

## The role of C-reactive protein and procalcitonin for early diagnostic accuracy and prognostic significance in sepsis

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### Abstract:

**Objective:** To determine the role of C-reactive protein (CRP) and Procalcitonin (PCT) in early diagnosis and prognosis of sepsis.

**Material and Methods:** A cohort study was conducted on 262 patients who were selected by convenience sampling, having age greater than eighteen years and presented with symptoms of Systemic inflammatory response syndrome (SIRS) or sepsis. Measurement of complete blood count (CBC), serum lactate, CRP, PCT and blood culture of each patient will be performed within the first 24 hours of admission and outcome was evaluated.

**Results:** Out of 262 patients of suspected sepsis, sepsis was diagnosed in 107 (40.8%) patients on the basis of blood culture which was and is the gold standard, whereas sepsis was diagnosed in 141 (53.8%) and 236 (90.1%) patients on the basis of PCT and CRP respectively. Mean PCT and CRP level in suspected sepsis patients was  $11.2 \pm 22.5$  ng/mL and  $163.8 \pm 154.5$  mg/L respectively. The sensitivity & specificity of PCT and CRP in detecting sepsis was: 51.8% and 90.7%, 44.7% and 10.4% respectively. Primary outcome in suspected sepsis patients was step down observed in 3 (1.1%) patients and discharged in 259 (98.9%) patients; whereas overall mortality was reported in 89 (34.0%) patients at day 28 and sepsis diagnosed mortality was reported in 48 (53.9%) patients as secondary outcome.

**Conclusion:** Elevated CRP and PCT levels are promising indicator in early diagnosis and prognosis of sepsis. Sepsis is significantly associated with increased rate of mortality. Blood culture is gold standard in detection of early sepsis followed by CRP and PCT.

**Keywords:** C-reactive protein, Procalcitonin, Diagnosis, Prognosis, Sepsis, Septic shock.

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### Introduction:

Sepsis is a serious illness with high rates of morbidity and significant death rate.<sup>1</sup> The diagnostic accuracy of sepsis is therefore important to avail a better prognosis and to decrease healthcare cost.<sup>2</sup> Early diagnosis and management of the patient has shown to be beneficial with respect to outcome of disease.<sup>3</sup> Therefore, identification of a laboratory parameter that should accurately

differentiate non-infectious SIRS from sepsis has now become a significant issue.<sup>4</sup>

Studies are being done to find out the role of biomarkers to diagnose sepsis such as lipopolysaccharide-binding protein (LBP), interleukins (IL), provasopressin, procalcitonin (PCT), C-reactive protein (CRP) and Triggering receptors expressed on myeloid cells-1 (TREM-1).<sup>5,6</sup> The

Table 1: Gender distribution, primary and secondary outcome in suspected sepsis patients

	Frequency	Percentage
Gender		
Male	151	57.60%
Female	111	42.40%
Total	262	100.00%
Primary Outcome		
Step down	3	1.10%
Discharge	259	98.90%
Total	262	100.00%
Secondary Outcome		
Death	89	34.00%
Alive	173	66.00%
Total	262	100.00%

guidelines mentioned under “Surviving Sepsis Campaign” recommend using procalcitonin levels for prescribing antibiotics and its duration in sepsis, however evidence does not seem significant.<sup>7,8</sup> Procalcitonin level demonstrated a very close relationship to septic shock, positive blood culture and altered mental status.<sup>9</sup> CRP and PCT are currently being used as the preferred biomarkers of sepsis.<sup>10,11</sup>

Cytokines cause the release of PCT from C-cells thyroid gland in sepsis and hypercalcemia. Likewise, liver secretes CRP in response to IL-6, an acute phase protein. IL-6 is used as diagnostic and prognostic marker of inflammation secondary to infection, as in sepsis its level increases markedly in acute phase.<sup>12,13</sup> In well managed sepsis, the decrease in the levels of markers like CRP and PCT is helpful in anticipating the response of treatment and the prognosis of the disease.<sup>14,15</sup>

Very few researchers have investigated the role of PCT in effective diagnosis of sepsis in comparison to CRP.<sup>16-20</sup> We have thus directed our current study in analyzing the accuracy of PCT and CRP and also comparing their sensitivity and specificity in diagnosis of sepsis and septic shock.

