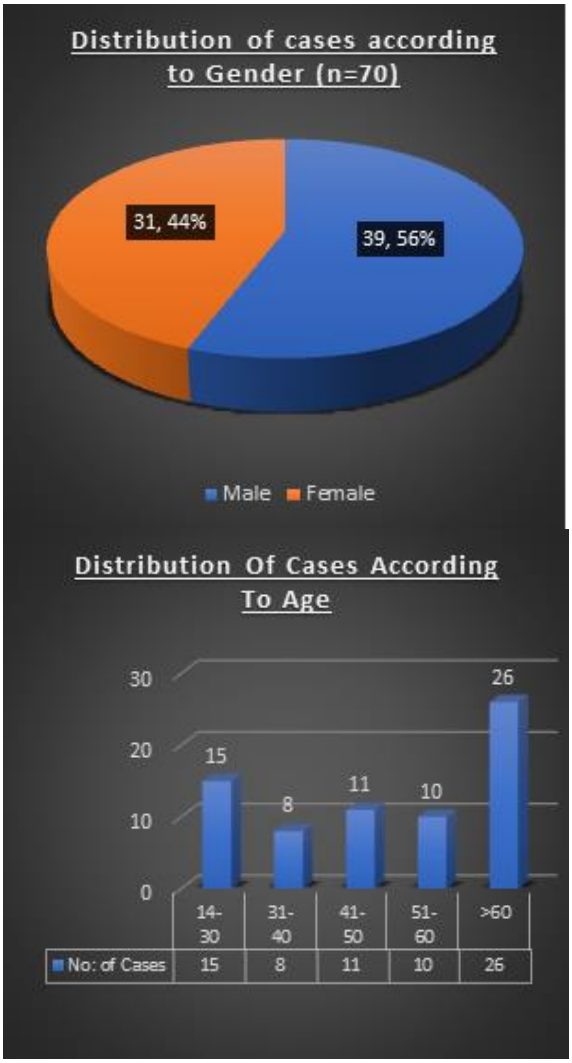
Statistical Software

The Statistical software namely SPSS 22.0, Stata 8.0, and MedCalc 9.0.1 were used for the analysis of the data. Microsoft Word and Excel have been used to generate graphs, tables etc.

RESULTS

This prospective study was conducted in Microbiology department of Shri Ram Murti Smarak Institute of Medical Sciences. The blood samples from 70 patients meeting the inclusion and exclusion criteria constituted the material for study. These 70 patients were categorized according to definition as SIRS, Sepsis, Severe Sepsis, Septic Shock. Further they were evaluated using CRP.

Among the 70 patients enrolled in this study, there were 39 (56%) males and 31 (44%) females. Maximum patients enrolled in the study belong to age group of >60 years followed by 14-30 years of age.



According to protocol patients enrolled in the study were categorized as SIRS, SEPSIS, SEVERE SEPSIS and SEPTIC SHOCK as per definitions. SIRS constituted major part of diagnosis in our study constituting 28 (40.0%) out of 70 patients enrolled in the study followed by Severe Sepsis constituting 20 (28.6%), Sepsis constituting 12 (17.1%) and Septic shock constituting 10 (14.3%) patients of study group.

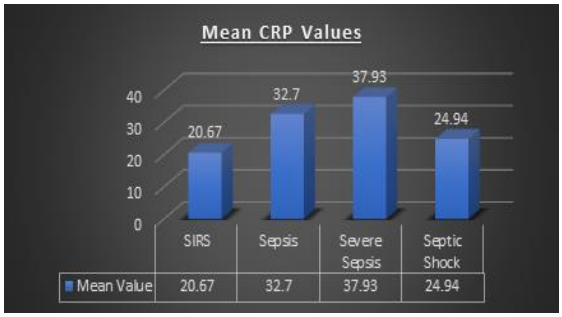
When CRP was performed on these 70 enrolled patients, it was found to be positive in 55 (78.6%) patients i.e. CRP value of >0.6 mg/dl. Further CRP values were used to classify into risk categories.

Table 1: Distribution of Cases according to Risk Category as per CRP Values

CRP Range	Risk Category	No: Of Cases	Percentage
< 0.6	Negative	15	21.4%
0.6 – 10	Low	2	2.8%
10 – 30	Average	20	28.6%
> 30	High	33	47.2%

Out of 70 patients enrolled in the study, 15 (21.4%) belong to no risk category, 2 (2.8%) belong to low risk category, 20 (28.6%) belong to average risk category and 33 (47.2%) belong to high risk as per CRP values.

