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Original Research Article

Serum procacitonin as a diagnostic marker of bacterial infection in febrile children

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ABSTRACT

Background: Early and accurate diagnosis of bacterial infections in children is important as the outcome is dependent on it. Various tests and biomarkers have been used for this among which serum procalcitonin shows a lot of promise. The aim of the study was to determine the role of serum procalcitonin as a diagnostic marker of bacterial infection in febrile children.
Methods: All acutely febrile children between 6 months to 12 years of age were enrolled in this prospective study. The efficacy of procalcitonin (PCT), highly sensitive C-reactive protein (hs CRP) and absolute neutrophil count (ANC) in diagnosing bacterial infections was compared.
Results: Among the three parameters, PCT has the highest area under the receiver operating characteristic curve (AUC) (O.755), followed by CRP (AUC 0.717) and ANC (AUC 0.628).
Conclusions: In summary, our study showed that PCT performs better than hs CRP and ANC in detecting bacterial infection in febrile children.

Keywords: Absolute neutrophil count, Highly sensitive C-reactive protein, Procalcitonin

INTRODUCTION

Acute febrile illness is the most common cause for seeking health care as far as children are concerned. Children do not have definite localizing signs at the time of presentation. Even if there is some localization, it is not possible to differentiate bacterial infection from viral infections based on subtle clinical signs alone.[1] The routine lab investigations on which we rely upon do not entirely differentiate serious bacterial infection from others.

In the era of evidence based medicine, definitive treatment like initiating antibiotics needs confirmatory evidence. But waiting for confirmatory reports like culture (blood, urine) is time consuming especially in sick children in whom delay of appropriate treatment can be detrimental. Added to that, most of the time physicians are faced with the difficult task of choosing among a variety of diagnostic tests that are available for the diagnosis of infections in children.[2]

The test must possess appropriate sensitivity and specificity, and the results of that particular test, when they become available, should have a certain amount of impact on the clinical management of the patient's given clinical problem. Hence, it is high time that we use a biomarker which can reliably differentiate bacterial from other infections, but with acceptable sensitivity and specificity.[3]

Till date, there has been no single biomarker discovered that offers clinicians, caring for sick children, the absolute diagnostic ability to distinguish sepsis from other inflammatory disorders or to monitor and predict its progression or response to treatment.[4,5] In this current scenario, serum procalcitonin is being used increasingly and is gaining in its application worldwide in the management of infective conditions.

All biomarkers must be used in their appropriate clinical context as adjuncts to the decision-making process. That being said, however, the use of serum PCT levels appear to be a significant improvement over CRP and ANC that has traditionally enjoyed broad historical usage.[6] PCT has been shown to improve the ability of clinicians in diagnosing, monitoring and predicting outcome in paediatric bacterial infections.

The aim of the study was to determine the role of serum procalcitonin as a diagnostic marker of bacterial infection in febrile children. The objectives of the study were to ascertain the possible diagnostic role of procalcitonin (PCT) in differentiating bacterial from viral infections in febrile children and to compare serum procalcitonin with highly sensitive 'C' reactive protein (hs CRP) and absolute neutrophil count (ANC) in order to identify the more sensitive and specific indicator of bacterial infection between the two.

METHODS

Design of the study was prospective descriptive study. The study was carried out at the Department of Paediatrics, ESIC Medical College and PGIMSR, K. K. Nagar, Chennai, India. The study period was about to 1½ years.

Study population

All acutely febrile children (temperature >100.4°F) between 6 months to 12 years of age who were admitted were enrolled in the study after informed written consent. Details of history and examination findings were recorded. The provisional diagnosis made by the admitting physician was subsequently revised after completion of investigations.

Inclusion criteria

Children >6 months with an acute febrile illness (<14 days) with a temperature of >100.4°F.

Exclusion criteria

Children who had received antibiotics within 48 hours of presentation to hospital, children with severe trauma/burns/major surgery/prolonged shock/collagen vascular disorders/vaccination in the previous 48 hours and immunocompromised children.

Investigations

Complete blood count, peripheral smear, procalcitonin, hsCRP, blood culture, dengue serology, urine routine, urine culture and chest x ray. CSF analysis was performed as and when the clinical situation mandated it.

2 ml of blood was taken by venipuncture in a heparinized tube for hsCRP and PCT estimation.

Procalcitonin (PCT)

PCT was measured using the BRAHMS-PCTQ semi quantitative assessment kit. The procalcitonin concentration range was documented as >0.5 ng/ml or <0.5 ng/ml. This kit has a sensitivity of 90-92% and a specificity of 92-98% compared to other methods of estimation.

