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Procalcitonin as a Sepsis Marker in Patients of Critical Care Unit

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Abstract

Introduction: The aim of this study was to observe the diagnostic role of procalcitonin to evaluate sepsis and assess the level of inflammation for the patients of Critical Care Unit of different departments.

Methods: This cross sectional, prospective and observational study was conducted at Armed Forces Institute of Pathology on the patients at Critical Care Unit of Paediatric, Surgery, Gynae and Medicine department in a tertiary care hospital (Combined Military Hospital, Dhaka) from June, 2020 to May, 2021. Total 106 patients were enrolled in this study. As the study was conducted during corona pandemic, RT-PCR test for Corona virus disease 2019 (COVID-19) along with serum procalcitonin and bacterial culture and sensitivity tests for different samples were prescribed for all 106 patients.

Result: Out of 106 patients, 30.2% (32) patients were found positive and 69.69% (74) were found negative for COVID-19 and 14.15% (15) patients had clinical documentation of bacterial co-infection, confirmed by blood, respiratory, or urine culture. After PCT test, 20.75 % (22) samples were found with severe sepsis or septic shock, 7.54% (08) samples were found with systemic infection, 18.06% (20) samples were with possible systemic infection, 31.13 % (33) samples were with local infections and 21.69% (23) were found within normal ranges of PCT.

Conclusion: This study supports the importance of the diagnostic role of PCT to assess the level of sepsis as well as presence of co-infection which suggests that PCT level is a good biomarker for early diagnosis, assessment and treatment of patients in CCU.

Key words*: procalcitonin; biological marker; sepsis; septic shock; intensive care unit*

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Introduction:

Procalcitonin (PCT) is a serum biomarker that helps distinguish bacterial infection from other causes of infection as well as, can serve as a helpful adjunct for guiding antibiotic therapy and resolving diagnostic uncertainty of patients in Critical Care Unit (CCU)[1]. In CCU common conditions that are treated include acute respiratory distress syndrome, septic shock, and other life-threatening conditions. The patients of Corona virus disease 2019 (COVID-19) caused by the SARS-CoV-2 with severe conditions are treated in CCU too[2]. They may present with cough, fever, headaches, myalgia, hemoptysis, diarrhea and infectious pneumonia which is the hallmark of severe disease. The consequences may include acute respiratory distress syndrome (ARDS), abrupt heart damage and secondary bacterial infection[3]. PCT is a potentially biomarker could therefore prove to be helpful in these cases. During inflammation, procalcitonin (PCT) is produced mainly by two alternative mechanisms; direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolite from microbes and indirect pathway induced by various inflammatory mediators like interleukins 1, 6 (IL-1, IL-6), tumour necrosis factor-α (TNF-α), etc[1,4]. But in COVID-19 patients, viral-induced hyper-inflammation is strongly linked to disease severity. A cytokine storm sometimes ensues, altering the immune system, which releases significantly higher levels of pro-inflammatory cytokines and chemokines, like IL-1α, 2, 6, 7, 8, 10 and 15, TNF-α

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and many more. Nevertheless, the synthesis of this biomarker is inhibited by interferon (INF)-ã, whose concentration increases during viral infections. As a result of an erroneous immune response, critical and severe cases are characterized by sepsis and multiple organ failure[5].

The serum PCT level rises rapidly and returns to normal range faster than other biomarkers if the patient responds appropriately to the treatment which makes it a better biomarker for sepsis[6]. Recently, it was shown that PCT guidance of antibiotic therapy reduced antibiotic consumption by almost 50% in patients suspected of having either a community-acquired pneumonia or an exacerbation of chronic obstructive pulmonary disease[7]. So PCT plays as a prognostic tool for bacterial infection and severity in patients to ensure further therapeutic measures and antibiotic guideline which should be appropriately applied. An algorithm based in serial measurement of PCT (chart-I) assist early diagnosis and differentiate the severity. The therapeutic decisions in patients were taken according to the level of serum PCT[8].

This biomarker is now widely used in Europe and recently it was approved by the FDA in USA for the diagnosis and monitoring of sepsis and evaluation of the systemic inflammatory response in the clinical arena[8]. This study here, we demonstrated that elevated PCT is an early independent predictor of development of septic shock in patients with sepsis induced by bacterial or viral infection caused by COVID-19, which added value to the clinical decision process, i.e. assist in diagnosis, assess prognosis, and assist in treatment selection and monitoring.

