Original Research Article

A study of serum procalcitonin in acute febrile illness as a predictor of bacterial infection and its comparision with leucocytosis

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Abstract

Background: Infectious diseases still remain a challenge despite great advances in medicine. It is often difficult, but necessary to differentiate between viral and bacterial infections to guide appropriate antibiotic usage. Serum Procalcitonin is a marker of bacterial infection and its level can be quickly available within a few hours making it a useful guide for prompt initiation of antibiotics in an acute febrile illness while awaiting bacterial culture and sensitivity results, which requires as long as 72 hours to be available.**Objectives:** To study the levels of serum procalcitonin in acute febrile illness and its correlation with bacterial culture and sensitivity. To compare the sensitivity, specifity and accuracy of serum procalcitonin to that of total leucocyte count in predicting bacterial infections.**Materials and methods:** A total of 68 adults presenting with an acute febrile illness were included in the study. Serum procalcitonin, total leucocyte count were measured and samples sent for bacterial culture and sensitivity immediately on admission, before the institution of therapy. The correlation of serum procalcitonin with bacterial culture and sensitivity was studied and its sensitivity, specificity and accuracy in predicting bacterial infection were evaluated.P value was calculated using Chi-square test.**Results:** A highly significant association was found between elevated serum procalcitonin levels of >0.5 mg/ml and a positive culture for bacteria (P <0.0001). The association between elevated total leucocyte count and a positive culture was not statistically significant (P value=0.231). The sensitivity and specificity of serum procalcitonin as a diagnostic marker of bacterial infection was 61% and 92%respectively with an accuracy of 94%. The sensitivity of elevated total leucocyte count in detecting bacterial infection was 55% and the specificity was 65% with an accuracy of 58%.**Conclusion:** Serum procalcitonin is a useful marker of bacterial infection and is more reliable than total leucocyte count in predicting bacterial infection.

Keywords: Procalcitonin, leucocyte count, bacterial infection.

Introduction

Infectious diseases are a major cause of mortality worldwide and exert a significant burden on the public health care system. Delay in timely initiation of appropriate therapy can have devastating consequences in infectious diseases. While early Antibiotic use in an acute febrile illness can be life saving in certain situations[1-3], inappropriate and excess antiobiotic use promotes development of antibiotic resistance[4-6].Hence it is prudent to initiate antibiotics in the presence of adequate evidence that the infection is bacterial. Although a positive culture for bacteria is the gold standard test for definitive diagnosis of bacterial infections, it requires a minimum of three days before results are available[7,8].Total leucocyte count (TLC) is a readily available test and may be elevated in bacterial infections. But it is non specific as it can also be elevated in non-infectious conditions like trauma, emotional stress, surgery, certain medications and smoking[9].Moreover a normal or low leucocyte count does not rule out bacterial infection[10]. A rapidly available test with reasonable sensitivity and specifity is required to detect bacterial infections and differentiate it from viral infections in the emergency setting. Such a test will aid in critical decision making such as initiation of broad spectrum antibiotics even before culture reports are available. Recently Serum procalcitonin(PCT) has been described as a specific biomarker for bacterial infection[11].

Procalcitonin is a 116-amino acid peptide production of which is increased in all parenchymal tissues in response to a bacterial infection and suppressed in viral infections[12,13]. Procalcitonin is detectable as early as 3-4 hours following infection and its degree of rise correlates with the severity of infection[11].These characteristics make serum procalcitonin a suitable marker for early detection of bacterial infection and to rule out viral infection. Serum procalcitonin levels is being increasingly utilised as a guide for starting antibiotic therapy in infectious condition. This study aims to evaluate the role of serum procalcitonin as a marker of bacterial infection in patients presenting with an acute febrile illness. The objectives of this study is to find the correlation between the level of serum procalcotonin and bacterial culture and to compare serum procalcitonin with total leucocyte count with respect to their sensitivity, specificity and accuracy in predicting bacterial infection.

