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Thrombocytosis as a Predictor of Serious Bacterial Infection in Febrile Infants

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ABSTRACT

Background: Most of the febrile infants <90 days old will have no more than a mild viral infection but there is a substantial minority that will be diagnosed as having serious bacterial infection at a reported prevalence of 10–14%. A simple, readily available, inexpensive diagnostic marker that yields results quickly and also accurately identifies bacterial infections in febrile infants would be of great value in management of these infants. This study aims to assess the role of thrombocytosis in predicting serious bacterial infection in young febrile infants beyond neonatal period.

Methods: A hospital based cross-sectional observational study was conducted from May 2016 to April 2017 on 76 febrile infants of age group 29-90 days in Kanti Children's Hospital.

Results: The incidence of serious bacterial infection was found 43 (56.6%). Thrombocytosis, elevated C-reactive protein and pyuria were significantly higher in serious bacterial infection cases (p value <0.05). Thrombocytosis alone had the sensitivity of only 53.5%, but had specificity of 90.9%. Elevated C-reactive protein had the best sensitivity (81.4%). Combination of leukocytosis, elevated C-reactive protein, pyuria and thrombocytosis had better sensitivity (93.0%) than these parameters alone. The overall ability of platelet count to identify infants with SBI was only moderate (AUC: 0.722). Elevated C-reactive protein was found to have better ability to identify infants with serious bacterial infection (AUC: 0.846).

Conclusions: Thrombocytosis is a common finding in young infants diagnosed with serious bacterial infection. It has however, moderate ability in identifying infants with serious bacterial infection. Combining thrombocytosis with elevated C-reactive protein, leukocytosis and pyuria has better sensitivity in diagnosing serious bacterial infection than these individual parameters alone. Hence, combining these parameters may help in early prediction of febrile young infants at risk of serious bacterial infection.

Keywords: Febrile young infants; serious bacterial infection; thrombocytosis.

INTRODUCTION

Fever of acute onset without localizing signs is a common diagnostic dilemma in children < 36 months. Its etiology and evaluation depends on the age of the child. Traditionally, 3 age groups are considered: neonates, infants 1 month to 3 months of age, and children 3 months to 3 years of age.[1]

Prevalence of Serious bacterial infection (SBI) in young infants below 90 days old ranges from 10% to 14%.[2] Although the majority of them have minor viral illness, it is important to identify SBI, as the management differs. As physical examination is often unrevealing and the results of the cultures are not immediately available for definitive diagnosis, risk stratification for severity of illness is based on history, and readily available laboratory testing. Complete blood count, absolute neutrophil count, C-reactive protein (CRP,) urinalysis and more recently procalcitonin and interleukin-6 have been evaluated as potential predictors of SBI.[3] Recently, thrombocytosis is extensively being evaluated as a potential marker of SBI.[4-8] Furthermore, a simpler, cheaper and readily available test like platelet count as a biomarker of SBI attains a great value in health centers of developing country like Nepal.

METHODS

A hospital based cross-sectional observational study was conducted from May 2016 to April 2017 after taking IRC clearance. Young febrile infants between 29 days to 90 days with axillary temperature >98.6^0 F,[9] who presented to emergency department, outpatient department and those who were admitted in wards of Kanti Children's Hospital were enrolled in the study after excluding secondary causes of thrombocytosis viz diagnosed case of primary thrombocytosis, hemorrhage, tissue damage (postsurgical, burn, trauma, fracture). Pneumonia, urinary tract infection (UTI), definite sepsis (positive blood culture), probable sepsis, probable meningitis and definite meningitis(positive cerebrospinal fluid culture) were considered as SBI.[1] Venous blood sample

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was sent to the laboratory for Complete blood count (CBC), blood culture and C-reactive protein (CRP). CBC was performed by Automated Coulter counter machine; ErbaLachema. Qualitative CRP and chest X-ray was done. Urine was collected by urine collection bag under aseptic conditions sent for routine and microscopy examinations and culture. Lumbar puncture was performed and Cerebrospinal fluid (CSF) was sent for cell count, differential count, glucose, protein and for culture.

Statistical analysis was done using SPSS version 21. P <0.05 was taken to be statistically significant. Receiver Operating Characteristic ROC Curves was plotted and Area Under Curve AUC was calculated. Linear regression curve was plotted between platelet count and WBC count and their relationship was evaluated.

Sample size was calculated to be 76. Prevalence of SBI or thrombocytosis (p) = 26% = 0.26; q: 1-p = 1-0.26 = 0.74; (prevalence of SBI was based on the study done by Manzoor et al[10])

RESULTS

Out of total of 76 young infants included in study, 55 (71.1%) were male and 22 (28.9%) were female. SBI was diagnosed in 43 (56.6.%) of cases of which 29 (67.5%) were male and 14 (32.5%) were female.19.7% of cases were from inside the Kathmandu valley whereas 80.3% infants were from outside. Most infants (63.3%) presented with cough/noisy breathing followed by irritability (35.5%) , feeding problem (22.4%), diarrhea (15.8%) and lethargy (11.8%).Among SBI cases, pneumonia was the most common diagnosis (58.1%) followed by probable sepsis (16.3%), probable meningitis (9.3%), and UTI (9.3%) .

