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Original Research Article

Thrombocytosis as an additional predictor of serious bacterial infection in febrile young infants

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ABSTRACT

Background: To estimate the incidence of Reactive Thrombocytosis among febrile young infants and to assess the utility of platelet count as a potential predictor of Serious bacterial infection (SBI).
Methods: This study was conducted as a prospective study between January 2014 to September 2015 at the tertiary care pediatric unit, Alappuzha, India. The participants were all infants 30 to 89 days of age, admitted with rectal temperature >38°C. The results of the sepsis evaluation on admission were recorded. SBI included cases of occult bacteremia, urinary tract infection, bacterial meningitis, pneumonia, bacterial gastroenteritis and infections of the soft tissues and bones.
Results: Of the 120 infants studied, 24 (28%) had SBI. Platelet count was significantly higher in infants with SBI compared to those without {Platelet count ≥ 4.5lakhs /mm3 in SBI (70.3%) vs. Non SBI (30.2%). Mean platelet count 4.82±1.4 in SBI vs. 3.9±1.2 in non SBI which was statistically significant ($p<0.05$). Thrombocytosis had moderate ability in predicting SBI (Area under curve area under the curve: 0.720). The combination of platelet count ≥450,000/mm3, WBC ≥15,000/mm3, C-reactive protein ≥1 mg/dl, pyuria ≥5 White blood cells (WBC) per High power field (HPF) and erythrocyte sedimentation rate (ESR) >30mm/hr resulted in identification of all infants with SBI.
Conclusions: Thrombocytosis in combination with leukocytosis, elevated C-reactive protein, ESR, and pyuria, may help in early recognition of febrile young infants at risk for SBI.

Keywords: Diagnosis, Fever, Infants, Serious bacterial infection, Thrombocytosis

INTRODUCTION

Febrile infants present a management challenge as many of these have no identifiable source of infection on clinical examination at the time of admission.[1,2] Serious Bacterial Infection (SBI) accounts for about 20-25% of cases in febrile infants without an apparent source of infection.[3] Serious bacterial infection includes bacterial pneumonia, bacterial meningitis, urinary tract infection (UTI), bacterial gastroenteritis, sepsis, bacteraemia and bone and soft tissue infections.[4,5]

There is no single reliable predictor to identify serious bacterial infection in infant population.[6] The screening criteria for prediction of SBI in 1month to 3 months old infants include total count>15000/mm^3,WBC count>10/hpf in centrifuged urine sample, CSF TC>8 cells/hpf or gram stain positive and chest X-ray showing infiltrate.[7] Laboratory markers which have been used to predict SBI include raised white blood cell (WBC) counts, C-reactive protein (CRP), procalcitonin (PCT) and even interleukin-6 levels.[2] WBC count is easily available and used widely as a predictor of SBI. But, it does not compare well with more recent markers like CRP and PCT. The present automated hematology

analyzers give results of platelet counts as a part of the routine hematology work-up, with a dependable accuracy.

Thrombocytosis (increase in platelet counts >4.5 lakhs/μL) have been documented in 3% to 15% of pediatric patients.[8] Secondary thrombocytosis in childhood is due to increased thrombopoiesis as a reactive process. Acute infection, chronic inflammation, childhood malignancies, iron deficiency anemia and chronic hemolytic states are the common causes of secondary thrombocytosis. Infections of the respiratory, urinary and gastrointestinal tract and the bones and meninges are the most common causes of reactive thrombocytosis. However, the platelet count has not been evaluated as a predictor of SBI among febrile infants. The study becomes significant in the emergency services where quick diagnosis is essential and in developing countries where cost constraints do not permit expensive investigative tools.

The objective of our study was to estimate the incidence of reactive thrombocytosis in febrile young infants, especially in those with bacterial infections, and assess the value of platelet count as a potential predictor of SBI.

METHODS

We followed the cases of all infants aged 1 month to 3 months, admitted to Government T. D Medical College Alappuzha a tertiary care pediatric hospital in Kerala, South India from January 2014 to September 2015 for investigation of fever (defined as rectal temperature >38°C/100.4^{0}F. Infants with anemia, those on oral iron or corticosteroids, those who had received antibiotics or vaccination within 48 hours were excluded.

All patients who fulfilled the inclusion criteria underwent sepsis evaluation including WBC count, platelet count, blood culture, urine microscopy and culture and serum CRP levels. Lumbar puncture for Cerebrospinal fluid (CSF) analysis and culture, pleural tap for pleural fluid analysis as well as stool culture and chest radiographs, were obtained at the discretion of the attending pediatrician.