### Material and Methods:

A cohort study was performed at department of emergency medicine of Ziauddin University Hospital Karachi from 1<sup>st</sup> January 2021 to 30<sup>th</sup> June 2021. After getting approval from Ethical Review Committee, Ziauddin University Karachi, Reference Code: 3130121ASEM.

Convenience sampling (Non-probability) technique was used for selection of 262-patients. Patients who presented with symptoms of sepsis and septic shock in emergency department were included. Systemic Inflammatory Response Syndrome (SIRS) has Four criteria were defined, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36 °C), and leukocytosis, leukopenia, or Bandemia (white blood cells >1,200/mm<sup>3</sup>, <4,000/mm<sup>3</sup> or bandemia ≥10%). Patients who met two or more of these criteria fulfilled the definition of SIRS.

Patients who have not had PCT and CRP levels done in the first 24-hours of admission and patients already on antibiotics, patients who have undergone surgery, history of trauma and autoimmune disease were excluded. Data was obtained through hospital Electronic Medical Record (EMR) system, in an attached proforma. Informed consent for the study was either obtained from patient or their next kin after explaining the purpose of study. Patient who fulfills the inclusion criteria were included in the study.

Measurement of CBC (complete blood count), serum lactate, CRP and PCT and other relevant investigations i.e. blood culture were performed at the time of admission within the first 24 hours of admission. The primary outcome was considered as shifting to a step down unit or to the ward and a secondary outcome was prolonged stay in the ICU and/or death of the patient. To assess the prognostic value of PCT levels the final clinical outcome would be recorded after four weeks through communication with the patient.

Statistical analysis: Data entry was done on ex-

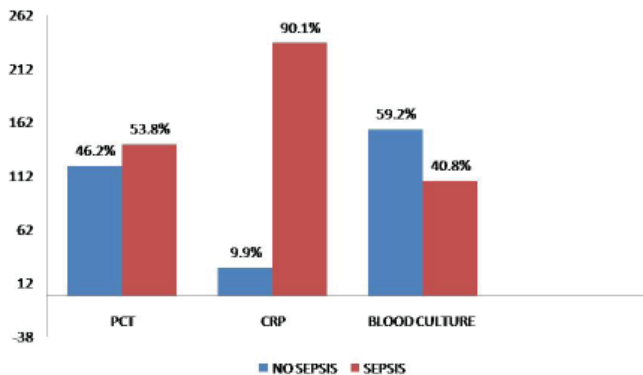


Figure1: Sepsis diagnosis on CRP, PCT and blood culture in suspected sepsis patients

Table 2: Sensitivity (Sn), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Diagnostic Accuracy (DA) of PCT and CRP in Suspected Sepsis Patients

Variable	PCT	CRP
Sn	51.8%	90.7%
Sp	44.7%	10.4%
PPV	40.4%	41.5%
NPV	56.2%	61.5%
DA	47.7%	43.5%

Table 3: Diagnosis of sepsis on CRP and PCT with outcome in suspected sepsis patients

	PCT With Outcome				CRP With Outcome			
	Death (%)		Alive (%)		Death (%)		Alive (%)	
Yes	47	52.80%	94	54.30%	86	96.60%	150	86.70%
No	42	47.20%	79	45.70%	3	3.40%	23	13.30%
Total	89	100.00%	173	100.00%	89	100.00%	173	100.00%
	*p Value		0.814		p Value		0.011	

cel; data was analyzed with SPSS (Statistical Package for Social Science) version 21.0. Analysis was done in 2 steps. In the 1<sup>st</sup> step variables were described. Categorical data was described through frequency and percentages and numeric data was described through mean and standard deviation. Chi-square test is applied to find out the significance difference between the groups.

The risk of death was calculated through stratification with p value < 0.05 was considered as significant.

**Results:**

262 suspected patients of sepsis were enrolled and evaluated for confirmation of sepsis by using CRP, PCT and gold standard culture. Out of 262 patient 151(57.6%) were male and 111(42.4%) were female as shown in table 1. The mean age of patients was 61.3±16.8.