HsCRP

The Roche/Hitachi Cobas C system was used for the estimation of HsCRP. The Roche CRP assay is based on the principle of particle enhanced immunological agglutination. Lower limit of detection 0.15 mg/L.

Total and absolute neutrophil count estimation

2 ml of blood was collected in an EDTA coated tube and analyzed using Cobas C5 part automatic cell count analyzer. The absolute neutrophil count was derived from the total leukocyte count and the percentage of neutrophils.

Statistical analysis

The results of procalcitonin, hsCRP and absolute neutrophil count were compared and analyzed using Pearson Chi square method. The statistical methods for quantitative data were represented by N, mean, standard deviation and range. For qualitative data, frequency count, N and percentage were used. To analyze data, Chi square test was used to find the association between parameters. Sensitivity, specificity and ROC curve have been calculated. The statistical analysis was done using statistical software SPSS (version 16.0). Significant at $p < 0.05$, very significant at $p < 0.01$ and highly significant at $p < 0.001$

The diagnostic accuracy of each parameter was also assessed by calculating its area under receiver operating characteristics curve (AUROCCs), which was plotted for the three main markers of infection namely procalcitonin, hsCRP and ANC. AUROCC is a validated way to measure the diagnostic accuracy of a test or the discriminatory power of a prediction rule. AUROCC values can have a range from 0.5 to 1.0 wherein a value of 0.5 would indicate a test that is of little use while a value of 1.0 would indicate a perfectly discriminatory test. In practice, a test with an AUROCC value of less than 0.75 would not be considered as contributory.

RESULTS

Group characteristics of the study population is shown is shown in Table 1.

Table 1: Group Characteristics.

Character	No. of cases (n%)
0-5 years	103 (60.1)
6-12 years	155 (39.9)
Male	150 (58.1)
Female	108 (40.3)
Fever <7 days at presentation	241(93.3)
Fever >7 days at presentation	17 (6.6)
No. of cases with procalcitonin	258 (100)
No. of cases with CRP	258 (100)
No. of cases with ANC	258 (100)
No. of cases with blood culture	152 (58.9)
No. of cases with urine culture	122 (47.2)

Analysis of data revealed that out of the total 258 cases in the study population, 56 were diagnosed as bacterial infection while 202 were viral infections thus having a 1:3 ratios (Table 2).

Table 2: Proportion of bacterial and viral infections in the study population.

Study population	Bacterial infections	Viral infections
258	56	202

Bacterial infection proven by the growth of pathogen in blood/urine/other body fluids and diseases known to have been caused by bacteria most commonly, though confirmatory evidence is not obtained, like pneumonia.

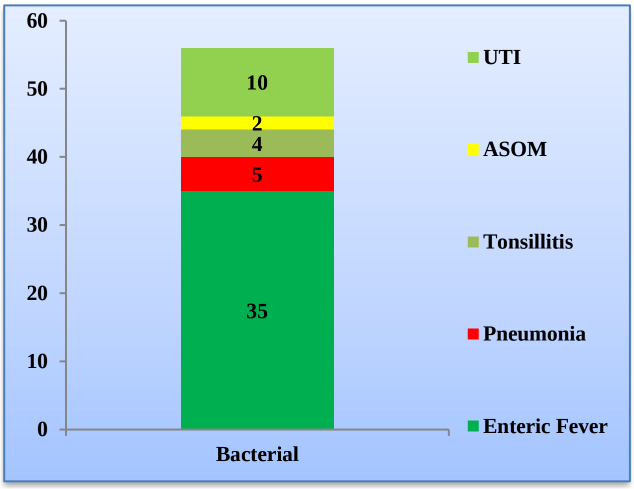

Figure 1: Bacterial infections in the study population.

Out of the total 56 cases diagnosed with bacterial infections, majority were enteric fever followed by Urinary tract infection. Other infections were very few (Figure 1). Among 22 children who defervesced after 5 days of admission, 14.9% cases had procalcitonin levels more than 0.5ng/ml. This association is statistically significant with P <0.05 (P=0.029) (Table 3).

Procalcitonin values were grouped into two, namely, <0.5 ng/ml and >0.5ng/ml. Of the total 56 cases with bacterial infections, 35 cases had serum procalcitonin values >0.5ng/ml (62.5%). Thirty-two cases with viral illness had (15.5%) procalcitonin values >0.5% (Table 3). Remaining 170 cases (84.2%) had procalcitonin values <0.5ng/ml.