The WBC count with differential and the platelet count were quantified using automated laboratory equipment (Sysmex KX 21). Blood cultures were monitored by an automated system (BacT/ALERT 3D). Urine was obtained by suprapubic aspiration or urethral catheterization using a sterile technique. The WBC in the urine were quantified by standard microscopic examination and expressed as WBC >5 per high power field (HPF) in centrifuged sample.[9] The urine, CSF, pleural and stool cultures were monitored using standard laboratory techniques. Serious bacterial infection is defined as bacteremia, UTI, bacterial meningitis, *pneumonia*, bacterial gastroenteritis and infection of bones or soft tissue. Isolates such as Staphylococcus epidermidis or Streptococcus viridans in the blood cultures were considered as contaminants isolated from 2 consecutive cultures. UTI was the diagnosis if a single known pathogen growth >/=1000 colony forming units (cfu)/ml of urine obtained by suprapubic needle aspiration or>/=100,000cfu/ml of urine obtained by urethral catheterization. The presence of a focal infiltrate on chest radiograph with clinical findings was diagnosed as pneumonia.[10] Bacterial meningitis was diagnosed by CSF analysis if a positive gram stain or culture, or all of WBC >100/mm^3, polymorphonuclear lymphocytes >80, protein >200mg/dl, glucose <40mg/dl or ratio of CSF/blood glucose<0.4.[11] Those getting diagnosed as serious bacterial infection were one group and those without were categorized as non SBI group. Data entered in MS excel and was analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 16. Data are expressed in its frequency and percentage. Non-parametric data are expressed as mean with standard deviation. Chi square test was used as the non parametric test to elucidate the association and comparison between different parameters. The quantitative variables were compared by independent student t test. For all statistical evaluations, a two-tailed probability of value, <0.05 was considered significant. The overall performance of individual parameters in predicting SBI was assessed by receiver operating characteristic (ROC) curve analyses and area under the curve (AUC) comparisons, using the statistical software MedCalc 8.1 (MedCalc, Mariakerke, Belgium). The study was approved by the ethics committee of the Government T.D Medical College Alappuzha, India.

RESULTS

During the study period, 164 infants 29 to 89 days of age, were admitted for investigation of fever >38°C. 44 patients were excluded out of 164. 18 were anemic, 7 were on oral iron 3 had recent vaccination history, and 16 were treated with antibiotics after the onset of fever. Among 120 infants, 64% had respiratory symptoms, followed by CNS symptoms in 13%, urinary symptoms in 6.7%, gastrointestinal symptoms in 5%. 5.3% of the study population had no focus of infection at presentation while both respiratory and CNS symptoms were present in 6% of the study subjects.

Of the 120 infants studied, 34 (28.3%) had SBI. Of these, 16 patients had pneumonia, UTI was documented in 7 patients. Sepsis was diagnosed in 4 patients. (1 with *Streptococcus pneumoniae*, 2 with Group B *Streptococcus*, 1 with *Staphylococcus aureus*), 6 were diagnosed with bacterial meningitis (1 was *Streptococcus pneumonia* others were culture negative) and 1 case of bacterial gastroenteritis (*Shigellla dysenteriae*). One infant had concurrent positive blood and CSF cultures for *Streptococcus pneumonia*. The remaining 86 infants (71.7%) were diagnosed as Non-SBI. Urine culture was positive in 7 cases of UTI, the organisms being *E. coli* in 5 cases multidrug resistant *E. coli* in 1 case and

Klebsiella in one case. There were 16 cases with bacterial pneumonia. None of them had a positive blood culture (Table 1).

Table 1: Percentage of SBI and non- SBI in the study population.

Diagnosis	Frequency	Percent
Meningitis	6	5
UTI	7	5.8
Pneumonia	16	13.3
Bacterial Gastroenteritis	1	0.8
Sepsis	4	3.3
Non SBI/Viral Illness	86	71.7
Total	**120**	**100**

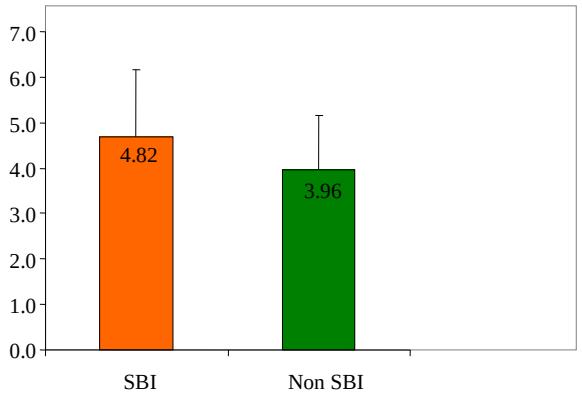
Table 2: Clinical and laboratory characteristics of the SBI and non-SBI groups.