Incidence of reactive thrombocytosis among SBI infants was found to be 53.5%. Among SBI cases, elevated CRP was present in almost three fourth cases and thrombocytosis in more than half of the cases.CRP, platelet count and total WBC count was significantly higher in SBI cases as compared to Non- SBI cases (Table 1).

Table 1. Comparison of laboratory parameters among SBI and Non-SBI cases.

Investigation			Non-SBI cases		P- value
	Number (n =43)	Percent (%)	Number (n =33)	Percent (%)	
Elevated CRP	35	81.4	4	12.1	0.000
Thrombocytosis (≥400 x 10^9/L)	23	53.5	3	9.9	0.000
Total WBC count (≥15,000/cmm)	11	25.6	0		0.007
Urinalysis (>5 cells/HPF)	4	9.3	0		0.128

Table 2. The mean platelet count of SBI cases.

Serious Bacterial Infection cases	Platelet count (/cmm), [mean±sd]
UTI	473,500 ± 21,920
Probable meningitis with pneumonia	463,000 ± 211,936
Pneumonia	410,520 ± 82,056
Probable meningitis with UTI	370,000 ± 84,853
Probable sepsis	330,000 ± 84,226
Probable meningitis	280,750 ± 94,069

Table 3. Validity of different platelet count in diagnosis of SBI.

Platelet count (/cmm)	N (23)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)	Accuracy (%)
≥400 x 10^9/L	23	53.5	90.9	88.5	60.0	69.7
≥450 x 10^9/L	12	27.9	100.0	100.0	51.6	59.2
≥500 x 10^9/L	4	9.3	100.0	100.0	45.8	48.7
≥600 x 10^9/L	2	4.7	100.0	100.0	44.6	46.1

Table 4. Validity of individual and combined laboratory parameters in predicting SBI in young infants (n=43).

Variables	N (43)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC (≥15,000/cmm)	11	25.6	100.0	100.0	50.8
Pyuria (>5 cells/HPF)	4	9.3	100.0	100.0	45.8
Platelet count (≥ 400x10^9/L)	23	53.5	90.9	88.5	60.0
Elevated CRP	35	81.4	87.9	89.7	78.4
WBC + Pyuria	14	32.6	100.0	100.0	53.2

WBC + Pyuria + CRP	40	93.0	87.9	90.9	90.6
WBC + Pyuria + CRP + Platelet ≥400 × 10^9/L)	40	93.0	78.8	85.1	89.7

Mean platelet count was highest in infants with UTI, followed by infants who presented with probable meningitis and with pneumonia (Table 2).

Specificity and positive predicitve value of thrombocytosis in diagnosing SBI was high but the sensitivity, negative predictive value and the accuracy of diagnosis were not high and decreased as the platelet count increases (table 3).

Thrombocytosis alone had the sensitivity of only 53.5%, but had specificity of 90.9%. However, when thrombocytosis was combined with other parameters namely WBC, pyuria, and CRP, sensitivity was increased. Elevated CRP had better sensitivity than other parameters for diagnosing SBI. Other parameters like leukocytosis and pyuria alone as well as combined had also low sensitivity but high specificity and better positive predictive value.

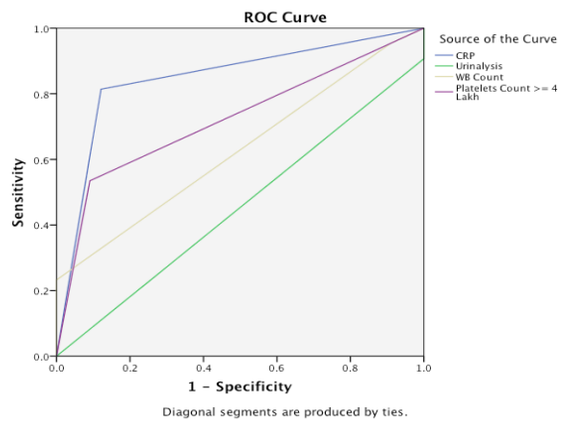

Figure 1. Depicting Receiver Operating Characteristic Curves (ROC) plotted for platelet, WBC, CRP, and pyuria predicting serious bacterial infection in febrile young infants.

Area under the curve (AUC) was found to be highest for CRP (0.846) followed by platelet count (0.722), WBC count (0.628) and pyuria (0.453). AUC for WBC and pyuria was significantly lower compared to thrombocytosis and CRP (p value = 0.000 for both) indicating that elevated CRP and thrombocytosis are better predictor of SBI in young infants.