Sepsis was diagnosed in 141(53.8%) suspected sepsis patients and not diagnosed in 121(46.2%) suspected sepsis patients on the basis of PCT level and the mean PCT level was 11.2±22.5 (0.04-100) ng/mL. Sepsis was diagnosed in 236(90.1%) suspected sepsis patients and not diagnosed in 26(9.9%) suspected sepsis patients on the basis of CRP level and the mean CRP level was 163.8±154.5 (0.99-569.26) mg/L as shown in figure 1.

Sepsis was diagnosed in 107 (40.8%) patients and not diagnosed in 155 (59.2%) patients on the basis of gold standard culture. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) of PCT and CRP in detecting sepsis was: 51.8% and 90.7%, 44.7% and 10.4%. 40.4% and 41.5%, 56.2% and 61.5% and 47.7% and 43.5% respectively as shown in table-3

Mean of hospital stay of suspected sepsis patients was as follows: ICU stay 4.5±3.1 (1-21) days and primary outcome stay 5.4±4.2 (1-28) days. Primary outcome in suspected sepsis patients was step down observed in 3(1.1%) patients and discharged in 259(98.9%) patients. Secondary outcome at 28 day in suspected sepsis patients was death observed in 89(34.0%) patients and alive in 173(66.0%) patients as shown in table 1.

Patients were distributed according to secondary outcome and their PCT and CRP level. Death was observed in 47(52.8%) diagnosed patients of sepsis on the basis of PCT level with p-

value=0.814 and 86(96.6%) diagnosed patients of sepsis on the basis of CRP level as shown in table-4 with significant p-value=0.011\*.

#### **Discussion:**

Sepsis is one of the notorious life-threatening infectious disorders, significantly associated with increased rate of morbidity and mortality. Sepsis is also significantly associated with increased intensive care unit admissions and this puts an extra burden on health care system, health care workers and patients.<sup>21,23</sup>

**Microbiological cultures:** Early diagnosis of sepsis and its prognosis is very crucial for appropriate management and can help in decreasing the high risk of mortality. Clinicians are aware of the fact that confirmation of sepsis necessitates the identification of the offending pathogen(s) that would lead to initiation of appropriate antibiotics. Considering the run-of-the-mill microbiological analysis which include blood cultures, single colony growth assays and other biochemical analyses, we are aware that these conventional tests would consume at least 72 hours or more before adequate results come forth.<sup>24,25</sup>

Hence in a race against time inadequate or inappropriate treatment is initiated in such sepsis patients (20-25% of them) resulting in a five-fold reduction in survival. Not only longer periods of time are needed to identify the pathogen(s), at times no pathogen is identified at all and this may require further sensitive testing.<sup>24,25</sup>

In sepsis majority of the causative organisms are bacteria (90%), with gram positive organisms being more common than gram negative ones. MRSA (Methicillin resistant Staph. Aureus), notoriously known as the drug resistant bacteria are becoming more clinically relevant as they increase hospital costs, require isolation and increase mortality. Fungal infections too account for a high mortality and amount to 10% of the cases of sepsis. The unfortunate dilemma is that blood cultures are able to detect only 20-40% of bacterial and fungal agents in patients with severe sepsis.<sup>24,25</sup>

With these disadvantages in the forefront the need for new technologies becomes more pertinent, such that rapid, sensitive and accurate detection of causative organisms in the blood stream of septic patients can be made. For academic purposes it may be mentioned that Nucleic acid testing (NAT) has actually revolutionized the diagnosis of several infectious agents in sepsis.<sup>24,25</sup>

Multiplex technologies are now being used for the large and diverse spectrum of bacterial and fungal pathogens in patients with sepsis. These multiplex technologies are particularly suited for two clinical applications: to improve the diagnosis from positive blood cultures and to identify the causative microorganisms directly from patient's blood samples at the time of phlebotomy.

In our setup at Ziauddin Hospital obviously these tests were not possible due to non-availability and for costs; hence more emphasis was placed on CRP and PCT in the early diagnosis and prognosis of sepsis as these tests are simple, inexpensive and less time consuming.