Materials and Methods

A total of 68 subjects aged>18 years, presenting with an acute febrile illness of less than 2 weeks duration were included in the study. Subjects who had already received antibiotics for the illness,those with trauma, burns, recent major surgery, shock,Vitamin B12/folic acid deficiency, history of malignancy and connective tissue diseases were excluded from the study.The study was carried out in accordance with the ethical standards of the institution's ethical committee.A detailed history was taken and physical

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examination was done for the study subjects. Blood samples were sent for complete blood count, peripheral smear, ESR, C reactive proteins, serum procalcitonin levels, dengue serology, renal function test and liver function test, immediately on admission. Based on the provisional diagnosis and clinical suspicion relevant samples like urine, sputum and blood were sent for bacterial culture and sensitivity.Urine routine, imaging studies like Chest x-ray and Ultrasound abdomen and pelvis were also obtained.

Serum Procalcitonin was measured using Finecare PCT rapid quantitative test which is a fluorescence immunoassay for quantitative measurement of Procalcitonin (PCT) in human whole blood,serum or plasma. Normal reference range was 0-0.5ng/ml. Levels of serum PCT > 0.5ng/ml were considered elevated. Total leucocyte count was documented as <4000 cells/ mm^3(leucopenia), 4000 -11,000 cells/ mm^3 (normal leucocyte count) and >11,000cells/ mm^3(leucocytosis).

Statistical methods used:Statistical analyses were performed using Statistical Package for Social Survey (SPSS) for Windows version 16.0 .Chi-square test was used to find the strength of association between serum PCT, TLC and Blood/urine/sputum culture. P value of <0.05 was considered statistically significant.Sensitivity, specificity and ROC were calculated for serum PCT and TLC. The diagnostic accuracy of PCT and TLC was assessed by calculating its area under receiver operating characteristics curve (AUROCCs).

Results

Out of the 68 subjects studied, a positive culture of blood/urine/sputum was obtained in 30(44%), indicating a bacterial infection. The remaining 38(56%) subjects who had a negative blood/urine/sputum culture were diagnosed as having a viral infection. Out of the 30 subjects with bacterial infection, 18(60%) of them had a positive urine culture (indicating urinary tract infection), 10(33%) had a positive sputum culture (indicating lower respiratory tract infection) and 2(7%) had a positive blood culture (indicating sepsis).Therefore urinary tract infection was the most common bacterial infection observed. Procalcitonin values were divided into two groups ≤0.5ng/ml and >0.5ng/ml. Out of the 30 subjects with a positive culture, 28(93%) had a serum procalcitonin level >0.5ng/ml and the remaining 2(7%) subjects had a value of ≤0.5ng/ml. Out of the 38 subjects considered to have a viral infection (as indicated by a negative culture report), only 4(11%) had a procalcitonin value of >0.5ng/ml, while 34(89%) of them had a value of ≤0.5ng/ml. A highly significant association was found between a positive culture and high serum procalcitonin levels of >0.5 as the p value obtained was <0.0001 for this association. This indicates a statistically significant association between bacterial infection and an elevated serum procalcitonin level. Table 1 shows the association between blood/urine/sputum culture and serum PCT levels.

Table 1: Association between Serum Procalcitonin and Blood/urine/sputum culture.

	Serum Procalcitonin			Chi-square	P value
Blood/urine/sputum culture	≤0.5	>0.5	Total		
Positive	2	28	30		
Negative	34	4	38	46.14	<0.0001
Total	36	32	68		

Out of the 18 cases with a positive urine culture, 16(88.8%) had a procalcitonin value of >0.5ng/ml, while only 2(11%) had a value of ≤0.5ng/ml. Among 50 cases with a negative urine culture, 34(68%) had a serum PCT value of ≤0.5ng/ml and only 16(32%) had a value of >0.5ng/ml. A statistically significant association was found between a positive urine culture and a serum procalcitonin value of >0.5ng/ml as the P value obtained was 0.00034.Table 2 shows the association between urine culture and serum PCT levels.

Table 2:Association between Serum PCT and Urine culture

	Serum Procalcitonin			Chi-square	P value
Urine culture	≤0.5	>0.5	Total		
Positive	2	16	18		
Negative	34	16	50	17.19	0.00034
Total	36	32	68		

Out of the 10 cases with a positive sputum culture, all (100%) had a serum procalcitonin level of >0.5ng/ml. Out of 58 cases with a negative sputum culture report 36(62%) had a serum PCT level ≤0.5ng/ml and 22(38%) had PCT level >0.5ng/ml. P value obtained was 0.0014.Hence a statistically significant association was found between a positive sputum culture and serum PCT values >0.5ng/ml. Table 3 shows the association between sputum culture and serum PCT levels.

