MEDWIN PUBLISHERS
Committed to create value for Researchers

Medical Journal of Clinical Trials & Case Studies
ISSN: 2578-4838

C Reactive and Procalcitonin Correlation with WBC Counts in Culture Positive Patients of Sepsis

Menka K[1], Tanu R[2], Gupta GN[1] and Rateesh S[3]*

[1]Consultant pathology, SDMH, India

[2]Department of Pathology, senior resident, SDMH, India

[3]Department of Pathology, Assistant Consultant, SDMH, India

Conceptual Paper

Volume 3 Issue 3

Received Date: May 18, 2019

Published Date: June 10, 2019

DOI: 10.23880/mjccs-16000225

***Corresponding author:** Rateesh Sareen, Santokba Durlabhji Memorial Hospital and Research Center, Bhawani Singh Marg, Bapu Nagar, India, Tel: 9414216471; Email: drrateeshsareen@yahoo.co.in

Abstract

C Reactive protein (CRP) and Procalcitonin (PCT) are now days used as surrogate marker of sepsis. Studies in literature have emphasized their role in inflammatory disorders and Infections. We conducted a retrospective study of 142 blood culture positive patients and evaluated CRP and PCT correlation with White blood cell (WBC) counts by stratifying the patients on the basis of WBC counts into three categories – low, normal and high. It was concluded that although CRP and PCT have role as a sepsis marker but their correlation in context to WBC count was poor. The diagnosis of sepsis still remains an enigma due to lack of an ideal marker and therefore mandates multidisciplinary approach in diagnosis. Isolated reliance on any laboratory parameter can be misleading causing loss of crucial window period of diagnosis making prognosis grim.

Keywords: CRP; PCT; Sepsis

Abbreviations: CRP: C Reactive protein; PCT: Procalcitonin; WBC: White blood cell.

Introduction

The early detection of infection has clinical importance as it could lead to timely intervention and lead to better clinical outcome [1]. There has been plethora of diagnostic markers in the field of medicine but a reliable clinical or microbiological parameter that could be obtained with great ease from specimens and used to rule out infections, is lacking [2]. The gold standard remains traditional culture but the diagnostic delay and suboptimal sensitivity and interplay of contaminants pose major impedance to quick reliable diagnosis [3].

These shortcomings in culture diagnosis led researchers to search for an ideal sepsis marker and over the years this quest gave rise to Procalcitonin (PCT) emerging as the blue eyed boy as an early marker for sepsis, infection and systemic inflammation [4,5]. Sepsis is the leading cause of non-cardiac causes of death in intensive care units accounting for nearly 30% of death of patients [6]. As per ACCP/ SCCM conference 1992, systemic inflammatory response syndrome (SIRS) is defined as the presence of two or more of the following: Fever (>38C^0), or hypothermia (<36C^0), tachycardia (>90 beats/min), tachypnea (>20 breath/min) or hyperventilation (pCo_2 <32 mm or Hg) and altered White blood cells count (>12,000 cells/mm^3 or <4000 cells/mm^3) or presence of 10% immature neutrophils [4,7]. Sepsis in SIRS arising out of infection may be bacterial, viral, fungal or parasitic in origin. Sepsis when associated with at least one organ dysfunction, hypotension or hypoperfusion is referred as severe sepsis. PCT and C - reactive protein (CRP) are systemic response markers that are currently

used for identification of early sepsis. Therefore, we performed institutional based study to elucidate the role of these markers in sepsis cases.

PCT is group of proteins related to Calcitonin gene. The 16kDa 141 amino acid protein gives origin to PCT from rough Endoplasmic reticulum [8]. The process under normal physiology is confined to C cells of thyroid. In the presence of infection, there is liberation of lipopolysaccharides from bacterial cell membrane resulting in the release of pro inflammatory cytokines mainly interleukin -1B (ILB) and Tumor necrosis factor alpha (TNF-A) which lead to generation of PCT by monocytes [9]. The PCT levels are detected in 4 hours of initiation, reaches peak level by 6 hours and diminishes at 18 hours [10]. The half-life of PCT is 25 to 30 hours [11] and in the presence of infection it is produced in tissues other than thyroid tissue [12]. PCT concentration above 0.1ng/ml are indicative of bacterial infection that need antibiotics [13] and for PCT levels >0.5ng/ml risk of severe sepsis should be considered [14,15]. The rapid early increase in PCT levels is advantageous for early diagnosis of disease [16] thereby better clinical outcome, shorter ICU stays and cost effectiveness.

