International Journal of Advances in Medicine
Kaneria MV et al. Int J Adv Med. 2016 Aug;3(3):675-680
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20162516

Research Article

Utility of procalcitonin as a diagnostic biomarker for bacterial infections and its comparison with C reactive protein and total leucocyte count

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Received: 14 May 2016
Accepted: 13 June 2016

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ABSTRACT

Background: Distinguishing bacterial fever from other fevers is important for early treatment and the judicious use of antibiotics. This study aimed to evaluate the levels of procalcitonin (PCT) in febrile adults and compare it with C reactive protein (CRP) and total leukocyte count (TLC).
Methods: 70 patients were classified clinically according to severity of infection into mild (Group A 30), moderate (Group B 23) and severe (Group C 17). 30 healthy controls were taken (Group D). After a detailed clinical history, their blood collected aseptically was sent for complete hemogram, culture, biochemistry, PCT and CRP. PCT was measured by immunochromatographic method (Result Range: <0.5, 2, >2, >10ng/ml). CRP was measured by immunoturbidometry. Chisquare, ANOVA, Pearson's Correlation were used.
Results: PCT was significantly elevated with higher degrees of infection (p value < 0.001). Sensitivity and specificity of PCT in Group 2 and 3 were both 100%. Group 1 had no rise in PCT proving that it is neither specific nor sensitive for mild infection. Mean CRP was significantly increased (p value <0.001) with severity of infection; sensitivity and specificity being 97.14% and 80%. TLC increased significantly (p value <0.001) with the severity of infection. However, it did not rise above the cut off, for mild infection.
Conclusions: PCT was highly sensitive and specific for moderate to severe infection and also determined prognosis. It could not identify mild local infection. CRP was sensitive for any grade of infection but not specific for bacterial fever. TLC was specific for moderate to severe infection though less sensitive.

Keywords: Procalcitonin, C reactive protein, Total leucocyte count, Sepsis biomarker

INTRODUCTION

Distinguishing infectious from non-infectious causes of fever is challenging. Besides infectious causes such as bacterial, viral, fungal, parasitic, mycobacterial and rickettsial infections, fever can also be caused by non-infectious causes such as autoimmune diseases, malignancy, drugs, venous thromboembolism, transplant rejection, gout, myocardial and cerebral infarction, etc.[1] Traditional markers of systemic inflammation, such as CRP, erythrocyte sedimentation rate (ESR) and total leucocyte count (TLC), have proven to be of limited utility due to their poor sensitivity and specificity for bacterial infection.[1] Blood culture, which is the gold standard for diagnosing bacterial infection has some drawbacks in the form of a long turnaround time, the inability to provide specific information on host response and the inability to distinguish between bacterial colonisation and infection.[2] Early diagnosis and prompt installation of specific therapies is associated with an improved outcome in patients with sepsis. Lack of early, reliable markers of infection may be responsible for

withholding, delaying or unnecessary antimicrobial treatment.[3] In the last decade, researchers have found procalcitonin (PCT) to have an important role in the diagnosis of bacterial infection.[4] Procalcitonin is claimed to be a diagnostic and prognostic marker of bacterial sepsis, which has been increasingly used as an inflammatory marker to identify patients with bacterial infection.[4] PCT is a prohormone of calcitonin, normally produced by thyroid gland C-cells in response to hypocalcaemia.[1-4]

PCT concentrations rise earlier than CRP levels and also normalize more rapidly, thus enabling earlier disease diagnosis and better monitoring of disease progression. This may lead to lower antibiotic usage, thus tackling the problem of antibiotic resistance, reduced hospital stay and lower costs. A procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical patients in intensive care units could reduce antibiotic exposure and selective pressure with no apparent adverse outcomes.[5]

This study was undertaken to evaluate the levels of Procalcitonin (PCT) in febrile adults suspected to have bacterial infection and correlate it with C Reactive Protein (CRP) and Total Leukocyte Count (TLC).

METHODS

This cross-sectional study was carried out at the B.Y.L. Nair Ch. Hospital in Mumbai, India over a period of 3 months. The study protocol was approved by the Institutional Ethics Committee. 70 adult indoor patients (both males and females) of acute febrile illness (temperature >38.5^{0}C for more than 72 hours) which was suspected to be of bacterial origin, were included, along with 30 controls. A written informed consent was taken from each patient. All the included patients had not received antibiotics in the previous 72 hours.