Mean of WBC counts, and platelet counts were found higher in SBI cases compared to Non SBI cases and the difference was statistically significant with p-value 0.001 and 0.000 for difference in mean WBC counts and platelet counts respectively. There was a positive correlation between platelet count and WBC count in SBI cases, but it was not significant. (p value = 0.062, R = 0.2149).

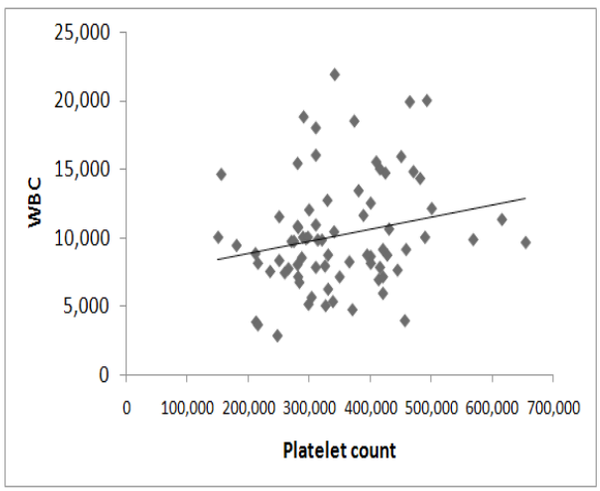

Figure 2. Depicting relationship between platelet count and WBC count in diagnosing SBI.

DISCUSSION

In this study, elevated CRP was the most common diagnostic marker among SBI cases, which was present in 81.4% of SBI cases; thrombocytosis (≥400 x 10^9/L) was present in 53.5%, leukocytosis (≥15,000/cmm) in 25.6% and pyuria in 9.3%. In contrast to our study, thrombocytosis (≥400 x 10^9/L) was the most common diagnostic marker among SBI cases (62.4%) followed by leukocytosis (29.5%), elevated CRP (23.5%) and pyuria (20.8%) in the study done by Chib et al.[11] In the present study, platelet count was significantly higher in febrile infants with SBI which is similar to findings in a study done by Sadawarti et al.[12] The overall ability of platelet count to identify infants with SBI was only moderate (AUC: 0.722) which is similar to the observation made in other studies.[11,13]

Platelet count thresholds of ≥400 x 10^9/L carried the best accuracy (69.7%), sensitivity and specificity of 53.5% and 90.9% respectively. However, in other studies platelet count threshold of ≥450 x 10^9/L carried best accuracy while retaining optimum sensitivity and specificity.[10,11,13] There was a positive correlation between platelet count and WBC count in SBI cases, but it was not significant. Similar positive correlationship between leukocytosis and thrombocytosis (p value =0.002, R = 0.017) was also found in study by Wang et al.[14] In prospective study by Sreenivasa et al. too, significant association between thrombocytosis and leukocytosis was found (p value <0.001).[15]

A combined high-risk criterion of ≥15, 000 /mm3 for TLC, > 5 WBC/HPF for pyuria, picked up 14/43 and

missed 29/43 cases of SBI. Further combination of three tests (TLC ≥15000 /mm3, pyuria>5 WBC /HPF, and elevated CRP) picked up 40/43 and missed 3/43 cases of SBI. whereas 4 /33 (12.1%) infants without bacterial infections (Non- SBI) were falsely classified as high-risk. However, the addition of platelet count of ≥400 x 10^9/L to the above combination of three tests (now combination of four tests), could not pick up any extra cases. As more number of parameters were combined sensitivity for diagnosing SBI increased, number of cases of SBI picked up increased and number of cases missed decreased showing that the combination of these tests may help in early prediction of febrile young infants at risk of serious bacterial infection. In a study by Manzoor et al, combined criteria of ≥15, 000 /mm3 for TLC, ≥ 5 WBC/HPF for pyuria, missed 7 cases of SBI while 26 infants were falsely classified as high-risk out of non SBI.[10] Further combination of ≥15, 000 /mm3 for TLC, ≥ 10 WBC/HPF for pyuria, and CRP ≥2 mg/dl, missed 4 infants with SBI (10.2% of SBI). The addition of platelet count of ≥450 x 10^9/L to the above combination of three tests missed only 2 SBI infants (5.1%) with improvement of picking up 2 more patients with SBI over the combination of three tests, with final pick up of 37 out of 39 SBI patients.[11]

CONCLUSIONS

Elevated CRP had the best sensitivity in diagnosing SBI in young febrile infants followed by thrombocytosis, whereas leukocytosis was found to have poor sensitivity. Thrombocytosis is a common finding in young infants diagnosed with SBI. Thrombocytosis of ≥400 x 10^9/L carried the best accuracy among other platelet count thresholds in diagnosing SBI among the febrile young infants beyond the neonatal period. It had however, moderate ability in identifying infants with SBI. Furthermore,combination of elevated CRP, WBC ≥ 15,000/cmm, thrombocytosis of ≥ 400 x 10^9/L and pyuria>5/HPF had the best sensitivity in diagnosing SBI in young febrile infants.

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