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Corresponding Author

K. Kiran,
S/O Shashidhar, Mastry Compound,
Kodangallu, Moodbidri, Dakshina
Kannada-574197, India.
kirankmuyyam6728@gmail.com

Author Designation

¹Assistant Professor
^{2,3}Consultant Physician
^{4,5}Senior Resident

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A Study to Assess Diagnostic Accuracy of Procalcitonin in Differentiating Gram Negative from Gram Positive Blood Stream Infections in Critically ill Patients Admitted to ICU

¹K. Kiran, ²Ahemer Siddiqui, ³K.S. Supritha, ⁴Mahesh koulagi and ⁵Akshay Biskop

¹Department of General Medicine, Kunhitharuvai Memorial Charitable Trust Medical College, Mukkam Kozhikode, India

²Department of General Medicine, CHC Kembavi Yadgiri, India

^{3,5}Department of General Medicine, S.S. Institute of Medical Sciences and Research Centre, Davangere, India

⁴Department of General Medicine Shri B.M. Patil Medical College and Research Centre, Vijayapura, India

ABSTRACT

Serum procalcitonin (PCT) levels differ in patients with bacterial infections and are significantly elevated in patients with Gram-negative bacteremia. In this study we aimed evaluation of diagnostic accuracy of inflammatory markers (PCT and CRP) to establish sepsis caused by different pathogens. Present study was aimed to determine the efficacy and accuracy of procalcitonin to differentiate Gram-negative bacteria from Gram-positive bacteria in blood stream infections. 100 Cases for study group were selected from patients admitted to medical wards. Patients included in the study group were subjected to thorough clinical evaluation in terms of history, clinical examination and relevant investigations so as to assess the causes of the bloodstream infections. The clinical profile of 100 patients with sepsis was studied. Study group included 60 male and 40 female patients. The mean procalcitonin was 0.8 and 6.1 ng/dl in gram positive and gram negative bacteria respectively ($P < 0.001$). ROC analysis revealed an optimal cut-off value of 2.3 ng/mL for PCT in discriminating Gram-negative from Gram-positive sepsis. Serum PCT levels were higher in patients with Gram-negative sepsis than in Gram-positive sepsis. PCT is a sensitive biomarker that can be used to distinguish Gram-negative from Gram-positive sepsis.

INTRODUCTION

Sepsis is a clinical syndrome that has physiological, biological and biochemical abnormalities caused by a dysregulated host response to infection and in most of the cases cause unknown^[1]. The defense mechanisms are complex and respond in different ways to various invasive pathogenic organisms. One of the earliest responses to a microbial infection is the development of the inflammatory response that happens through a number of biochemical messengers^[2]. Increased microbial load is associated with increased mortality^[3]. The severity is determined by the number of the microbes which is referred to the microbial load and also if there are more than one type of microorganism, then severity proportionately increases leading to increased morbidity and mortality^[3-6]. "Bloodstream infection is defined by positive blood cultures in a patient with systemic signs of infection and may be either secondary to a documented source or primary-that is, without identified origin". The source of infections is very important to note as they may dictate the severity of the illness, the morbidity, pharmacological protocol, management decisions, prognosis, outcome and mortality. Early recognition and treatment of sepsis will help in reducing the morbidity and mortality. This mandates the presence of serum biomarkers like Procalcitonin that may help in early diagnosis and management. Procalcitonin is a hormone which is a propeptide and is the pro hormone of calcitonin^[7]. Present study was aimed to assess diagnostic accuracy of procalcitonin in differentiating gram negative from gram positive blood stream infections in critically ill patients admitted to ICU.

MATERIALS AND METHODS

Present study was Single centered randomized prospective observational study, conducted in department of General Medicine, Karnataka Institute of Medical Sciences, Hubballi, India. Study duration was of 2 years (December 2020-December 2022). Study was approved by institutional ethical committee.

Inclusion Criteria:

- Patients with <18 years of age of either sex with diagnosis of sepsis (Acute organ dysfunction as of SOFA score by 2 or more points from baseline. OR Suspected infection), willing to participate in present study.

Exclusion Criteria:

- History of immune disorder or taking immuno suppressive therapy.
- History of acute pancreatitis.
- History of major burns or severe trauma.
- History of chronic kidney disease.