Patients with fever of longer duration, confirmed or probable cases of malaria, dengue, enteric fever, viral fever, viral hepatitis, tuberculosis, fungal infection, immuno-compromised patients and autoimmune conditions were excluded.

The patients were divided into 4 groups based on the severity of infection viz.

- *Mild infection:* Local organ infection (noninvasive) which did not incapacitate the patient.
- *Moderate infection:* Severe local organ infection (invasive) causing a moderate systemic inflammatory response.
- *Severe infection*: Appearing toxic and likely to be in sepsis (invasive infection) that needed immediate intervention in the form of higher antibiotics and an Intensive Care Unit (ICU) referral.
- *Controls:* Subjects who were admitted for reasons other than fever.

In group A, there were 17 patients of urinary tract infection (UTI) and 13 patients of upper respiratory tract infection (URTI), total 30 patients.

In group B, there were 12 patients of pneumonia, 7 of meningitis and 4 of infective endocarditis, total 23.

In group C, there were 11 patients of sepsis with an identified or occult focus of infection, 3 patients of meningitis and 3 patients of empyema, total 17.

In group D, there were 30 patients who were admitted for indications other than fever.

Demographic data such as age, sex and consumption of antibiotics before admission were obtained from each patient. Vital signs such as fever, pulse rate, respiratory rate and blood pressure were monitored.

Blood was sent for TLC, CRP and PCT, besides other investigations to identify the likely focus of infection. Additionally, blood culture was sent whenever indicated in groups A, B and C. PCT was measured by immuno-luminometric quantitative assay using the kit manufactured by BRAHMS Diagnostica, Berlin, and Germany. PCT levels were performed only once in all the patients i.e. at enrolment. The levels of TLC, CRP and PCT of these patients were compared using various statistical tests within groups as well as with the values of the 30 controls.

PCT levels were divided into four groups viz. PCT<0.5 ng/mL, PCT=2ng/mL, PCT 2-10 ng/ mL and PCT>10 ng/mL, the cut off value being 0.5 ng/ml. CRP was measured by immuno-turbidometry and cut off value was taken as 5 mg/l . The normal TLC range was 4000 to 10,000/mm$^{3.}$ Data was analysed using Pearson chi square test, one way ANOVA, Pearson correlation and sensitivity and specificity. Blood cultures wherever sent were reported with no significant growth.

RESULTS

All the 17 patients in group C (severe infection) had PCT levels >10 ng/ml. In group B (moderate infection), 11 patients had PCT levels >2 and 12 patients had PCT levels=2. In groups A and D (mild infection and controls), the PCT levels were <0.5 ng/ml (Figure 1). On applying the chi square test, there was a significant difference in the PCT levels in the various groups (p value <0.0001). This suggests that mild local non-invasive infection did not produce significant levels of PCT in the system, whereas the levels of PCT rose with the increase in the severity of infection.

The CRP levels showed an increase in the mean values from mild to moderate to severe infections (Table 1). On applying Anova to the means of the CRP levels in the various groups, there was a significant statistical difference between them (p value<0.0001) (Table 3).

The mean values of the TLC increased from moderate to severe infection and this was statistically significant. The mean of TLC in the mild group did not cross the cut off value suggesting infection.

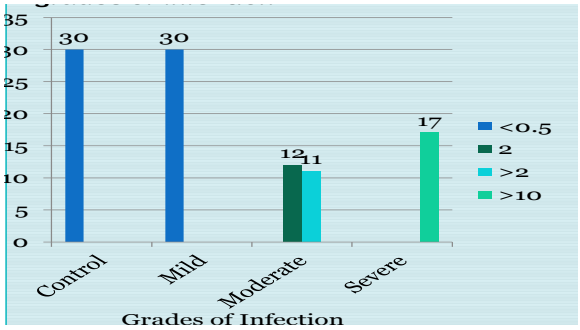


Figure 1: PTC levels in patient with different grades of infection.

Table 1: The mean levels of CRP in patients with different grades of infection.