Table 3:Association between serum PCT and Sputum culture

	Serum procalcitonin			Chi-square	P value
Sputum culture	≤0.5	>0.5	Total		
Positive	0	10	10		
Negative	36	22	58	10.12	0.0014
Total	36	32	68		

Among the 4 cases with sepsis as indicated by a positive blood culture report, all 4(100%) had a serum PCT value of >0.5ng/ml. Out of the 64 subjects with a negative blood culture, 36(56%) had a PCT level of ≤0.5ng/ml and 28(44%) had a level of >0.5ng/ml. A statistically significant association was found between a positive blood culture and serum PCT level >0.5ng/ml, as the P value obtained for this association was 0.03. Table 4 shows the association between blood culture and serum PCT levels.

Table 4:Association between Serum PCT and blood culture

	Serum Procalcitonin			Chi square	P value
Blood c/s	≤0.5	>0.5	Total		
Positive	0	4	4	4.68	0.03
Negative	36	28	64		
Total	36	32	68		

The sensitivity and specificity of serum PCT as a diagnostic test of bacterial infection was 61% and 92% respectively within 95% confidence interval. The positive predictive value of serum PCT was 45% whereas the negative predictive value was 95%.The diagnostic accuracy of serum PCT in detecting bacterial infection was 94%.Table 5 shows the sensitivity, specificity and accuracy of serum PCT for diagnosing bacterial infection.

Table 5:Evaluation of Serum Procalcitonin as a marker of bacterial infection

Statistic	Value	95% CI
Sensitivity	0.61	0.42 to 0.78
Specificity	0.92	0.86 to 0.96
Area under curve	0.81	0.70 to 0.90
Positive Predictive value	0.45	0.27 to 0.65
Negative Predictive value	0.95	0.88 to 0.99
Accuracy	0.94	0.89 to 0.99

Among the 30 subjects with a bacterial infection (as indicated by a positive blood/urine/sputum culture), only 12(40%) had an elevated total leucocyte count of >11,000 cells/mm^3 whereas the remaining 18(60%) subjects had a TLC of ≤11,000 cells/mm^3.Among 38 subjects with a negative culture, 10(26%) had a TLC of >11,000 cells/mm^3 and 28 had a TLC of ≤11,000 cells/mm^3.The association between elevated total leucocyte count and a positive culture was not statistically significant as the P value obtained was 0.231(Table 6).

Table 6:Association between Total leucocyte count and bacterial culture

	Total leucocyte count			Chi-square	P value
Culture	≤11000	>11000	Total		
Positive	18	12	30	1.4344	0.23104
Negative	28	10	38		
Total	46	22	68		

The sensitivity of TLC in detecting bacterial infection was 55% and the specificity was 65%.The diagnostic accuracy of elevated leucocyte count in detecting bacterial infection was 58%. Table 7 shows the sensitivity, specificity and accuracy of TLC for diagnosing bacterial infection.

Table 7:Evaluation of Total Leucocyte count as a diagnostic marker of bacterial infection

Statistic	Value	95% CI
Sensitivity	0.55	0.39 to 0.70
Specificity	0.65	0.55 to 0.75
Area Under Curve	0.59	0.47 to 0.77
Positive Predictive Value	0.22	0.12 to 0.32
Negative Predictive Value	0.88	0.82 to 0.94
Accuracy	0.58	0.48 to 0.68

The association between serum PCT and TLC was analysed. It was found that 31% of subjects with PCT value >0.5ng/ml had a TLC of >11,000 cells/mm^3 and 67% of subjects with PCT values ≤0.5ng/ml had a TLC of <11,000 cells/mm^3 (Table 8).

Table 8: Association between total leucocyte count and serum PCT

	Serum procalcitonin			Chi -square	P value
Total leucocyte count	≤0.5	>0.5	Total		
≤11000	24	22	46	0.0131	0.91
>11000	12	10	22		
Total	36	32	68		

ROC curve for serum procalcitonin and total leucocyte count with respect to sensitivity and specificity is presented in Figure 1 and Figure 2 respectively. Serum PCT has a greater AUC (0.81) as compared to total leucocyte count(0.59).