Variables	SBI	Non SBI	p value
Temperature (°F)	38.6±0.5	38.3±0.7	<0.05
Duration of Fever (Hrs)	50.3± 22	51.6±21.5	>0.05
Total Leukocyte count (000's/mm^3)	15,910±6156	12316±4597	<0.01
Total Platelet Count (lakh/mm^3)	4.82± 1.4	3.96 ± 1.2	<0.01
CRP (mg/dl)	1.48±1.7	0.587±1.09	<0.01
Urine Pus cells per HPF	4.4± 6	1.75±1	<0.01
ESR	27.26± 17.1	15.45±13.02	<0.001

The Mean ±1 SD of the different variables

Age, gender and residence were non-significant across both SBI and Non SBI groups. p-value non-significant (p>0.05). Thrombocytosis (Platelet count more than 4.5 lakh/mm3) was significantly higher in SBI, 24 out of 34 vs. Non SBI 26 out of 86 (p<0.05), CRP and Total leucocyte count (TLC) was significantly high on SBI than Non SBI (p<0.05). Temperature, TLC and total platelet count was higher in SBI group than in Non SBI (P<0.05) (Table 2).

The incidence of thrombocytosis in SBI was 70.6%vs non-SBI which was 30.2%. Thrombocytosis was present in 71.4% cases of UTI and 87.5% cases of bacterial pneumonia and 50% cases of meningitis. Only 30.2% cases of non-SBI had reactive thrombocytosis. The mean platelet count in SBI was 4.82±1.4 lakhs/mm^3 vs 3.9±1.2 lakhs/mm^3 in non-SBI (p<0.001) (Figure 1). The mean platelet count was highest in pneumonia (Table 3).



The mean platelet count in SBI was 4.82±1.4lakhs/mm^3 vs 3.9 ± 1.2lakhs/mm^3 in non-SBI (p<0.001)

Figure 1: Mean platelet count in SBI and non-SBI groups.

Table 3: The mean platelet count in lakhs/mm3 in SBI subgroups and Non SBI.

Diagnosis	Mean±1SD
Pneumonia	5.51±1.49
Bacterial meningitis	4.33±1.06
UTI (urinary tract infection)	4.36 ± 1.10
Sepsis	3.64±1.57
Bacterial gastroenteritis	4.66
Non -SBI	3.9±1.2

According to test characteristics for different platelet count thresholds we came to know that platelet count of ≥4.5 lakh/mm3 carried an accuracy of 70.2 %, sensitivity 70.59%, specificity 69.77%, Negative predictive value (NPV) 85.7% and Positive predictive value (PPV) 48% than any other platelet threshold. So, the platelet count of ≥4.5 lakh/mm3 had a differential tendency to pick up the maximum patients out of SBI and lesser patients out of Non SBI.

Table 4: Test characteristics of different platelet threshold.

Platelet count (Lakhs/mm^3)	N (34)	Sensitivity (%)	Specificity (%)	PPV%	NPV%	Accuracy (%)	LR +	LR-
>4	**25**	**73**	**63**	**43.9**	**85.7**	**62.5**	**1.97**	**0.43**
>4.5	24	70.59	69.77	48	85.7	70	2.34	0.42
>5	15	43.30	88.9	60	80	75.8	3.9	0.64
>6	4	13.30	95.9	57.1	96.5	72.5	3.24	0.90

PPV: positive predictive value; NPV: negative predictive value; LR + likelihood ratio for positive test; LR – likelihood ratio for negative test

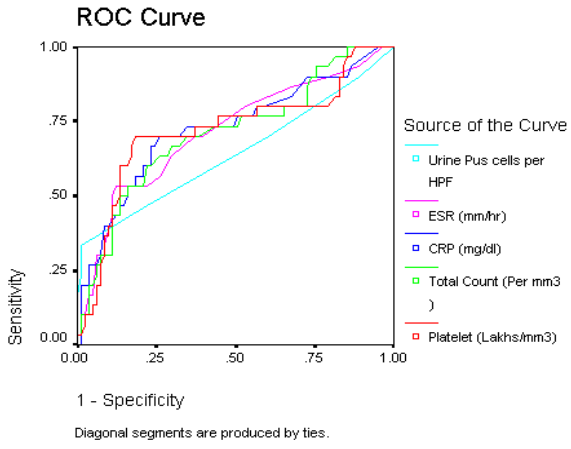
At this decision threshold 10 infants with SBI (29% of SBIs) were classified as low risk and 26 infants without SBI (30.2%) were falsely classified as high risk (Negative LR 0.42, positive LR 2.34). At higher platelet count thresholds, the sensitivity of the test was so low to recommend as a cut off (Table 4).