Table 3: Association between day of defervescence of fever and serum procalcitonin values.

Procalcitonin (ng/ml)				Pearson Chi-square value (a), df	P-value
Fever defervescence (days)					
	≤0.5	>0.5	Total		
≤5	179 (93.7%)	57 (85.1%)	236 (91.5%)	4.75, 1	0.029*
>5	12 (6.3%)	10 (14.9%)	22 (8.5%)		
Total	191 (100%)	67 (100%)	258 (100%)		

This indicates a strong association between high serum procalcitonin values and bacterial infections (p<0.0001). The P value for this observation is <0.0001* which is highly significant i.e. there is a strong association between culture positive cases and PCT >0.5ng/ml.

Of the total 191 cases with PCT <0.5ng/ml, 171 cases had culture negativity and 12 cases had culture positivity who turned out to be enteric fever (Table 4). A total of 8 urine culture positive cases (11.9%) had PCT values >0.5ng/ml and only one case has the PCT <0.5. Of the total of 249 cases with negative urine culture, 190 cases (99.5%) had PCT <0.5ng/ml and only 59 cases had PCT (88.9%). As per the pearson chi square test, the P value is <0.0001*** and this association is highly significant statistically (Table 5).

The sensitivity and specificity of this test is 62.5% and 84.16% according to Wilson's test within 95% confidence interval. The positive predictive value, which rules in an infection, is 52.24% but the negative predictive value, which rules out an infection, is 89% (Table 6).

Of the 56 cases with bacterial infection, only 48 cases had CRP values of more than 10mg/l (85.7%) and the remaining 8 cases had CRP values of less than 10mg/l (14.3%). Of the total of 202 cases with viral infection, 125 cases had raised CRP values (61.9%) and the rest had CRP values less than 10mg/l. Thus, CRP is very sensitive in detecting bacterial infections, with p value <0.001 which is highly significant (Table 7 and 8).

As per Pearson-Chi square test, the sensitivity of CRP in detecting bacterial infection is 85.71% and the cut off limit is 10mg/l and specificity is 38.12%. Positive predictive value is 27.75% and the negative predictive value is 90.59 % as per Wilson's method of analysis

Table 4: Association between blood C/S and serum procalcitonin.

	Procalcitonin(ng/ml)			Pearson chi-square value (b), df	P- value
Blood c/s	≤0.5	>0.5	**Total**	22.864,1	<0.0001***
Positive	12 (6.3%)	19 (28.4%)	31 (12%)		
Negative	179 (93.7%)	48 (71.6%)	227 (88%)		
Total	191 (100%)	67 (100%)	258 (100%)		

Table 5: Association between urine c/s and serum procalcitonin.

	Procalcitonin(ng/ml)			Chi square (continuity correction) (b) value, df	P- value
Urine c/s	≤0.5	>0.5	Total	15.962,1	<0.0001***
Positive	1 (0.5%)	8 (11.9%)	9 (3.5%)		
Negative	190 (99.5%)	59 (88.1%)	249 (96.5%)		
Total	191 (100%)	67 (100%)	258 (100%)		

Table 6: Evaluation of serum procalcitonin as a diagnostic test.

Parameter	Estimate	Lower- upper 95% CIs	Method
Sensitivity	62.50%	(49.41, 73.99)	Wilson score
Specificity	84.16%	(78.49, 88.55)	
Positive predictive value	52.24%	(40.48, 63.75)	
Negative predictive value	89.01%	(83.78, 92.7)	
Diagnostic accuracy	79.46%	(74.11, 83.94)	

Table 7: Association between hs CRP and final diagnosis.

	Final diagnosis			Pearson chi-square value, df	P- value
hs CRP mg/L	Bacterial illness	Viral illness	Total	11.273(b), 1	<0.001**
≤10	8 (14.3%)	77 (38.1%)	85(32.9%)		
>10	48(85.7%)	125(61.9%)	173 (67.1%)		
Total	56 (100%)	202 (100%)	258 (100%)		

Table 8: Evaluation of hs CRP as a diagnostic test.

Parameter	Estimate	Lower - upper 95% CIs	Method
Sensitivity	85.71%	(74.26, 92.58)	Wilson score
Specificity	38.12%	(31.7, 44.98)	
Positive predictive value(PPV)	27.75%	(21.61, 34.85)	
Negative predictive value (NPV)	90.59%	(82.51, 95.15)	
Diagnostic accuracy	48.45%	(42.42, 54.53)	

Table 9: Association between absolute neutrophil count (ANC) and final diagnosis.