PCT is markedly elevated (upto 5000 fold) within 2 to 4 hours in sever forms of systemic inflammation or in bacterial infections and the levels are sustained until recovery [17-19]. PCt elevation is rarely seen in viral infections, postulated theory is that viral infections triggers alpha-interferon by macrophages which inhibit TNF synthesis, hence PCT is a discriminator between bacterial and viral infections [20]. There are literature studies to suggest that PCT is superior to CRP in detecting pyelonephritis in children with febrile Urinary tract infection [21], in infective endocarditis [22], intra-abdominal infections [23], exclusion of perforation in obstructive bowel syndrome [24], in appendicitis [25], pancreatitis and in febrile neutropenia [26-28].

CRP on the other hand is protein belonging to pentatraxim family, having five identical subunits codified by single gene on chromosome-1. CRP is 118kD protein synthesized in response to tissue injury [29]. It is synthesized by hepatocytes and vascular endothelial cells and its secretion mediated by IL-6, IL-1 and TNF-Alpha [30]. The levels increase following inflammatory stimulus and diminish rapidly when the stimulus is resolved. It was discovered in 1930 by Tillet and Francis from patient's sera of acute stage of Pneumococcus infection and was named for its reaction with the capsular ©polysaccharides of Pneumococcus [31]. It binds to polysaccharides in presence of calcium on surface of microorganisms to trigger classical compliment pathway [32]. It is elevated in rheumatoid arthiritis, inflammatory disorders and in some bacterial infections (1000 folds) [30,33]. It exponentially decreases over 18-20 hour period [34]. Tissue damage like trauma and cancer increase it from 1ug/ml to 500ug/ml within 24-72 hours [35]. Increased CRP levels in various infections are well documented in literature- Streptococcus Pneumoniae [36], Salmonella enteric serovar Thyphimurium [37], H Influenzae [38] and S Aureus [39].

Material and Methods

The retrospective study was conducted in the department of pathology in tertiary care hospital in western India. All patients were adults (> 18 years) admitted in the hospital during study period between Jan, 2018 to December, 2018 who had Blood count, CRP, PCT and blood culture done were included in the study. The study subjects were categorized into three groups on the basis of WBC count. (Table 1) Data was collected using laboratory software maintaining confidentiality and statistical analysis was done using medicals online free software.

WBC Count in /mm 3	Number of patients	Percentage
<4000	7	4.9
4000-10,000	49	34.5
>10,000	86	60.6
	142	

Table 1: Stratification on WBC Count.

Results

The study comprised of 142 patients 90(63.4%) males and 52(36.6%) females with average age 36.7 +_ 5.6 years. All cases were culture positive. They were categorized into three groups on basis of WBC count. 7(4.9%) patients had WBC count less than 4000/cumm. 86(60.6%) patients had high WBC count (>10,000/cumm). 49(34.5%)

patients had normal WBC counts. CRP was elevated in 23(16.2%) patients. Among these patients majority, 11 had elevated WBC counts, 9 had normal and 3 had below normal counts. (Table 2) PCT was in normal range in 66(46.5%) of cases. For cases with elevated PCT value 41(28.9%) had values between (0.5-2.0 ng/ml), 18(12.7%) between 2-10.0ng/ml and 11 had values more than 10ng/ml (Table 3). The chi square test showed that the three variables – WBC Count, CRP and PCT are dependent variables with statistically significant result. ($p<0.00001$)We calculated coefficient of correlation between WBC count and with CRP & PCT. The results as shown in Table 4 indicate that CRP has weak correlation with both low and high WBC count. PCT had positive correlation with low WBC count and weak positive correlation with high WBC count. As all cases were positive for culture the overall correlation of CRP with WBC count was 0.0982 and of PCT0.0659 which are very low values.

WBC Count in /mm3	0-1mg/dl	>1 mg/dl	
<4000	4	3	7
4000-10,000	40	9	49
>10,000	75	11	86
	119(83.8%)	23 (16.2%)	142

Table 2: CRP in patients with sepsis.

WBC Count in /mm3	<0.5	0.5-2.0	2.0-10	>10	
<4000	4	2	0	1	7
4000-10,000	28	8	8	5	49
>10,000	34	31	10	11	86
	66(46.5%)	41(28.9%)	18(12.7%)	17(11.9%)	142

Table 3: PCT in patients with sepsis.

