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Original Article

Microbiology Section

Role of Sepsis-3 Criteria and C-Reactive Protein in the Diagnosis of Sepsis in Critically ill Patients

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ABSTRACT

Introduction: In the recent days, large proportion of the Intensive Care Unit (ICU) admissions ending in poor outcomes is impacted by pathological conditions like sepsis and septic shock. Hence, early diagnosis and appropriate therapy within the first hours of hospital admission plays a major role. Simple markers like C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), blood counts are still relied upon for suspected sepsis cases.

Aim: To study the prevalence of sepsis and to evaluate the utility of the simple ideal markers like CRP, ESR, and blood counts for early diagnosis of sepsis in critically ill patients.

Materials and Methods: This was a prospective observational study performed in the ICU of KMCH Institute of Allied Health Sciences, Coimbatore, Tamil Nadu, India, using 112 blood samples collected from patients admitted with clinical suspicion of sepsis. The samples were subjected to CRP estimation using turbidimetric immunoassay and blood culture. The data obtained were analysed using Statistical Package for the Social Sciences (SPSS) software version 21.0. The sensitivity, specificity, negative and positive predictive values were calculated.

Results: Among a total of 112, the number of patients who abided the sepsis-3 definitions with positive qSOFA (quick Sepsis related Organ Failure Assessment) score was 50%. The most common co-morbid condition among the sepsis patients were diabetes mellitus (39.2%). The most frequent site of infection was respiratory tract (37.5%). Majority of infections were by gram-negative organisms (82%), the commonly isolated gram negative organisms were Klebsiella pneumoniae (25.9%) and Escherichia coli (25.9%). The sensitivity of CRP was 81% and specificity was 49% while the Positive Predictive Value (PPV) and Negative Predictive Value (NPV) was 60% and 56%, respectively. The prevalence of sepsis in present study was 50%.

Conclusion: The study highlights the usefulness of CRP in identifying patients with sepsis in those who present with positive qSOFA score. Also, CRP could be very useful in resource-limited places, where newer biomarkers and guidance of an intensivist or sepsis expert are not available.

Keywords: Biomarkers, Blood culture, Intensive care units

INTRODUCTION

In the recent days, large proportion of the ICU admissions ending in poor outcomes is impacted largely by pathological conditions like sepsis and septic shock [1]. Sepsis ensues following infection due to deregulated host response to infection leading to uncontrolled inflammation and organ dysfunction and potentially a hypotensive state known as septic shock [2]. In such cases, early diagnosis and appropriate therapy within the first hours of hospital admission plays a major role in improving patient outcome [3]. The gold standard for sepsis diagnosis being the culture of microorganisms, which is diagnostic and treatment delay is inevitable [4,5]. So there is a demand for an efficient biomarker that would be crucial to diagnose sepsis quickly.

Numerous bloodstream biomarkers in sepsis have been investigated previously [6], like Procalcitonin (PCT), Interleukin-6 (IL-6) and CRP [7]. PCT, which is typically secreted by C-cells of the thyroid in response to hypercalcemia induced by sepsis. CRP, on the other hand is an acute phase reactant primarily synthesised by the liver in response to IL-6. IL-6, a cytokine whose levels rise significantly during early sepsis generates an initial response to injury or infection [7,8]. Though these biomarkers are commonly used because of their easy accessibility and availability, they had few limitations, due to lack of sepsis specificity [9,10]. Another interesting approach has been to employ a combination of markers and clinical parameters, known as a bioscore [11]. Recently, Gibot S et al., demonstrated high diagnostic performance by a bioscore that combined the intensity of CD64 expression on Polymorphonuclear cells (PMN CD64 index) together with PCT and the soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) serum levels [11]. However, routine availability in all hospitals has deferred the use of these biomarkers on a day to day basis.

According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), put forward by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine or clinical operationalisation, organ dysfunction can be represented by an increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10% and adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have atleast two of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22 beats/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less [12].

Therefore, simple markers like CRP, ESR, blood counts are still relied upon for suspected sepsis cases. Apart from laboratory parameters, scoring systems like qSOFA and others are also used to risk stratify patients entering the emergency within a short period of time. Earlier suspicion of sepsis helps the patients to access proper treatment and improves the outcome. Thus, the study aimed to study the prevalence of sepsis and to evaluate the utility of the simple ideal markers for early diagnosis of sepsis.