ANC cells/mm^3	Final Diagnosis			Pearson Chi-Square value, df	P-value
	Bacterial infection	Viral infection	Total		
≤5000	27(48.2%)	135 (66.8%)	162(62.8%)	6.504(b), 1	<0.011*
>5000	29(51.8%)	67(33.2%)	96 (37.2%)		
Total	56 (100%)	202(100%)	258 (100%)		

The diagnostic accuracy of CRP in detecting bacterial infection is 48.45%. Absolute neutrophil count is not a very sensitive or specific marker of bacterial infection in children because of age dependent variation in the leucocyte count in children. In present study, of the total of 258 children, 135 children (66.8%) who had viral infections had ANC of <5000 cells/mm3 (Table 9).

Table 10: Association between absolute neutrophil count (ANC) and procalcitonin.

ANC cells/mm^3	Procalcitonin ng/ml		
	≤0.5	>0.5	Total
≤5000	132 (69.1%)	30 (44.8%)	162 (62.8%)
>5000	59 (30.9%)	37 (55.2%)	96 (37.2%)
Total	191 (100.0%)	67 (100.0%)	258 (100.0%)

Table 11: Evaluation of ANC as a diagnostic test.

Parameter	Estimate	Lower- upper 95% CIs	Method
Sensitivity	51.79%	(39.01, 64.33)	Wilson Score
Specificity	30.93%	(22.6, 40.7)	
Positive predictive value	30.21%	(21.93, 40.01)	
Negative predictive value	52.63%	(39.92, 65.01)	
Diagnostic accuracy	38.56%	(31.22, 46.47)	

On analysing the correlation between PCT values and ANC, it was found that 55.2% of the children with PCT >0.5ng/ml have ANC value of >5000 cells/mm^3 and 69.1% children with ANC <5000cells/mm^3 have PCT value of <0.5ng/ml (Table 10).

Table 12: Determination of area under curve (AUC) with ROC.

Area Under the Curve (AUC)	
Test Result Variable(s)	Area
ANC	0.628
HS CRP	0.717
PCT	0.755

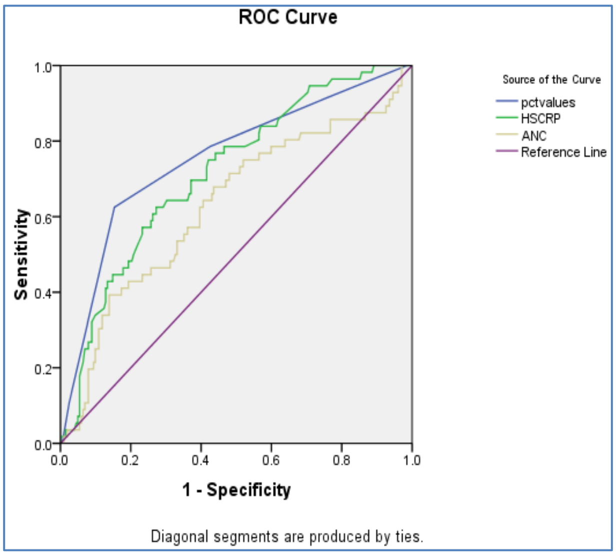

Figure 2: Receiver operating characteristic (ROC) curve for PCT, hs CRP and ANC.

As per pearson-chi square test, the sensitivity of ANC in detecting bacterial infection is 51.79% and the specificity is 30.93%. Positive predictive value is 30.21% only and the negative predictive value is 52.63% as per Wilson's method of analysis.

The diagnostic accuracy of ANC in detecting bacterial infection is only 38.56% (Table 11). ROC curve for procalcitonin, ANC and HS CRP with respect to sensitivity and specificity (Figure 2). Procalcitonin has the greater AUC (0.755) as compared to hs CRP (0.717) and ANC (0.628) (Table 12). Comparison of characteristics of PCT, Hs CRP and ANC are given in Table 13.

Table 13: Comparison of characteristics of PCT, Hs CRP and ANC.

Parameter	PCT	Hs CRP	ANC
Sensitivity	62.50%	85.71%	51.79%
Specificity	84.16%	38.12%	30.93%
PPV	52.24%	27.75%	30.21%
NPV	89.01%	90.59%	52.63%
Diagnostic accuracy	79.46%	48.45%	38.56%
Odds ratio	8.854	3.696	0.4809

DISCUSSION

Fever is a very common problem encountered in paediatric practice. While a majority of them are viral, it is important to recognize bacterial infections early, especially in children less than 3 years of age, as they have the potential to evolve into serious bacterial infections like sepsis and meningitis. Much research has gone into finding the ideal marker that would pinpoint bacterial infections from amidst many viral infections.