Patients admitted to MICU and Medical Wards of KIMS Hubli hospital with various medical condition fulfilling the inclusion/exclusion criteria were included into the study after obtaining written informed consent. A pre-structured Performa was used to collect relevant information (patient data, clinical findings laboratory investigations) from all the selected patients. Collected data subjected to relevant statistical analysis and observation. Informed consent was obtained, and subjected to detailed clinical history and through clinical examination. Blood pressure and GCS measurements in both treated and untreated subjects. The following investigations are done in all patients such as complete hemogram, ESR, RFT, serum electrolytes, blood culture and sensitivity, liver function test, ABG analysis, HIV, HBsAg, ECG, 2D Echo, Chest X-ray, urine routine and microscopy, urine culture sensitivity, Sputum culture sensitivity, Imaging studies including USG abdomen, CT abdomen (if needed). Observations made and conclusion drawn. Then the association between serum procalcitonin as a biomarker and culture positive blood stream infections was assessed. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. $P > 0.5$ was considered as statistically significant.

RESULTS AND DISCUSSIONS

Among the study group, 60 subjects were males and 40 subjects were females. Study group included 57 subjects whose age was above 50 years. As the age advances the patient population increased. Among the study group diabetes mellitus (68%) is the most common comorbidity followed by hypertension (59%) and coronary artery disease.

Table 1: General Characteristics

Characteristics	No. of subjects	Percentage
Age groups (Years)		
20-29	12	12.0
30-39	14	14.0
40-49	17	17.0
>50	57	57.0
Gender		
Male	60	60.0
Female	40	40.0
Co-morbidities		
Diabetes mellitus	68	68.0
Hypertension	59	59.0

Among subjects most of the cases had respiratory complaints followed by urinary system.

Table 2: System wise Distribution of Cases

System	Number	Percentage
Respiratory system	44	44.0
Urinary system	33	33.0
Digestive system	3	3.0
Soft tissue	20	20.0

44 subjects presented with history of breathlessness, cough. In the study population, Myalgia was the most common presenting complaints followed by fever and cough. Among study population, 27% showed bilateral heterogenous X-ray findings, 9% showed homogenous opacity and 63% normal X-ray findings.

Table 3: Symptoms and X-ray Findings Among Study Population

Symptoms and X-ray findings	Number of subjects	Percentage (%)
Symptoms		
fever	54	54
Cough	23	23
Breathlessness	26	26
myalgia	60	60
Loose stools	18	18
Burning micturition	16	16
X-ray findings		
Bilateral heterogeneous opacity	27	27
Homogenous opacity	9	9
Bilateral hyperinflation, flattened diaphragm	1	1

Among the subjects 42 were showed gram positive culture results and 58 showed gram negative culture results.

Table 4: Gram positive and gram negative culture positive results

Culture results	Number	Percentage
Gram positive	42	42.0
Gram negative	58	58.0

Mean duration of hospital stay among gram positive and gram negative group were 11.1 and 12.6 days respectively.

Table 5: Comparison of Hospital Stay and Culture Results

Culture results	Number	Mean	SD	P value
Gram positive	42	11.1	2.7	<0.001
Gram negative	58	12.6	2.2	
Independent t-test				
P value-significant				

Mean procalcitonin among gram negative group was 6.1, which is significantly higher among gram negative group compared to gram positive group.

Table 6: Descriptive Statistics-Blood-Investigations Parameters-Gram negative Group

Gram negative	Mean	SD	Median	Minimum	Maximum
Procalcitonin	6.1	4.1	4.3	2.3	16.8
C-reactive protein	117	68.2	106	2.9	286
Total count	16439.7	4450.6	16000	10000	28000
Platelet count	1.3	0.4	1.2	0.5	2.1
Total bilirubin	1.7	0.8	1.5	1	5.4
Direct bilirubin	0.8	0.3	0.7	0.3	1.5
Blood urea	38.3	10.7	40	11	56
Creatinine	1.2	0.3	1.3	0.4	2.1
Sofa scores	7	1.9	7	3	12

Mean procalcitonin was 0.8 among gram positive group, which is low compared to gram negative group.

Mean total count and CRP were higher in gram negative group compared to gram positive group.