MATERIALS AND METHODS

This prospective study was performed in the three ICU's (medical ICU, surgical ICU and trauma ICU) in Kovai Medical Center Hospital, Coimbatore, Tamil Nadu over a period of three months (December 2019 to February 2020). The protocol was approved by the Institutional Ethics Committee (EC/AP/775/10/2019). An informed consent was obtained from the patients or the guardians.

Inclusion criteria: Patients diagnosed with sepsis or being suspected for sepsis according to American College of Chest Physicians (ACCP)/ Society of Critical Care Medicine (SCCM) criteria [12], patients willing to participate in the study were included in the study.

Exclusion criteria: Patients who received prior antibiotic therapy, patients who were suffering from cancer, immunosuppressive disorders and chronic illnesses, patients who did not gave consent to participate in the study were excluded from the study.

According to the ACCP/SCCM, sepsis is defined by the fulfillment of the Sepsis-3 criteria which is an increase of score 2 or more in the qSOFA score to be defined as sepsis and organ dysfunction.

qSOFA scoring for sepsis:

- Altered mental status (Glasgow Coma Scale (GCS) score <15)
- Systolic blood pressure <100 mmHg
- Respiratory rate >22/min [12]

If 2/3 of these 3 criteria are positive, the qSOFA is positive and the patient is suspected to have sepsis and organ dysfunction. The blood samples were collected from these patients, immediately transported to the laboratory and centrifuged at 2000 rpm for 10 minutes at room temperature and serum subjected to CRP estimation and blood culture. As per the manufacturer's instructions, the CRP estimation in serum was performed through turbidometric immunoassay based on the principle of agglutination reaction on the BT1500 analyser. The serum sample was mixed with activated buffer and later with antibody reagent provided in Quantia- CRP UV BT System pack from Tulip diagnostics, they are allowed to react. Presence of CRP produces turbidity which was measured at 340 nm by the photometer. Quantia- CRP UV BT System pack can measure CRP as low as 0.6 mg/dL. The results obtained were analysed. The blood culture was carried out using automated BACT ALERT blood culture system.

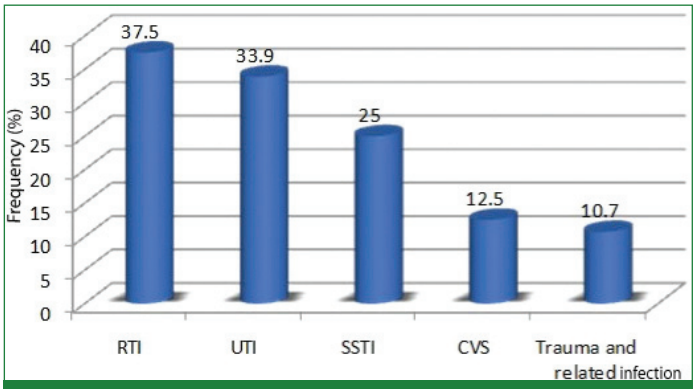
STATISTICAL ANALYSIS

The data obtained were analysed using SPSS software version 21.0. The sensitivity, specificity, positive and negative predictive value were calculated. The p-value was determined using t-test and value <0.001 was considered significant. The mean, median, range and standard deviation of the CRP values obtained were also calculated.

RESULTS

Among a total of 112 total sepsis patients admitted in the various ICUs during the study period, the number of patients who abided the sepsis-3 definitions with a positive qSOFA score was 50% (n=56) and among them 7.1% (n=4) had severe sepsis and 19.6% (n=11) had septic shock. Out of this 56, the culture proven sepsis cases were 48.2% (n=27) and culture negative sepsis was 46.4% (n=26). The culture was not performed among 5.4% (n=3) as these patients were critically ill and were dead before the culture was planned.

Most admissions were due to medical reasons. The most common co-morbid condition among the sepsis patients was diabetes mellitus in 44 (39.2%) patients. Other co-morbidities found among the participants were systemic hypertension (34, 30.4%), arthritis (15, 13.4%), obesity (10, 8.9%), allergic disorders (4, 3.6%). Out of 112 total sepsis patients, the most frequent site of infection among sepsis patients was respiratory tract infection in 42 (37.5%) patients, followed by urinary tract infection in 38 (33.9%) patients, Skin and soft tissue infections in 28 (25%) patients, Cardiovascular system in 14 (12.5%) patients, trauma related infections in 12 (10.7%) patients [Table/Fig-1].