WBC	CRP	PCT
Low	-0.2398	0.2384
Normal	0.3001	-0.1521
High	-0.0255	0.0388
Total WBC	0.0982	0.0659

Table 4: Correlation coefficient.

Discussion

The diagnosis of sepsis prior to culture is of paramount importance in early initiation of treatment. CRP was raised in 26(16.2%) of cases having culture proven sepsis. The positivity of CRP increased with higher WBC count, 11 cases with WBC count > 10,000/ cumm and 3 cases with WBC count<4,000/cumm. Elevated PCT was seen in 76(53.5%) of all cases of culture positive patients where majority had above normal PCT values with WBC count on higher side. The retrospective study of all blood culture positive 142 patients independently studied the three parameters- WBC count, C Reactive protein and Procalcitonin. A low WBC count as well as high WBC count was taken as highly suspicious of sepsis, in the study 93 (65.3%) patients had abnormal WBC Counts (Table 1).

CRP was higher in only 23(16.2%) of patients (Table 2) and PCT was above normal reference range in 78 (53.5%) patients (Table 3). Our study clearly indicates that of the three parameters for sepsis, none of the index can confidently rule out presence or absence of sepsis. In spite of novel new markers like PCT the likelihood of missing sepsis remains high and therefore it is essential for clinician not to rely solely on laboratory parameters for taking decisions regarding initiation of antibiotic treatment for sepsis. All clinical judgments should accomplish patient examination and multidisciplinary approach where sole reliance on any particular laboratory parameter can be misleading which could lead to loss of critical window period in sepsis leading to an unfavorable outcome for patients.

We further stratified patients on the basis of WBC counts into three categories- low, normal and high. As our

study group comprised of only adults (>18 years age) patients the age adjustment for normal WBC count reference range was not required. The coefficient of correlation of CRP and PCT with reference to WBC counts for prediction of likelihood of sepsis was done and it showed that both CRP and PCT had weak correlation with WBC counts. In terms of CRP surprisingly both the low and high WBC counts showed weak negative correlation that was statistically insignificant. PCT showed weak positive correlation with abnormal WBC count (Table 4). PCT was elevated more with increased WBC count above normal although the result was statistically non-significant. CRP and PCT both had weak correlation with overall total WBC count. Our study clearly indicates that CRP and PCT are mere predictors of sepsis with no correlation with WBC counts. There is rampant use of PCT as marker of sepsis marker but the gold standard still remains blood culture. Moreover high CRP and PCT do not mandate treatment unless supported by a positive culture report.

The diagnostic performance of PCT in numerous studies from literature has suggested PCT to be useful marker in diagnosis of sepsis comparing to CRP [13-26]. Our study is unique where we demonstrated that both CRP and PCT have poor correlation with WBC count albeit statistically insignificant. It is also necessary to perform more studies with larger sample size and more number of patients could yield greater statistically weight age. An ideal biomarker for sepsis should have high sensitivity and specificity with early phase elevation, low cost and quick result.

Conclusion

Currently an ideal biomarker guide for sepsis is lacking. In the future, better biomarkers as well as combination of biomarkers shall be the driving force for decision making till then blood cultures remain gold standard.

References

1. Bagshaw SM, Bellomo R (2007) Early diagnosis of acute kidney injury. Curr Opin Crit Care 13(6): 638-644.

2. Schuetz P, Albrich W, Mueller B (2011) Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med 9: 107.

3. Chung TP, Laramie JM, Province M, Cobb JP (2002) Functional genomics of critical illness and injury. Crit Care Med 30(1): S51-S57.

4. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, et al. (2003) (2001) SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31(4): 1250-1256.

5. Mitaka C (2005) Clinical laboratory differentiation of infectious versus noninfectious systemic inflammatory response syndrome. Clin Chim Acta 351(1-2): 17-29.

6. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, et al. (2010) The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med 36(2): 222-231.

7. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20(6): 864-874.

8. Balc C, Surgertekin H, Gurses E, Surgertekin U, Kaptanoglu B (2003) Usefulness of procalcitonina for diagnosis of sepsis in the intensive care unit. Crit Care 7(1): 85-90.

9. Linscheid P, Seboek D, Schaer D, Zulewski H (2004) Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. Crit Care Med 32(8): 1715-1721.

10. Clec´h C, Ferriere F, Karoubi P, Fosse J, Cupa M, et al. (2004) Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit Care Med 32(5): 1166-1169.

11. Brunkhorst F, Al-Nawas B, Krummenauer F, Forycki Z, Shah P (2002) Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med 26(2): 148-152.