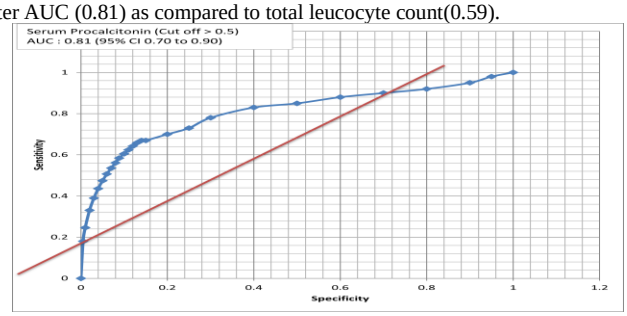

Fig 1:ROC for serum procalcitonin

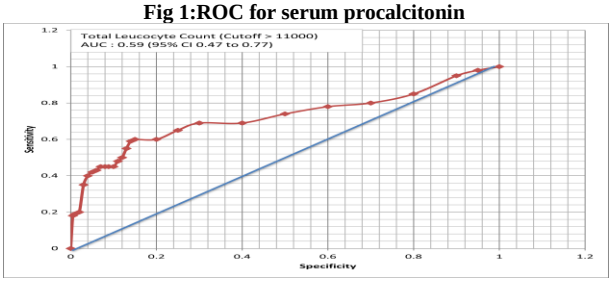

Fig 2:ROC for Total leucocyte count

Discussion

Acute febrile illnesses are extremely common and pose a diagnostic and therapeutic challenge.While viral infections are the most common cause for acute febrile illnesses, it is of utmost importance to recognize bacterial infections at the earliest. Early detection of bacterial infection leads to early initiation of antibiotic therapy, thereby preventing life threatening complications like sepsis. On the other hand irrational use of antibiotics in the absence of evidence of bacterial infection should be avoided. Therefore a highy sensitive, specific and rapidly available marker of bacterial infection, which is detectable soon after the onset of infection is the need of the hour.The C cells of the thyroid glands secrete pre-procalcitonin under normal physiological conditions. This pre-procalcitonin is then converted to procalcitonin through enzymatic cleavage. Calcitonin which is the hormone involved in serum calcium regulation is formed from procalcitonin through the action of the enzyme pro-hormone convertase. Under physiological conditions, procalcitonin has a negligible blood concentration (typically < 0.05 ng/mL). However, in patients with severe bacterial infections, serum procalcitonin concentration can be enhanced from 100-fold to 10000-fold over, due to extra-thyroid synthesis of procalcitonin in several organs, such as liver, lung, pancreas, kidney and intestine, as well as in leukocytes [14,15]. This increased extra-thyroidal production of procalcitonin is due to the stimulation of the calcitonin gene *CALC-1* by bacterial lipopolysaccharides and pro inflammatory mediators like IL-1β and TNF-α. The IFN-γ secreted during viral infections has an inhibitory effect on calcitonin m-RNA induction, thereby reducing the increase in PCT levels in response to an inflammatory stimulus13.The increased synthesis of PCT occurs within 2-4 hours of onset of severe bacterial infection, reaches peak blood levels after 6 to 8 h and persists throughout the course of the inflammatory process. The above characteristics make PCT a suitable marker of bacterial infection.This study was conducted to evaluate the role of PCT as a biomarker of bacterial infection in patients presenting with an acute febrile illness in a tertiary care centre. This study also intended to compare serum PCT with a widely used marker such as leucocytosis, with respect to their accuracy in predicting bacterial infection.

A statistically significant correlation was found between a positive sputum culture for bacteria and an elevated serum PCT levels (PCT >0.5ng/ml)in our study, thus indicating a bacterial respiratory tract infection. Similarly, a statistically significant association was found between a positive culture of lower respiratory tract secretions and an elevated serum PCT levels in a study conducted by N. Boussekey et al.[16] among 110 patients with community acquired pneumonia admitted in ICU. In a study conducted by Chang C et al.[17],in patients with acute exacerbation of COPD, a significant association was reported between a positive sputum culture and elevated PCT levels(Mean PCT =0.24ng/ml). Yanhui Zhu et al.[18] also found higher PCT(~0.42ng/ml) levels in the group which showed bacterial growth in sputum as compared to the group without growth in sputum and this association was statistically significant.