The current study, therefore, has been conducted on role of CRP and PCT in early diagnosis and prognosis of sepsis by selecting suspected sepsis patients from emergency department of Ziauddin University Hospital, North Campus Karachi. CRP and PCT has been considered as more accurate than other available markers, so results will be helpful in finding their significance in early diagnosis and disease prognosis in sepsis.

In the current study, out of 262 suspected patients of sepsis, majority of the patients were males [n=151 (57.6%)] and 111(42.4%) patients were females with mean age of 61.3±16.8 (20-90) years. Similar Pakistani study by Ahmed S, et al. also reported the 60% male predominance with median age of 48 years.<sup>19</sup>

In our study, sepsis was diagnosed in 107(40.8%) patients on the basis of gold standard i.e., microbial culture. Coagulase Negative Staphylococci was most the commonly isolated microorgan-

ism in 40(37.4%) diagnosed cases of sepsis, followed by *Escherichia coli* 16(15.0%), *Acinetobacter* species 19(17.8%) and *Streptococci* 10(9.3%).<sup>19</sup>

Ahmed S, et al. reported the sepsis diagnosis in 62.1% patients on the basis of microbial culture. Staphylococcal infections most commonly isolated microorganisms in 34.3% diagnosed cases of sepsis followed by *E. coli* 32.8%, *Acinetobacter* species 14.0% and *streptococcus* species 9.3%.<sup>19</sup>

Microbial culture is gold standard and helps in accurately diagnosing sepsis. Staphylococci species are commonly responsible for sepsis followed by *Escherichia coli*, *Acinetobacter* species and *Streptococci*.

In our study, sensitivity, specificity, PPV, NPV and diagnostic accuracy of PCT and CRP in detecting sepsis was: 51.8% and 90.7%, 44.7% and 10.4%. 40.4% and 41.5%, 56.2% and 61.5% and 47.7% and 43.5% respectively. Ahmed S, et al. reported the higher sensitivity 93.75% and lower specificity 43.59%, NPV 80.95% and PPV 73% of PCT in diagnosis of sepsis.<sup>19</sup>

In our study, the primary outcome in suspected sepsis patients was step down observed in 3(1.1%) patients and discharged in 259(98.9%) patients; whereas overall mortality was reported in 89(34.0%) patients at day 28 and sepsis diagnosed mortality was reported in 48(53.9%) patients as secondary outcome. Rate of mortality associated with sepsis patients was high.

Mortality was significantly high in male patients [n=61 (68.5%)] with p-value of 0.010\*, in age group of 71-80 years 30(33.7%) patients with p-value of <0.001\*, in CRP diagnosed sepsis patients 86(96.6%) with p-value of 0.011\* and in culture diagnosed sepsis patients 48(53.9%) with p-value of 0.002\*, whereas non-significantly associated with PCT diagnosed sepsis patients 47(52.8%) with p-value of 0.814. Asghar A, et al. also reported the overall mortality in 32.31% patients and sepsis diagnosed mortality in 51.15% patients.

As this is a single centre study performed over limited number of patients, done for shorter duration of time. Further studies are required to be done in order to find out more significant association on larger scale.

#### **Conclusion:**

Elevated CRP and PCT levels are promising indicators in early diagnosis and prognosis of sepsis. Sepsis is significantly associated with increased rate of mortality. Blood culture is gold standard in detection of early sepsis followed by CRP and PCT.

Staphylococci species are commonly responsible for sepsis followed by *Escherichia coli*, *Acinetobacter* species and *Streptococci*. Rate of mortality in sepsis is significantly associated with: Male gender, Age, Culture and CRP (diagnosed sepsis patients).

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#### **Role and contribution of authors:**

Abdul Sami Qureshi, conceived, concept design and definition of intellectual content, literature search, data acquisition.

Shua Nasir, did literature search and manuscript preparation did final layout and data entry.

M.Z. Jilani, did write up, manuscript preparation, final layout.

Inayat Ali Khan, data entry and final layout.

Erum Soomro, literature search and data entry.

Nida Shahid, collected the references and also helped in material and methods writing.

Sadiqa Ali, data entry and final layout.

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