Grade of Infection	Number of patients	Mean	Std. Deviation
Severe	17	338.671	75.6249
Moderate	23	180.091	80.4178
Mild	30	111.650	53.9754
Controls	30	24.943	17.8821
Total	100	139.973	121.3040

On applying Anova to the means of the TLC levels in the various groups, there was a significant statistical difference between them (p value <0.0001). Thus TLC levels show a significant rise with the severity of infection. However, the mean of TLC in the mild infection group was within the cut off level suggesting that TLC was not a reliable marker of infection in mild cases.

Table 2: The mean TLC levels with different grades of infection.

Grade of Infection	Number of patients	Mean	Std. Deviation
Severe	17	0802.94	2666.837
Moderate	23	5090.43	2133.055
Mild	30	7836.67	1810.810
Controls	30	6160.00	2156.063
	100	1206.30	5912.658

As PCT levels increased with the severity of infection, so did CRP (p value <0.0001). When PCT levels were compared with each other and with CRP as the dependent variable, all comparisons showed significant difference (p value <0.001) (Figure 2).

As PCT levels increased, TLC levels also increased with the severity of infection (p value <0.0001). However, there was no correlation between the mean TLC values and the PCT levels between the 2 sub-groups of the moderate infection group i.e. PCT levels 2 ng/ml and >2 ng/ml.

So, though PCT levels could show different grades of severity in the two subsets of the moderate infection group, TLC could not do so (Figure 3). The sensitivity and specificity of CRP for any grade of infection was 97.14% and 80% respectively. Its positive predictive value was 91.89% and negative predictive value was 92.31% (Figure 4).

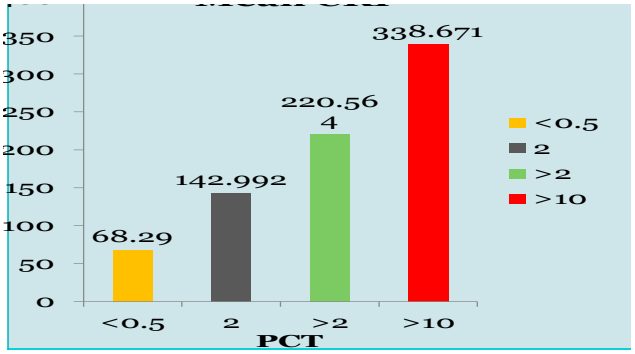


Figure 2: As PCT levels increased with the severity of infection, so did CRP.

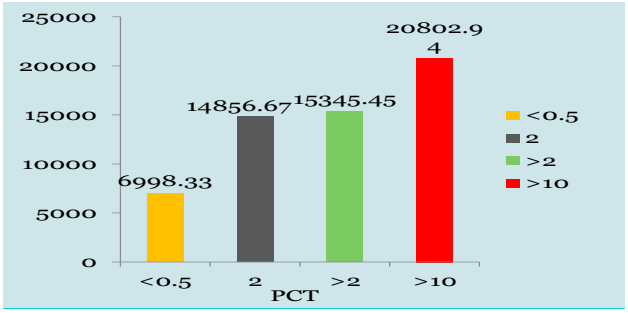


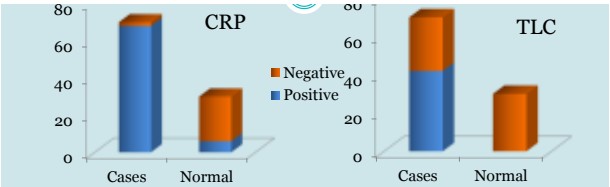
Figure 3: As PCT levels increased with the severity of infection, so did TLC. There was no correlation between the mean TLC values and the PCT levels between the 2 sub-groups of the moderate infection group i.e. PCT levels 2 ng/ml and >2 ng/ml.

The sensitivity and specificity of TLC for any grade of infection was 60% and 100% respectively. Its positive predictive value was 100% and negative predictive value was 51.72% (Figure 4). The sensitivity, specificity, positive predictive value and negative predictive value of PCT for infection of moderate and severe grade were 100% (Figure 5).

Out of the 17 patients with PCT>10ng/ml, 13 died in the 1st week of admission, 2 in the 2nd week. The remaining 2 were critical at the end of the study.