[Table/Fig-1]: Causes of sepsis (N=112).
RTI: Respiratory tract infection; UTI: Urinary tract infection; SSTI: Skin and soft tissue infection; CVS: Cardiovascular system

There was a significant preponderance of males (71.4%, n=80) affected more than females (28.6%, n=32). The most common age group affected was between 51 to 60 years (28.5%) [Table/Fig-2]. Microbiological documentation was available in 54 (48.2%) patient records. Majority of infections were caused by Gram-negative organisms (82%). The commonly isolated gram negative organisms were *Klebsiella pneumoniae* (25.9%) and *Escherichia coli* (25.9%), followed by *Acinetobacter baumannii* (18.8%), *Pseudomonas aeruginosa* (11.6%). Among the gram positive bacteria, *Staphylococcus* species was commonly isolated (13.4), followed by *Enterococcus faecium* (4.4%).

Age (years)	Percentage (n=112)
<40	12 (10.7%)
41-50	14 (12.5%)
51-60	32 (28.5%)
61-70	20 (17.9%)
71-80	20 (17.9%)
>80	14 (12.5%)

[Table/Fig-2]: Age wise distribution of samples.

The various laboratory parameters assessed during the study for the total 56 sepsis cases is shown in [Table/Fig-3]. The mean of total number of white blood cells and neutrophils were higher among the group which had culture proven sepsis than the culture negative group. The mean values of basophils were also significantly higher among the culture proven sepsis cases. The CRP mean values of the blood culture positive cases were also on the upper hand. The vital measurements like blood pressure, heart rate, respiratory rate and temperature did not show significant difference.

The values of CRP obtained within 48 hours of admission to the ICU were categorised as shown in [Table/Fig-4]. It was also found that the values of CRP were widespread among the cases of sepsis (1-601 mg/dL). Among them, 75% had CRP elevation above 50 mg/dL while the remaining patients had CRP elevation of <50 mg/dL [Table/Fig-4]. Among the culture proven sepsis cases, CRP was elevated more among cultures that grew gram negative organisms than the gram positive organisms. The highest CRP value of (>600 mg/dL) was observed among culture positive sepsis cases while in culture negative the maximum value of CRP elevation was 397 mg/dL.

The CRP values among the cases were analysed and the ranges of CRP amongst the sepsis cases are tabulated in [Table/Fig-5].

The sensitivity of CRP was 81% and specificity was 49% while the positive predictive value and negative predictive value was 60% and 56%, respectively. The prevalence of sepsis in this study was 56 (50%) [Table/Fig-6].

	Culture positive sepsis (n=27)		Culture negative sepsis (n=26)		Sepsis cases with no culture performed (n=3)	
	Range	Mean	Range	Mean	Range	Mean
CRP (mg/dL)	1-601	144.3	5 -397	134.8	2-271	95.34
Age group (years)	25-85	56.4	24-84	53.5	76-78	77
M:F ratio	19/8		18/8		3/0	
Temperature (°F)	95.1-101.7	98.9	96.4-102	99.23	98.6-101.8	98.8
Systolic BP (mmHg)	70-210	122	84-173	119.23	106-143	119.67
Diastolic BP (mmHg)	40-144	68.96	50-91	66.8	43-78	60.34
Respiratory rate (breath per minute)	8-37	24.9	9-31	23.7	22-30	25.34
Heart rate (beats per minute)	54-118	98.7	60-143	101.23	104-117	111.67
GCS score (out of 15)	6-15	10.5	8-15	10.8	7-12	9.3
Total WBC (cells per cu.mm of blood)	6100-104200	19188.8	4200-38900	12369.23	7300-9100	8266.67
Lymphocytes (cells per cu.mm of blood)	3-37	13.38	3-36	13.1	7-30	17.3
Neutrophils (cells per cu.mm of blood)	54-97	84.2	56-97	77.12	66-92	80
Platelets (cells per cu.mm of blood)	1-5	1.8	1-4	1.31	1-3	2
Monocytes (cells per cu.mm of blood)	1-7	0.5	1-3	0.4	0-1	0.67
Eosinophils (cells per cu.mm of blood)	0	0	0	0	0	0
Basophils (cells per cu.mm of blood)	14-120	45	2-120	29.67	21-26	23.5
ESR (millimeters per hour)	6.3-15.1	11.1	6.7-16.4	10.87	10.8-14.1	12.13
Haemoglobin (grams per decilitre)	19.7-34.7	25.6	18.2-34.6	25.6	25.9-34.1	29.2
MCH (Picograms per cell)	31.3-34.9	30.6	29.1-34.7	29.4	33.5-34.1	33.83
MCHC (grams/dL)	12.4-30.7	15.31	13-28.7	14.45	13.4-18.5	15.47
RDW (%)	9.3-103.1	73.7	60.8-100.8	76.89	77.3-92.6	86.23
MCV (femtolitres)	19.4-45	33.4	4.8-45.6	29.7	32.3-41.5	35.9
PCV (%)	1-601	144.3	5-397	134.8		