The platelet count of ≥4.5 lakhs alone identified 24 out of 34 infants with SBI; while total count ≥15,000/mm^3 identified 16 of them and CRP>1 mg/dl 18 of them. A combined high-risk criterion of two tests (≥15,000/mm^3 for WBC and ≥4.5 lakhs for platelet), did not pick up more SBI than platelet count alone did; while 76 infants were falsely classified as high-risk out of non SBI. Further combination of platelet count ≥4.5 lakhs, WBC ≥15000/mm^3, pyuria ≥5 WBC /HPF, and CRP ≥1 mg/dl, ESR >30 mm/hour led to the identification of all 34 infants with SBI. Thus, the combination of five tests may help in early prediction of serious bacterial infection in febrile young patients (Table 5).

Table 5: Test characteristics for different decision thresholds.

Investigation	Value	SBI (n=34)	Non SBI (n=86)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Platelet count	≥4.5lakhs/mm^3	24	26	70.6	69.8	48.0	85.7	70.0
Total count	≥15000/mm^3	16	17	47.1	80.2	48.5	79.3	70.8
CRP	≥1mg/dl	18	11	52.9	87.2	62.1	82.4	77.5
Urine WBC	≥5/HPF	13	6	38.2	93.1	68.4	79.2	77.5
ESR	≥30 mm/hr	17	12	50	86	58.6	81.3	75.8
Plt count +CRP		24	76	70.5	45.3	33.8	79.59	52.5
Plt count+TC		24	76	70.59	11.63	24	50	28.33
Plt +TC+Pyuria		31	83	91	3.4	27	50	28.33
Plt+TC+Pyuria+ ESR		32	85	94	1.16	27	33	27.5
Plt+TC+CRP+ ESR+Pyuria		34	85	100	1.16	28.57	100	29.7

The incidence of SBI was 28% (34/120 infants); SBI: serious bacterial infection; PPV: positive predictive value; NPV: negative predictive value



Receiver operating characteristics curve for PLT, WBC, CRP and pyuria predicting serious bacterial infection in febrile young infants. Area under the curve (AUC) for PLT 0.720; for WBC 0.711; for CRP 0.725; for ESR 0.711 and for pyuria 0.642. No statistically significant differences were found between the AUCs of the different parameters. WBC white blood count; PLT platelets count; CRP C reactive protein

Figure 2: ROC curve for different parameters.

Receiver operating characteristics curve (ROC) was plotted for platelet (PLT), WBC, CRP, ESR and pyuria predicting serious bacterial infection in febrile young infants. Area under the curve (AUC) for PLT was 0.720; for WBC 0.711; for CRP 0.725 and for pyuria was 0.642; for ESR 0.711. The AUC for pyuria was lowest for pyuria. No statistically significant differences were found between the AUCs of the parameters, thus PLT with 0.720 AUC carry moderate ability in predicting patients with SBI (Figure 2).

DISCUSSION

In this study, platelet count was significantly higher in febrile infants with documented bacterial infection, particularly in those with UTI and pneumonia. However, due to a substantial overlap, it was difficult to identify a threshold value that could clearly differentiate infants with SBI from other febrile infants. According to test characteristics for different platelet count thresholds we came to know that platelet count of ≥4.5 lakh/mm^3 had a good accuracy in identifying infants with SBI with less false positive and false negative results.

The incidence of SBI in our study population was 28.3% and this was higher than the reported incidence of 20 - 25%.[3] This can be explained by the fact that the study was conducted in a tertiary care pediatric unit. The mean

temperature was higher in SBI group when compared to non-SBI ($p < 0.05$). The parameters like platelet count, WBC Count, CRP, ESR and urine WBC >5/hpf were found to be significantly higher in SBI group when compared to non SBI group ($p<0.01$). The platelet count was second only to CRP when the accuracy of test and AUC were taken into consideration. The overall ability of platelet count to identify infants with SBI was moderate (AUC 0.720), but comparable to the other parameters.

It is a known fact that platelets behave like an acute phase reactant. During an infection interleukin -6 and tumour necrosis factor-alpha stimulate megakaryopoiesis both directly and by stimulating hepatic thrombopoietin.[12,13] So the role of reactive thrombocytosis, especially in the immature immune system of young infants, needs to be further explored. Thrombocytosis secondary to anemia is a matter of concern in this age group.[14-16] But our study was done after excluding anemic infants and platelet count was still significantly higher in infants with SBI compared to those without. Reactive thrombocytosis in combination with WBC, CRP, ESR and pyuria seems to be a useful tool that could help clinician to decide further investigation and follow-up strategy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of the College

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