Mean value of CRP for each category of septicemia was derived. Mean values of CRP of SIRS, Sepsis, Severe Sepsis & Septic Shock were 20.67 mg/dl, 32.70 mg/dl, 37.93 mg/dl & 24.94 mg/dl respectively. We observed that mean CRP values were higher in severe grades of sepsis as compared to lower grades of sepsis.



Further CRP risk categories were correlated with the diagnosis.

CRP Range	Risk Category	SIRS	Sepsis	Severe Sepsis	Septic Shock
< 0.6	Negative	9	0	1	5
0.6 – 10	Low	0	1	1	0
10 – 30	Intermediate	9	4	7	0
> 30	High	10	7	11	5
Inference	CRP risk category correlates significantly with the diagnosis (p-value = 0.037)				

On correlation of CRP risk category with diagnosis we concluded that 9 patients of SIRS, 1 patient of Severe Sepsis & 5 patients of Septic Shock belong to NO risk category. Similarly, 1 patient of Sepsis & 1 patient of Severe Sepsis belong to LOW risk category; 9 patients of SIRS, 4 patients of Sepsis & 7 of Severe Sepsis belong to INTERMEDIATE risk category; 10 patients from SIRS, 7 from Sepsis, 11 from Severe Sepsis and 5 from Septic Shock belong to HIGH risk category. CRP risk category correlates significantly with the diagnosis (p-value = 0.037).

On association of CRP with diagnosis it was found that SIRS patients showed a positivity rate of 67.9% (19 cases), Sepsis patients showed a positivity rate of 100.0% (12 cases), Severe sepsis patients showed a positivity of 95.0% (19 cases) and Septic Shock patients showed a positivity of 50.0% (5 cases).

Diagnosis	No: of Cases	CRP	
		Negative (n=15)	Positive (n=55)
SIRS	28	9 (32.1%)	19 (67.9%)
Sepsis	12	0 (0.0%)	12 (100.0%)
Severe Sepsis	20	1 (5.0%)	19 (95.0%)
Septic Shock	10	5 (50.0%)	5 (50.0%)
Inference	CRP values are significantly associated with diagnosis (p-value = 0.028)		

Diagnosis validity shows that CRP has sensitivity & specificity of 78.6% & 65.7% respectively. Further its Positive & Negative Predictive Value is 69.6% % 75.4%. This gives us a diagnostic accuracy of about 72.1%.

DISCUSSION

The term 'sepsis' is used to define systemic inflammatory response to an infectious agent (bacterial, viral, fungal or parasitic).[9] In our study 70 patients were enrolled with diagnosis of sepsis and there CRP was done.

The frequency of the disease in our study group was found to be high in elderly patients (38% were above the age of 60 years) with strikingly predominant involvement of the male sex (56%).[10]

According to protocol, 70 patients enrolled in this study were divided into grades of sepsis on basis of clinical findings. Thus, in our study SIRS constituted major part of the study i.e. 28 (40.0%) patients followed by Severe Sepsis 28.6%, Sepsis 17.1% and Septic Shock 14.3%. Similar finding was seen in a study done by Yi-Ling Chan et al where maximum number of patients belong to SIRS category (37.9%), followed by 21.5% patients in Severe Sepsis, 8.9% patients in Septic Shock category.[11]

Out of 70 patients enrolled in this study 55 (78.6%) patients showed positive CRP values i.e. >0.6 mg/dl while remaining 15 (21.4%) patients were negative for CRP i.e. value <0.6 mg/dl.

On dividing patients into risk categories on basis of CRP values (<0.6, 0.6-10, 10-30, >30 mg/dl) and then correlating these risk categories with grades of sepsis we found that 50% cases of Septic Shock were negative for CRP followed by 32.1% cases of SIRS. HIGH risk category with CRP values >30 mg/dl was seen maximum in Sepsis grade patients (58.3%) followed by Severe Sepsis (55%), Septic Shock (50%) and minimum in SIRS i.e. 35.7%. Maximum mean CRP value was seen in severe sepsis cases i.e. 37.93 mg/dl followed by Sepsis and Septic Shock. Therefore, no correlation was seen between CRP values and severity of the disease. Thus, we can conclude that CRP value had maximum positivity of 100% in Sepsis patients followed by 95.0% in Severe Sepsis patients, 67.9% in SIRS and 50.0% in Septic Shock. Similar results were shown by Castelli et al who mentioned least sensitivity of CRP among septic shock cases as compared to other grades.[12]

CONCLUSION

Determination of CRP is a cheap, consistent and reproducible test and is available in almost every hospital. Despite having a small size, our study has shown the usefulness of CRP in identifying patients with sepsis in those who present with the manifestation of SIRS. Furthermore, CRP could be very useful in resource-limited places, where newer biomarkers such as procalcitonin or interleukins are not available, and where there is no guidance of an intensivist or a trained sepsis expert.

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