Material and Methods:

This observational, comparative and prospective study was carried out in Armed Forces Institute of Pathology amongst the patients, who were admitted at Critical Care Unit (CCU) of Paediatric, Surgery, Gynae and Medicine department in a tertiary care hospital (Combined Military Hospital, Dhaka Cantonment) from June, 2020 to May, 2021. Total 106 patients were enrolled in this study.

As the study was conducted during corona pandemic RT-PCR tests for Covid-19 along with serum procalcitonin, and microbiological tests were prescribed to assess the level of sepsis. After collecting the sample in proper aseptic procedure, serum procalcitonin was done at Biochemistry Department and RT-PCR test and blood for C/S (culture and sensitivity) were done at Microbiology Department in AFIP. Other samples like urine, tip of the catheter, bronchial wash, and tracheal aspirates were cultured in some patients to diagnose the local infection that ought to correlate with the findings of PCT. Though inflammation due to any viral disease may increase PCT level, but only COVID-19 patients are documented in this study.

We also screened references from the relevant literature including all identiûed studies. We avoided duplication of data, examining for each publication authors and medical centers.

Chart-I, PCT algorithm for detection of sepsis and initial antibiotic therapy

PCT level (ng/mL)	Level of sepsis	Recommendation for Antibiotic treatment.
PCT- d”0.05	Healthy individuals.	Not recommended.
PCT- 0.05-.5	Local bacterial infection.	Recommended for local infection.
PCT- 0.5-2	Systemic infection is possible; Re-assess within 6-24 hours.	Recommended.
PCT- >2	Systemic infection (sepsis).	Strongly recommended.
PCT- >10 ng/ mL	Severe sepsis or septic shock.	Strongly recommended.

Results:

Procalcitonin serum level was obtained for patients suspected of developing infection either on admission or during intensive care unit stay. Among 106 admitted patients in ICU, majority of them were male, that is 65% (69) and female were 35% (37), thereby, ratio is 1.86:1, (Figure-1).

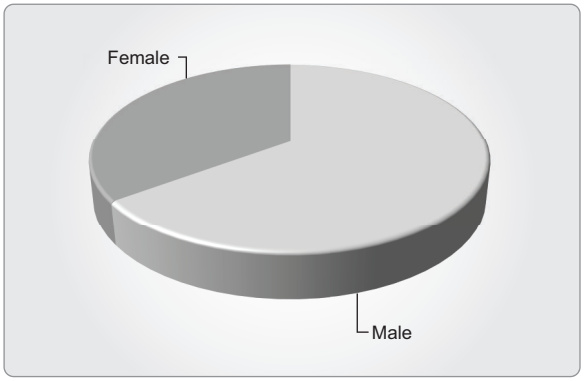

Fig.-1: *Distribution according to gender among total 106 patients*

In Table-I, it is shown that among 106 cases, RT-PCR for COVID-19 is shown where 30.31% (32) patients were positive and 69.69% (74) were negative for COVID-19 in ICU.

Table-I

RT-PCR positive cases among critical patients (N=106)

Total patients in ICU	COVID-19 positive (%)	COVID-19 negative (%)
106	32(30.2%)	74(69.8%)

In Table-II, 106 cases were divided into six groups according to age of fifteen years differences and majority i.e. 33.01% (35) patients were from Group-4 (51-65 years) while least patients were seen in Group-6 that is 4.71% (05).

Main characteristics are presented in Table III, where frequencies of PCT are shown amongst 106 patients of different age groups. After PCT test of all cases, 20.75 % (22) samples were within the range of severe sepsis or septic shock, 7.54% (08) samples were within range of systemic infection, 18.06% (20) samples were within the ranges of possible systemic infection, 31.13 % (33) samples were within range of local infections and 21.69% (23) were within the normal ranges.

Table-IV showed the distribution PCT of COVID-19 positive patients according to age group, here it is shown that PCT is higher in elderly patients. Among 32, patients from Group-

Table-II

Distribution of patients according to age (N=106)

Age group	Age (in years)	Frequency	Percent (%)
Group-1	<20	21	19.81
Group-2	21-35	06	5.66
Group-3	36-50	19	17.92
Group-4	51-65	35	33.01
Group-5	66-80	20	18.86
Group-6	>80	05	4.71

Table-III

PCT level in patients according to age group (N=106)