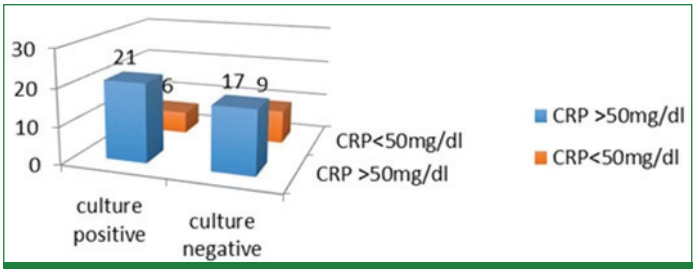
[Table/Fig-3]: Laboratory parameters of sepsis cases.
CRP: C-reactive protein; M:F: Male:female; BP: Blood pressure; GCS: Glasgow coma scale; WBC: White blood cells; ESR: Erythrocyte sedimentation rate; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; RDW: Red cell distribution width; MCV: Mean corpuscular volume; PCV: Packed cell volume

CRP (mg/dL)	Percentage (%)
<50	28 (25)
50-100	22 (19.6)
>100-150	19 (17.0)
>150-200	18 (16)
>200-250	13 (11.6)
>250-300	6 (5.4)
>300	6 (5.4)

[Table/Fig-4]: Values of CRP.

CRP values among	Range	Mean	Median	Standard deviation
Cases of culture proven sepsis	1-601	144.3	101.5	130.67
Cases of culture negative sepsis	5-397	134.8	98	112.15
Cases of culture not performed cases	2-271	95.34	13	124.3
Cases with gram negative organisms	5-601	162.42	115	147.75
Cases with gram positive organisms	1-228	89	95	71.38

[Table/Fig-5]: CRP among various categories of cases.



[Table/Fig-6]: Cultures and CRP levels.

DISCUSSION

Sepsis is considered as one of the major causes of morbidity and mortality in ICUs. In order to avoid unnecessary treatment, development of multidrug resistance organisms, unwanted prolonged hospitalisation and economic burden, mainly in developing countries with poorly-equipped ICUs, an early, sensitive and specific laboratory test would be helpful. Decision-making based on symptoms of infection is often subjective. As such, detecting an infection or sepsis in hospitalised patients remains a challenge, and there is a need for reliable biomarkers for this purpose, the acute phase reactants have been used as biomarkers of bacterial sepsis in adults and children. Biomarkers such as PCT, CRP, and ESR are known indicators of bacterial infection. Amongst them, CRP, which is an acute phase reactant produced by the liver has been used widely in many laboratories in diagnosing the onset of sepsis [13].

In this study, nearly 50% of suspected cases of sepsis had positive qSOFA score. Similar findings was documented in a study done by Shahsavarinia K et al., who documented a 60% positive qSOFA score highlighting the higher sensitivity of qSOFA for patients in ICUs compared to the patients in other wards [14]. An overall male preponderance (71.4%) was noted in this study as evidenced by Chatterjee S et al., and Finfer S et al., in their study [15,16]. In this study, higher qSOFA have been associated with significantly higher quantitative CRP concentrations. Observations identical to this finding were observed with another important biomarker PCT in studies conducted at various places [17,18].