The ideal marker would be one with very high sensitivity and specificity, one which should rise very rapidly after the onset of the infection and most of all, should be easily available and not too expensive.

From amongst the various bio markers PCT, hs CRP and ANC have been studied rather frequently with varying reports on their reliability in predicting bacterial infections. This study was designed to compare these three parameters among febrile children, presenting to the OP/IP as to their accuracy in predicting bacterial infections.

In this study, majority of the children admitted had viral infections (202 cases out of a total of 258 cases, 78%). The remaining 56 cases had various bacterial infections namely urinary tract infection (UTI), enteric fever (both groups had bacterial isolates on culture), pneumonia and acute suppurative otitis media. The ratio of bacterial to viral illnesses was approximately 1:3 in present study population. Among the bacterial infections, we noted a higher proportion of enteric fever (35 cases), followed by UTI (10 cases).

Procalcitonin (PCT)

Serum procalcitonin level was >0.5 ng/ml in 62.5% of children with bacterial infections, whereas only 15.8% of children diagnosed with a viral infection had a PCT >0.5 ng/ml. Eighty four percent of children who had a PCT <0.5 ng/ml were diagnosed with a viral illness. It was inferred that the true positive values of PCT are more in bacterial infections. PCT has a good predictive value for bacterial infections and as per the Pearson Chi square test, this is statistically significant (P <0.0001, Table 11). This result is similar to those obtained by Simon et al and Yo et al in their meta-analysis.[7]

The sensitivity and specificity of procalcitonin in detecting bacterial infections at a cut off of >0.5 ng/ml are 62.5 and 84.1 respectively. This is similar to the results obtained by Andreola et al.[8] In present study, with the above sensitivity and specificity, the positive predictive value (PPV) of PCT is 52.4% and the negative predictive value (NPV) is 89.01%. The diagnostic odds ratio for PCT is 8.854 (4.577-17.13). The positive likelihood ratio of PCT in predicting bacterial illness is 3.945 (3.588-4.338) and the negative likelihood ratio is 0.4456 (0.405-0.4902).

Present study has remarkable similarities to the one done by Gendrel et al in that we too recruited all children less than 12 years of age, our proportions of children with bacterial and viral infections were about the same, PCT performed much better than hs CRP as a diagnostic tool to rule out bacterial infections and lastly, all recruited patients were hospitalised.[9]

Thus, in present study, PCT has a diagnostic accuracy of 79.46% in predicting bacterial infections in febrile children. Hence, PCT <0.5 ng/ml, is the best marker in reasonably excluding bacterial infections. PCT has a higher NPV (89%) than PPV (52%), hence it can be used to exclude or 'rule out' serious bacterial infections in children.

On comparing the characteristics of culture proven bacterial infection with PCT values one can infer that PCT can be safely used in the exclusion of septicaemia. Of the total 31 blood culture positive cases, 19 (61.3%) cases had PCT values >0.5 ng/ml while in 227 cases with sterile blood culture, 179 cases (93.7%) had PCT values <0.5 ng/ml. The association is statistically significant with p <0.05 as per Pearson Chi square test.

Among the loco-regional infections i.e. UTI, it was found that PCT had a significant predictive value. Literature review shows that the rise in PCT can be used to predict upper urinary tract involvement. Leroy et al found that PCT was found to demonstrate a reasonable diagnostic accuracy for both acute pyelonephritis and renal scarring and was more accurate than either hs CRP or WBC count.[10]

The rise of PCT correlates well with UTI with or without upper urinary tract involvement. Hence, it can be concluded that UTI can be mostly excluded if PCT is <0.5 ng/ml. The Pearson Chi square correlation test for PCT in diagnosing UTI is highly significant (p<0.0001).

HsCRP

HsCRP had a cut off level of 10 ng/ml in current study for the presumptive diagnosis of bacterial infection. This low value was taken as cut off because the kit used had a very high sensitivity for detecting values as low as 0.2 ng/ml. With this cut off, of the total 173 children with values more than 10 ng/ml, 48 had bacterial infections and 125 had viral illnesses.

The sensitivity of hsCRP in detecting bacterial infection is 85.71% and specificity is 38.12%. The low specificity of CRP in present study can be because of the lower cut off used for the diagnosis and the fact that CRP was evaluated early in the course of the disease probably well before the values actually started to peak.