	<.05 ng/ml	.05-.5 ng/ml	.6-2 ng/ml	2-10 ng/ml	>10 ng/ml	Total
Group-1 (< 20 yrs)	04	06	03	01	07	21
Group-2 (21-35 yrs)	01	01	01	02	01	06
Group-3 (36-50 yrs)	07	04	03	03	02	19
Group-4 (51-65 yrs)	08	10	08	01	08	35
Group-5 (66-80 yrs)	02	10	04	01	03	20
Group-6 (>80 yrs)	01	02	01	00	01	05
Frequency	23	33	20	08	22	106
Percentile	21.69	31.13	18.06	7.54	20.75	

4 (51-65 years) are shown highest frequencies of PCT that is 37.51% (12), then Group-3 (36-50 years) and Group-5 (66-80 years) showed 21.87% (07) of PCT, least are shown in Group-1 (<20 years), Group- 2 (21-35 years) and Group-6 (>80 years) that is 6.25% (02). Only 06 patients were having normal range of PCT amongst 32 cases.

In Table-V, we also identified that,14.15 % (15) samples were positive for bacterial culture amongst all 106 patients. Out of 15, 20% (03) were with severe sepsis or septic shock,26.67% (04) were with systemic infection, 13.33% (02) were with possible systemic infection, 13.33% (02) were with local infections and 26.67% (04) were found as individuals with no infection. Higher PCT levels were observed in patients with bacteremia, urinary tract infection (UTI), and other systemic infections.

Among 106 cases, 66.66% (10) were found positive for blood culture, 20.02% (03) for urines, 6.66% (01) for tracheal aspirates, and 6.66% (01) for tip of the catheter were found positive for bacterial culture (Table-VI).

In Table-VII, it is shown that, total 15 samples were found positive for bacterial culture from different clinical specimens. Gram-negative microorganisms were present in 14(93.33%) whereas, Gram-positive microorganisms were present in 01(6.67%) among all positive cultures. The major isolate was Gram-negative bacteria (GNB) of which *Burkholderia cepacia* was predominant. Other Gram-negative organisms were *E. coli*, *Proteus*, *Klebsiella,* and *Acinetobacter.* In Gram-positive bacteria (GPB), *Enterococcus* was identified.

Table-IV

PCT level in COVID-19 positive patients according to age group (n=32)

	<.05 ng/ml	.05-.5 ng/ml	.6-2 ng/ml	2-10 ng/ml	>10 ng/ml	Frequency	Percent (%)
Group-1 (<20 yrs)	00	01	00	00	01	02	6.25
Group-2 (21-35 yrs)	00	01	00	01	00	02	6.25
Group-3 (36-50 yrs)	03	01	03	00	00	07	21.87
Group-4 (51-65 yrs)	03	06	02	01	00	12	37.51
Group-5 (66-80 yrs)	00	05	01	00	01	07	21.87
Group-6 (>80 yrs)	00	01	01	00	00	02	6.25
Total	06	15	07	02	02	32	

Table-V

Frequencies of bacterial culture positivity among critical patients(N=106)

S/L	Variables	PCT (ng/mL)	Bacterial culture	Percent (%)
1	Individuals with no infection	<0.05	04	26.67
2	Local bacterial infection	0.05-.5	02	13.33
3	Possible systemic infection	0.5-2	02	13.33
4	Systemic infection	2-10	04	26.67
5	Severe sepsis or septic shock	>10	03	20.00
	Total cases		15	

Table-VI

Distribution of bacterial cultures in different samples(n=15)

Variables	Frequency	Percent (%)
Blood	10	66.66
Urine	03	20.02
Tracheal aspirates	01	6.66
Tip of the catheter	01	6.66
Total	15	

Table-VII

Distribution of Gram-positive and Gram-negative isolates among culture positive cases (n=15)

Isolates from bacterial culture	Frequency	Percent (%)
Gram-negative bacillus (GNB)		
Burkholderia cepacia.	07	
Klebsiella spp	02	
Acinetobacter spp.	02	
E. coli	02	
Proteus spp.	01	
Total GNB	14	93.33
Gram-positive bacillus (GPB)		
Enterococcus spp.	01	6.67
Total (GNB+ GPB)	15	

Discussion:

There is an alarming number of 18 million new sepsis cases reported each year worldwide with mortality rate ranging from 30–50%[8]. Critical disease (i.e. respiratory failure, septic shock, and/or multiple organ dysfunction) has been reported in approximately 5% of the symptomatic patients amongst COVID-19 patients. These patients meet criteria for sepsis. Additionally, bacterial co-infection or secondary infection can aggravate the condition and perpetuate organ dysfunction[9]. In this study, we evaluated the utility and prognostic value of PCT in case of sepsis and infection in critical care unit. In a review article Richard Taylor suggested that gender, perhaps through differences in sex hormones, may be an important risk factor for adverse outcome in infection and sepsis.[10] A multicentral trial from 12 medical centers in India by Todi et al reported that sepsis was common in males.[11] We included total 106 cases in our study, majority of them were males, as 65% and female were 35% thereby, ratio is 1.86:1. There was higher incidence in male patients affected with infection and sepsis in our study which is similar to other studies. Our findings are comparable with the findings of above-mentioned authors.