Table 7: Blood-Investigations Parameters-Gram Positive Group

Gram Positive	Mean	SD	Median	Minimum	Maximum
Procalcitonin	0.8	0.3	0.7	0.4	1.1
C-reactive protein	39.3	13.6	40	12	56
Total count	8545.2	1610.4	9000	4000	10000
Platelet count	1.4	0.4	1.3	0.5	2.7
Total bilirubin	1.7	0.6	1.4	1.1	3.5
Direct bilirubin	0.8	0.3	0.7	0.4	1.3
Blood urea	37.5	10.1	40	12	52
Creatinine	1.2	0.3	1.2	0.3	1.8
Sofa scores	7.5	1.9	7.5	3	12

Mean SOFA score was gram positive and gram negative 4.0 and 7.5 group respectively.

Table 8: Comparison of Sofa Scores

Culture results	Number	Mean	SD	P-value
Gram positive	42	4.0	1.9	<0.001
Gram negative	58	7.5	1.9	
Independent t-test	P value- significant			

Mean procalcitonin in gram negative and gram positive group were 6.1 ng/ml and 0.8ng/ml respectively. Procalcitonin level was significantly higher in gram negative group compared to gram positive group.

Table 9: Comparison of Procalcitonin in Gram Positive and Gram Negative Group

Culture results	Number	Mean	SD	P value
Gram positive	42	0.8	0.3	<0.001
Gram negative	58	6.1	4.1	
Independent t-test	P value-significant			

Cut off value for procalcitonin for differentiating gram negative from gram positive sepsis was 2.3 ng/dl

Table 10: Diagnostic Accuracy of Procalcitonin Compared Against Culture Results

Procalcitonin	Culture results		
	Gram negative	Gram positive	Total
Up-2.3	0	42	42
>2.3	58	0	58

Our study showed sensitivity and specificity of 96% and 84% respectively.

Table 11: Sensitivity and Specificity of Study Results

	Point estimate	95% CI
Sensitivity	96.0	93.8-100
Specificity	84.0	91.6-100
Positive predictive value (PPV)	93	93.8-100
Negative predictive value (NPV)	87	91.6-100

The present work intends to study: The efficacy of procalcitonin in differentiating gram negative from gram positive blood stream infections, in critically ill patients. The Mean age of the patients of our study group was 50±11.321 which was comparable with various similar studies conducted by Jian Chang^[8] (53±10.8 years) and other authors. In a study conducted by Shunyuan Guo^[9] mean age of the patients was 64±18.6 years, where patients with

trauma and sepsis were also included. In a study by Christian Leli^[10] it was 57.4±13.4 years and Jinquan Wang^[11] it was 55.5±6.2 years as depicted in Table No1. Our study was conducted during covid pandemic where more younger patients were admitted who were included in our study as compared to other studies done during non-pandemic conditions. In our study, there were 60% male and 40% female patients which was comparable with several other studies In a study conducted by Shunyuan Guo^[9] (male and female were 73% and 26% respectively) and Christian Leli^[10] (male and female were 42% and 57% respectively). In a study by conducted by Jinquan wang^[11] there were 78 (52.18%) male and 72 (48.81%) female patients, where sepsis secondary to trauma were also included. In a study by Jian Chang^[8] which was conducted only on septic shock patients 26 (52.18%) were male and 24 (48%) were females. In our study majority of them had diabetes as most common comorbidity followed by hypertension and ischemic heart disease respectively. In a study conducted by Shunyuan Guo^[9] (China) majority of them had diabetes as most common comorbidity followed by hypertension and ischemic heart disease respectively. In a study conducted by Christian Leli^[10] (Italy) 64% had hypertension as most common comorbidity followed by diabetes (32%) and ischemic heart disease (31%). In a study conducted by Jian Chang^[8] 56% had hypertension as most common comorbidity followed by diabetes (28%) and ischemic heart disease (28%). All the patients of study group were subjected to basic investigations including culture sensitivity. Based on the culture reports study group was divided into Gram Positive (n=42) and Gram Negative Group (n=58) which were comparable with Shunyuan^[9] whose study group included 53.18% patients with Gram Negative and 46.8% patients with Gram Positive Infections. Christian^[10] showed 52% gram negative and 48% gram positive culture results. Among Basic investigations, total counts and CRP levels were found to be higher in gram negative group than gram positive group. In our study mean total count, C reactive protein and platelet count were 8,545, 39.3, 1.4 (lakh) respectively which were comparable to other studies conducted by Shunyuan Guo^[9] (mean total count, c-reactive protein and platelet counts were 6,500, 26.2 and 1.5 (lakh) respectively) and by Christian Leli^[10] (mean total count, c reactive protein and platelet count were 6500, 28.3 and 1.4 lakh respectively). In our study mean total count, C reactive protein and platelet count were 16,439, 117, 1.1 (lakh) respectively which were comparable with other studies conducted by Shunyuan Guo^[9] (mean total count, c-reactive protein and platelet counts were 17,000, 126 and 0.99 (lakh) respectively) by Christian Leli^[10] (mean total count, c reactive protein and platelet count were 15600, 121 and 1.2 lakh respectively) by