Our study found a statistically significant association between elevated PCT level and a bacteria positive urine culture. Papagiannopoulos D et al.[19] demonstrated serum PCT as a statistically significant predictor of positive urine culture result in patients with ureteral calculi. Similarly in a study conducted by Patil HV et al.[20], serum procalcitonin was elevated (range 2.12-100 ng/ml) among all patients who had a bacterial growth on urine culture. Leng et al.[21] also found a elevated PCT level with a mean value of 11.25ng/ml, among patients with urinary tract infection and the PCT levels were significantly higher for gram negative bacteria infection as compared to gram positive bacteria infection.

A statistically significant association was found between a positive blood culture and elevated serum PCT levels in our study. Similarly, in a study conducted by Webb A L et al.[22] a significant correlation was found between elevated serum PCT levels (>2ng/ml) and a positive blood culture among emergency department patients with an admission diagnosis of severe sepsis. Chirouze C et al.[23] also found a significantly higher PCT levels in bacteremic patients than in nonbacteremic patients in a study conducted among adult patients with acute febrile illness. Lee G H et al. [24] demonstrated a statistically significant correlation between elevated serum PCT levels(mean PCT=4.89ng/ml)and a positive blood culture among patients with acute pyelonephritis.

Our study found a statistically significant association between presence of bacterial infection (as indicated by a positive blood/urine/sputum culture) and an elevated serum PCT level. Thus our study found serum PCT to be a reliable predictor of bacterial infection among febrile patients. Similary, Qu J et al.[25] and Singh G et al.[26] demonstrated that serum PCT was a valuable marker of bacterial infection in febrile patients.No significant association was found between leucocytosis and bacterial infection in our study. Similarly in a study conducted by U P Dior et al. [27]among febrile parturients, leucocytosis was not found to be reliably associated with bacterial infection. P. Hausfater et al.[28] also reported that leucocyte count was not found to be independently associated with systemic bacterial infection.According to our study, at a cut-off point of 0.5ng/ml, serum procalcitonin had a sensitivity of 61%, specificity of 92%, positive predictive value of 45%, negative predictive value of 95% and an accuracy of 94% for detecting bacterial infection. Except for a lower sensitivity and positive predictive value, the above finding of our study is similar to that obtained by A A El-Azeem et al.[29] who demonstrated that serum PCT(at a cut-off of 0.5ng/ml) gave a sensitivity of 94.1%, specificity of 88.4%, positive predictive value (PPV) of 91.4%, negative predictive value (NPV) of 92% and diagnostic accuracy of 91.6% for diagnosis of respiratory tract bacterial infections. In a study conducted by Delèvaux I et al.[30] ,serum PCT >0.5ng/ml was found to be a marker of bacterial infection with a sensitivity of 65%, a specificity of 96%,and an area under the ROC curve of 0.84, for the prediction of bacterial infection. The above findings of Delevaux I et al[30] was therefore similar to that obtained in our study. According to our study leucocytosis had a sensitivity of 55%, specificity of 65% and an accuracy of 58% for predicting bacterial infection. The AUC for TLC was 0.59. Charles-Eric Lavoignet et al.[31] found a similar sensitivity of 59.4%, but a higher specificity of 82.2% and AUC (0.77)for leucocyte count >12,000 cell/mm^3 in predicting bacterial infection. In a study conducted by Wasserman et al.[32] among elderly patients, WBC count at a cut-off level of ≥11,000 cells/mm^3 had a sensitivity of 65% and specificity of 70% for detecting bacterial infection. This data is similar to that obtained in our study. Thus from the above data, serum PCT was found to be a better diagnostic marker than leucocytosis for bacterial infections. With a higher specificity and negative predictive value as compared to its sensitivity and positive predictive value, serum PCT <0.5 ng/ml can be useful in excluding bacterial infections.

Limitations of the study

The study population was small.

Conclusion

Serum PCT is a useful marker for detecting bacterial infection in patients presenting with acute febrile illness. Serum PCT<0.5ng/ml can be used to exclude bacterial infection in the acute setting. Leucocytosis is a less reliable marker than serum PCT for predicting bacterial infection

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