George A Alba et al. stated that PCT concentrations allowed for accurate diagnosis, early recognition and treatment of such patients is of importance given their higher risk.[6] In this study, patients with any positive culture had significantly higher PCT levels (0.5–10ng/mL). We found that 14.15% (15) were found positive for blood culture which correlated with the higher levels of PCT. The difference of PCT levels between cases with positive and negative cultures from blood, urine, tracheal aspirates, and other fluids reached statistical significance. Among all obtained culture site, patients with septic shock had the highest PCT levels (>10 ng/ml). In a study, Shefali Gupta et al showed about 75.7% of the septic patients, the cultures were positive and PCT levels being highest in culture positive sepsis which correlates with our study.[9] Our results are important, in that we not only showed that PCT provides useful discriminatory information for sepsis but does so in patients assessed with bacterial culture, where PCT provided optimal operating characteristics and guide to antibiotic therapy.

Shefali Gupta et al. also showed in a study that, majorities were infected by Gram-negative bacteria (GNB) and rest of them by Gram-positive bacteria (GPB).[12] In Gram-negative cultures, Klebsiella pneumoniae was the most common pathogen followed by Escherichia coli. In our study, major isolate was Gram-negative bacteria (93.33%) of which Burkholderia cepacia was predominant (28.57%). Other Gram-negative bacterias were E. coli, Klebsiella, Acinetobacte and Proteus. The rest of the isolates were Gram-positive microorganism (6.67%) of which Enterococcus was identified.

Rui Hu stated in one study that, PCT may be an indicator of disease severity and may contribute to determining the severity of patients with COVID-19. In our study we found high level of PCT in COVID-19 patients, moreover elderly patients showed the higher frequencies.[5] It is hence not surprising that the procalcitonin value would remain within the reference range in several patients with non-complicated SARS-CoV-2 infection, whereby

its substantial increase would reflect bacterial coinfection stated Giuseppe Lippi.[13]

Viallon recommended the usefulness of serum PCT levels as a guide to antibiotic prescription in patients admitted to critical care unit.[14] Antibiotics are strongly recommended for patients due to systemic infections with COVID-19. In this study, the patients who were admitted in critical care unit were advised procalcitonin routinely to get the guidance to treat and discontinue the antibiotics as well. The recommendations are largely consistent with the 2016 Surviving Sepsis Campaign and the 2016 Infectious Diseases Society of America antimicrobial stewardship guidelines, which both give a recommendation for using serial procalcitonin levels to guide antibiotic discontinuation in patients with suspected infections in the ICU. But PCT cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients.[1-4]

Angus DC et al. showed that beyond the implications for clinical trials, sepsis is a disease of the elderly also mandates consideration of the appropriateness of care, including determination of patient preferences[15]. Our data suggest that there are already differences in the PCT level which express the aggressiveness of infections in the Group- 4 and 5 which include 51-65 and 66-80 years.

This study has some limitations. First, this was a single medical centre-based study and we did not collect enough clinical data regarding patients' severity. Lack of pathogen analysis was a weakness in this study because only Corona Virus Disease-19 (COVID-19) was identified, whereas, another virus could be the causative agent. PCT variations after antibiotic therapy may influence the outcome of patients with acute infectious diseases also. There are no fixed intervals to check PCT in our clinical practice, so we were not able to determine the PCT variations.

Conclusion:

With few limitations PCT is a good biological marker to identify the origin of systemic inflammation and seems to appear as a promising prognostic biomarker in COVID-19. Though PCT is not a specific test to identify the etiology of infection, the microbiologic and molecular data are still needed for optimization of antimicrobial therapy. Hence, the clinical correlation between patients' prognosis and their PCT concentration in blood, which was expected to be a prognostic marker for elderly people at risk of infectious diseases, especially during corona pandemic. The outcome of this study supports the usefulness of PCT level which can be used to early diagnosis and to support shortening the duration of antimicrobial therapy.

Conflict of interest: none.

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