The predominant causes of infection were Respiratory Tract Infection followed by UTI and skin and soft tissue infections similar to findings of study done by Finfer S et al. Also, in this study, Gram negative infections outnumbered the gram positive infections similar to Chatterjee S et al., which is against the finding of Finfer S et al., with gram positive infection 48.3% and gram-negative 38.5% of all infections. *E. coli* and *Klebsiella pneumoniae* were the commonly isolated gram negative organisms while *Staphylococcus aureus* was the predominant gram positive organism as opposed to *Acinetobacter* (21.2%) and Methicillin-resistant *S. aureus* (8.7%), respectively in the findings of Chatterjee S et al., [15,16].

In this study, increase in the level of CRP was observed in the sepsis cases. This finding is supported by Dhananjaya CD and Sunil BN, in their study done among paediatric patients [19]. It was found that the CRP elevation was higher among the culture proven sepsis than among the culture negative cases of sepsis. These findings do not highlight the importance of combining biochemical information from biomarkers and clinical status for diagnosing sepsis. However, the observed increase in CRP levels and other parameters imply that these biomarkers are clinically useful for predicting sepsis, despite their levels being elevated in some patients in the negative blood culture group.

This study demonstrated that septic patients and patients with clinically suspected sepsis had significantly elevated levels of CRP. This was in line with the previous studies [14,20] and this means that this parameter can differentiate healthy individuals from those with proven or suspected sepsis.

It was observed that CRP as a useful parameter to determine if a patient with sepsis even though cultures are negative is in concordance with the findings of study done by Lopez FRE and Jimenez AER [21]. No statistically significant observations in this study were noted which was due to the lesser sample size taken in the study due to the pandemic situation. But there are many studies [22-26] which has considered increased number of samples and has shown statistical correlation.

The findings regarding the accuracy of CRP as a diagnostic tool for sepsis, matched those found by Cheval C et al., who found 93% sensitivity and 40% specificity for CRP [27]. The study performed by Póvoa P et al., has the best diagnostic accuracy for CRP, with values of 98.5% sensitivity and 75% specificity [28]. Most other studies [29-31] have a sensitivity of 70-75% and a specificity of 66-78%. Also, study done in India showed a sensitivity and specificity of 84.3% and 46.15%, respectively [32]. Such differences in observation could be attributed to the accuracy of the diagnostic kits used, aetiology of infections, and various other patient-related factors. Further, always individual responses to sepsis and CRP levels are known to be influenced by genetic variation [33].

As the sensitivity and the specificity of an individual test may not justify their individual use, significant improvement of diagnostic capability when used in various combinations has been studied. An above 80% sensitivity by the combination of any 2 or more positive tests in culture positive sepsis was also reported earlier from Indian studies [26,34]. In a study performed at Udaipur, both CRP and haematological parameters were done for all cases of sepsis, and was found that the sensitivity of the haematological screening parameters and CRP varied from 73.03-92.30% [26].

Hence, qSOFA scoring along with laboratory biomarkers like CRP would be really helpful for physicians with clinical suspicion of sepsis. The other biomarkers when combined for evaluation will certainly prove useful making the commonly performed haematological parameters as important indicators of sepsis along with the biomarkers.

Limitation(s)

Due to the unforeseen pandemic due to COVID-19, the exact number of samples was not collected for the study leading to poor statistical correlation. The study was conducted in adult population in the ICU and hence the epidemiology may be different in paediatric, neonatal, transplant, and oncology ICUs. Other biomarkers of sepsis were not included in this study. Serial measurement of CRP would be a better guide to provide antibiotic therapy.

CONCLUSION(S)

Despite having a small size, this study has highlighted the usefulness of CRP in identifying patients with sepsis in those who present with positive qSOFA score. Also, in resource-limited places, where newer biomarkers such as PCT or ILs are not available, and guidance of an intensivist or a trained sepsis expert is inadequate, CRP could be very useful. Additionally, due to the high sensitivity of CRP it has a lesser risk on missing those who are at a risk of poorer clinical outcome or mortality, so that treatment or referral to a higher centre could begin early. Nevertheless, research on a larger scale is required to define an accurate cut-off value, which may prove to be invaluable in the diagnosis of sepsis.

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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

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