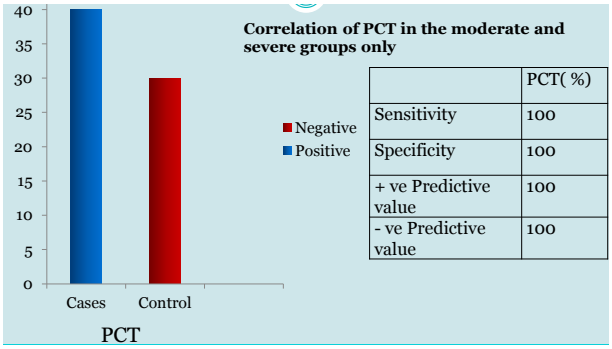
In the moderate infection group, 5 out of 11 patients with PCT>2ng/ml required ICU care in the first week. They

however gradually recovered. In the same group, patients with PCT levels=2ng/ml recovered completely by the 2nd week with appropriate antibiotics. This shows that PCT is a reliable marker of the severity of infection as well as of prognosis.



	CRP(%)	TLC(%)
Sensitivity	97.14	60
Specificity	80	100
+ ve Predictive value	91.89	100
- ve Predictive value	92.31	51.72

Figure 4: This shows the sensitivity, specificity, positive predictive value and negative predictive value of CRP and TLC for any grade of infection.



	PCT(%)
Sensitivity	100
Specificity	100
+ ve Predictive value	100
- ve Predictive value	100

Figure 5: This shows the sensitivity, specificity, positive predictive value and negative predictive value of PCT for infection of moderate and severe grade.

DISCUSSION

The diagnosis of bacterial infections in febrile patients is not always straightforward. Early and appropriate usage of antibiotics is crucial in decreasing the mortality in patients with sepsis. Moreover, ruling out an infectious cause of fever, would avoid the injudicious use of antibiotics, thus reducing costs and preventing antibiotic resistance.

It is perhaps unsurprising, therefore, that the search for a highly accurate biomarker of sepsis has become one of the holy grails of medicine.[6]

The ideal biomarker of bacterial infection, if any, should be sensitive enough to detect the presence of infection in patients with minimal or even no host response, should be specific enough to discriminate infection from other stimuli which may cause systemic inflammatory response syndrome (SIRS), should be detectable early in the course of the illness, should have the ability to be rapidly and conveniently measured and should be of prognostic significance.[7]

Procalcitonin has emerged as the most studied and promising sepsis biomarker[8]. For diagnostic and prognostic purposes in critical care, PCT is an advance on C-reactive protein and other traditional markers of sepsis, but is not accurate enough for clinicians to dispense with clinical judgement.[8]

A decade ago, Assicot et al reported that elevated levels of PCT could reliably discriminate between fever due to bacterial infections and other non-infectious causes[4]. Considering the need for a reliable biochemical marker of infection, we decided to evaluate levels of PCT in 70 patients of suspected bacterial infection of various grades. CRP levels were also evaluated, in order to do a comparative study. Total leucocyte count being an inexpensive test, was also added to the comparative study. 30 patients who had no evidence of infection were taken as controls.

PCT levels in all the 30 controls and the 30 patients of mild infection (groups A and D) were <0.5ng/ml. This was expected, as mild localized organ infection does not produce significant levels of PCT in the system and in healthy subjects, only minute amounts of PCT appear in the serum.[4] This was in accordance with the results obtained by Galetto – Lacour et al and other authors.[9] All the 23 patients in the moderate infection group (group B) had PCT levels 2 or >2ng/ml. A similar result was obtained by Gramm et al in their study of 149 cases of community acquired pneumonia.[10]

All 17 patients classified as clinically severe, had PCT >10 ng/ml. Our results are in concordance with other workers such as Hergert M et al who found the mean PCT to be 54 ng/ml in their study on patients with sepsis and polytrauma.[11] Thus, there was a significant difference in the PCT levels between the patients in the 3 groups with a p value <0.0001.

Observing the fact that PCT did not rise in mild infection, we could say that PCT is neither sensitive nor specific for mild local infection. However, as a marker of moderate and severe infection, PCT showed sensitivity and specificity of 100%. The positive and negative predictive value of PCT was also 100%, thus proving to be a reliable marker of bacterial infection.