In a study by Olaciregui et al, a higher cut off was used i.e. 30 ng/ml. The sensitivity of the test was 63.4% and specificity was 84.2%. This study was reviewed as part of a meta-analysis by Yo et al wherein they found the mean AOC for CRP to be 0.84 which correlates with present study in which the AOC for CRP is 0.717.[8,11]

The positive predictive value of CRP in present study is 27.75% which is less than that for PCT. The negative predictive value of CRP is high i.e. 90.5% and is comparable to PCT i.e. 89%.

Thus, it can be concluded that CRP is inferior to PCT in diagnosing or 'ruling in' bacterial infection. The positive likelihood ratio for CRP is 1.385 (1.354-1.417) and the negative likelihood ratio is 0.374 (0.2815-0.499) which are inferior to those obtained with PCT. The diagnostic odds ratio comes to 3.696 for CRP.

Absolute neutrophil count (ANC)

Moving to the third marker in present study, namely, ANC, statistical analysis shows that it does not correlate well with bacterial infections. Based on group statistics, the mean value of ANC in the cases with bacterial illness is 6135 cells, a standard deviation of 3549 cells and a standard error of 474 cells.

ANC alone is not a reliable indicator for diagnosing bacterial infections. In our study, the sensitivity of ANC in detecting bacterial infections was found to be 51.79% and the specificity, 30.93%. Thus, ANC is inferior to both PCT and hs CRP in detecting bacterial infections in febrile children.

The positive predictive value of ANC is 30.21% and the negative predictive value is 52.63% with a diagnostic accuracy of 38.56%. This is in accordance with the study conducted by Thayyil et al.[12] They found a sensitivity of 50% and a specificity of 53.1% in diagnosing bacterial infection. In this study, the positive likelihood ratio of ANC in detecting bacterial infection is 0.7497 (0.6837-0.8221) and the negative likelihood ratio is 1.559 (1.253-1.94) which is third after PCT and hs CRP. The diagnostic accuracy of ANC is thus 38.56% which is much less than that for PCT and CRP. This was further supported by the area under the curve being the least for ANC (0.628) which makes it a poor test. These findings are similar to those reported by Andreola et al.[9]

The accuracy of the diagnostic test is to be evaluated with the positive predictive of that test and the area under curve given by the receiver operating characteristic curve. The positive predictive value of procalcitonin is higher compared to hs CRP and absolute neutrophil count in predicting bacterial infection. Thus, procalcitonin when used in isolation can be relied upon to diagnose bacterial infections. This is in accordance with several studies available in literature.

CRP at a cut off of 10 mg/l is inferior to procalcitonin in detecting bacterial infection in this study. The results of hs CRP have to be interpreted in accordance with the clinical condition of the patient. ANC cannot be reliably used in the diagnosis of bacterial infection in isolation.

Likewise, among all the three parameters, PCT has the highest AUC (O.755), followed by CRP (AUC 0.717) and ANC (AUC 0.628). This is in accordance with the review study done by Yo et al in which PCT had the highest AUC compared to CRP and total leucocyte count.

To conclude, in present study PCT emerges as the single best diagnostic marker in diagnosing bacterial illness in febrile children. PCT is a more specific rather than sensitive marker in diagnosing bacterial infection. Therefore, PCT can be used to exclude possible serious bacterial infections when the values are <0.5 ng/dl and when used as a single parameter. In the emergency department, PCT can be used either singly or in combination with hs CRP in diagnosing bacterial infections. Having said that, since the costs associated with missing serious bacterial infection is high hence it is recommended that PCT should not be used in isolation but along with other biomarkers. Many clinical trials have shown a high cost benefit ratio when PCT was used in the management algorithm. In summary, present study showed that PCT performs better than hs CRP and ANC in detecting bacterial infection. Considering that the sensitivity is poor and the specificity is acceptable, values <0.5 ng/ml can be used to rule out bacterial infections. Values of PCT >0.5 ng/ml however are not confirmatory evidence of bacterial infections. At this point, available literature does not show how to combine PCT with clinical data to improve the overall diagnostic performance. For this, larger studies are needed.

CONCLUSION

Procalcitonin may be useful, as a single test, in identifying bacterial infections in febrile children. Bacterial infections may be reasonably excluded if PCT values are <0.5 ng/ml. Hs CRP is comparable to PCT in identifying bacterial infections. ANC is less useful in identifying bacterial infections.

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