Jian Chang^[8] (mean total count, c reactive protein and platelet counts were 16,600, 118 and 1.1 (lakh) respectively). Mean duration of hospital stay in our study was 11.1 and 12.6 among gram positive and gram negative group respectively, comparable with Shunyuan Guo^[8] 8 and 11.4 days, Christian Leli^[10] 10 and 13 days, Jian Chang^[8] 9 and 11.3 among gram positive and gram negative group respectively. In our study mean procalcitonin level in gram negative and gram positive group were 6.1ng/ml and 0.8ng/ml respectively which were comparable with other studies. Jian Chang^[8] mean PCT levels were 6.51ng/ml and 1.2ng/ml in gram negative and gram positive group respectively. In Shunyuan Guo^[9] mean PCT levels were 6.7ng/ml and 0.84 ng/ml in Gram Negative and Gram Positive group respectively. In Christian Leli^[10] showed mean procalcitonin were 6.8 in gram negative group and 0.9 in gram positive respectively. In our study receptor operating characteristic analysis showed an area under the curve for procalcitonin of 1 in discriminating gram negatives from gram positive infections which was comparable with other studies. Shunyuan^[9] (area under curve for procalcitonin was 1), Christian Leli^[10] (showed area under curve for procalcitonin was 0.965) Jian Chang^[8] (showed area under curve for procalcitonin was 0.99) in discriminating gram negative from gram positive blood stream infections. In our study, receptor operating characteristic analysis showed PCT cut off value of >2.3ng/ml to distinguish gram negative sepsis from gram positive sepsis. It yielded a sensitivity and specificity of 96% and 84% and PPV and NPV of 93% and 87% respectively. Shunyuan Guo et al.,⁹ showed PCT cut off value of 2.89 ng/ml and resulted in 90% sensitivity and 88% specificity which had largest study population among all studies. Jian Chang^[8] showed PCT cut off value of 2.44ng/ml and resulted in 92.5% sensitivity and 85.5% specificity in distinguishing gram negative from gram positive sepsis. Christian Leli^[10] showed PCT cut off value of 2.6 ng/ml and resulted in 91% sensitivity and 83% specificity.

Table 12: Comparison Sensitivity and Specificity Results of our Study with other Studies

Study	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Shunyuan et al ^[9]	90%	81%	88%	91%
Christian Leli et al ^[10]	91%	83%	84%	86%
Jian Chang et al ^[8]	92.5%	85.5%	92.1%	84.2%
Present study	96%	84%	93%	87%

These observations suggests that level of procalcitonin is significantly different between two groups, hence it can be used as noninvasive tool to differentiate gram negative and gram positive sepsis. Although, blood culture remains the gold standard to differentiate gram negative and gram positive and to establish the type of organism but it takes longer time to establish it, hence procalcitonin level may be used to differentiate between gram positive and gram negative sepsis.

However, Multicentric larger trials are required to establish the facts. Limitations of present study were single centered study. Study population was small. Diagnostic performance of procalcitonin was compared with blood culture results and didn't use other identification methods such as real time polymerase chain reaction.

CONCLUSION

In our study gram negative sepsis more common than gram positive sepsis. Inflammatory marker CRP level was significantly higher in gram negative group compared to gram positive group. Procalcitonin level significantly higher in gram negative group and our study results showed sensitivity and specificity of 96% and 84% respectively.

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