Out of the 17 patients with PCT >10, 13 died in the first week of admission and 2 in the 2nd week. The remaining 2 were on life support system at the end of the study. The patients with PCT >2 had a variable outcome. 5 out of the 11 patients were admitted to the ICU in the first week. They however gradually recovered. All the rest who had PCT levels=2 had positive outcome by the 2nd week after an antibiotic course. Thus, PCT is a reliable marker of the severity of infection as well as prognosis.[12]

The mean CRP values in groups A, B, C and D were 24.943, 111.650, 180.091 and 338.671 respectively. This difference was statistically significant. Thus, CRP does show a significant rise according to the severity of infection. When all 100 patients were taken into consideration, CRP showed sensitivity of 97.14% and specificity of 80%. The positive predictive value of the test was 91.89% and negative predictive value was 92.3%. Thus, the specificity was low as expected due to the fact that CRP is raised in other inflammatory conditions of non-bacterial origin as well.

Several authors have compared the diagnostic and prognostic ability of PCT versus CRP. The first study by Uzzan et al published in 2006, reviewed and analysed 25 studies with a total of 2966 patients.[13] A subanalysis was performed on 15 studies to compare the diagnostic ability of PCT versus CRP. In the 25 studies that looked at PCT, the sensitivities ranged from 42% to 100% and the specificities from 48% to 100%. The sensitivities and specificities for CRP ranged from 35% to 100% and from 18% to 84%, respectively. Similar results were found by Tang *et al.* in their meta-analysis.[14]

Rau et al also found PCT to be useful, and better than CRP, in predicting infections and multiorgan dysfunction syndrome in 104 patients with acute pancreatitis.[15] Though CRP is the most commonly measured acute parameter in infection and sepsis, it is not a reliable marker in identifying bacterial infection because of its low sensitivity and specificity.[16]

TLC levels were raised in the moderate and severe infection group but not in the mild infection group suggesting that it is not a reliable marker for mild infections. The sensitivity and specificity of TLC, when all 100 patients were considered, was 60% and 100% respectively. The positive predictive value was 100% but the negative predictive value was only 51.72%. However, when only the 40 patients in the moderate and severe infection groups (B and C) were considered, the sensitivity rose to 97.5% and the negative predictive value to 96.77%. This reiterated the fact that TLC is not a reliable biomarker of bacterial infection in mild cases and thus inferior to PCT.

This was in concurrence with other studies which also showed the superiority of PCT over both CRP and TLC as a biomarker of infection.[17] Given that PCT can be elevated in certain non-infectious conditions, it is probably better used to rule out rather than rule in systemic bacterial infections.[18]

However, false-negative results can occur if samples are taken too early in the course of infection and few physicians will be persuaded not to prescribe antibiotics on the basis of a single low PCT value performed on or shortly after admission to hospital for a critically ill patient without a clear diagnosis; therefore, ideally, a repeat test should be performed at 6–12 h.[5,19]

PCT provides better sensitivity and specificity than C-reactive protein (CRP) for the diagnosis of infection and for monitoring response to antibiotics, and it is probably a better prognostic indicator than CRP in this population, most likely because of a faster rise in PCT serum levels compared with CRP levels after bacterial challenge and a rapid decline after appropriate treatment due to its shorter half-life.[12]

Present study had certain limitations. Firstly, fever was probably of bacterial origin but this was not proved using a gold standard such as blood culture or PCR. Secondly, ours being a tertiary care hospital, many of the patients may have received antibiotics prior to admission , thus affecting the levels of the biomarkers. Lastly, the biomarkers were measured only once at the time of enrollment, but were not repeated.

CONCLUSION

Both PCT and CRP were reliable markers of systemic bacterial infection. PCT was highly sensitive and specific in infections of moderate to severe grade. PCT gave an idea regarding the severity of infection and also the likely prognosis of the patient. In mild local organ infection, PCT was neither sensitive nor specific.

CRP was sensitive for infection of any grade. However, CRP was not specific for fever of bacterial origin. TLC was sensitive and specific in infection of moderate to severe grade but not for mild grade. The admission PCT concentration is a better diagnostic marker of infection than CRP or TLC. This is in agreement with other similar studies. Large scale studies are however needed to validate this.

Funding: This research was funded by the Indian Council of Medical Research (ICMR) and the T. N. Medical College Research Society
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Kaneria MV, Jakharia KK. Utility of procalcitonin as a diagnostic biomarker for bacterial infections and its comparison with C reactive protein and total leucocyte count. Int J Adv Med 2016;3:675-80.