12. Remolina-Schlig M (2005) Procalcitonina marcador de inflmación sistemica. Med Sur 12(4): 1-4.

13. Becker KL, Snider R, Nylen ES (2008) Procalcitonin assay in systemic inflammation, infection, and sepsis:

Clinical utility and limitations. Crit Care Med 36(3): 941-952.

14. Chua AP, Lee KH (2004) Procalcitonin in severe acute respiratory syndrome (SARS). J Infect 48(4):303-306.

15. Cone JB (2001) Inflammation. Am J Surg 182(6): 558-562.

16. Luster AD (1998) Chemokines-chemotactic cytokines that mediate inflammation. N Engl J Med 338(7): 436-445.

17. Gilbert DN (2010) Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J Clin Microbiol 48(7): 2325-2329.

18. Pfafflin A, Schleicher E (2009) Inf lammation markers in point-of-care testing (POCT). Anal Bioanal Chem 393(5): 1473-1480.

19. Brunkhorst FM, Heinz U, Forycki ZF (1998) Kinetics of procalcitonin in iatrogenic sepsis. Intensive Care Med 24(8): 888-889.

20. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, et al. (2000) Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 28(4): 977-983.

21. Pecile P, Miorin E, Romanello C, Falleti E, Valent F, et al. (2004) Procalcitonin: a marker of severity of acute pyelonephritis among children. Pediatrics 114(2): e249-254.

22. Knudsen JB, Fuursted K, Petersen E, Wierup P, Molgaard H, et al. (2010) Procalcitonin in 759 patients clinically suspected of infective endocarditis. Am J Med 123(12): 1121-1127.

23. Kafetzis DA, Velissariou IM, Nikolaides P, Sklavos M, Maktabi M, et al. (2005) Procalcitonin as a predictor of severe appendicitis in children. Eur J Clin Microbiol Infect Dis 24(7): 484-487.

24. Markogiannakis H, Memos N, Messaris E, Dardamanis D, Larentzakis A, et al. (2011) Predictive value of procalcitonin for bowel ischemia and necrosis in bowel obstruction. Surgery 149(3): 394-403.

25. Anielski R, Kusnierz-Cabala B, Szafraniec K (2010) An evaluation of the utility of additional tests in the preoperative diagnostics of acute appendicitis. Langenbecks Arch Surg 395(8): 1061-1068.

26. Mofidi R, Suttie SA, Patil PV, Ogston S, Parks RW (2009) The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. Surgery 146(1): 72-81.

27. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K (2008) The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection 36(5): 396-407.

28. Koivula I, HMLI S, Jantunen E, Pulkki K, Kuittinen T, et al. (2011) Elevated procalcitonin predicts Gram-negative sepsis in haematological patients with febrile neutropenia. Scand J Infect Dis 43(6-7): 471-478.

29. Amescua L, Springall R, Bojalil R (2007) Proteína C reactiva aspectos cardiovasculares de una proteína de fase aguda. Arch Cardiol Mex 77(1): 58-66.

30. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340(6): 448-4544.

31. Tillet WS, Francis T (1930) Serological reactions in pneumonia with a non- protein somatic fraction of Pneumococcus. J Exp Med 52(4): 561-571.

32. Volanakis JE (2001) Human C-reactive protein: expression structure and function. Mol Immunol 38(2-3): 189-197.

33. Du Clos TW, Mold C (2004) C-reactive protein: an activator of innate immunity and a modulator of adaptive immunity. Immunol Res 30(3): 261-277.

34. Ridker PM (2003) Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 107(3): 363-369.

35. Ciubotaru I, Potempa LA, Wander RC (2005) Production of modified C-reactive protein in U937-derived macrophages. Exp Biol Med 230(10): 762-770.

36. Mold C, Nakayama S, Holzer TJ, Gewurz H, Du Clos TW (1981) C-reactive protein is protective against Streptococcus pneumoniae infection in mice. J Exp Med 154(5): 1703-1708.

37. Szalai AJ, VanCott JL, McGhee JR, Volanakis JE, Benjamin WH (2000) Human C-reactive protein is protective against fatal Salmonella enterica serovar typhimurium infection in transgenic mice. Infect Immun 68(10): 5652-5656.

38. Marnell L, Mold C, Du Clos TW (2005) C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 117(2): 104-111.

39. Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, et al. (2005) C-reactive protein as a marker of infection in critically ill patients. Clin Microbiol Infect 11(2): 101-108.