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RESEARCH ARTICLE

ASSESS THE UTILITY OF PLATELET COUNT AS A POTENTIAL PREDICTOR OF SERIOUS BACTERIAL INFECTION.

Rohit Chib , Mohsin Rashid,Tanveer Bashir.

Post –Graduate Department Of Pediatrics,GB Pant Hospital,GMC Srinagar,India

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Corresponding Author

Rohit Chib.

Abstract

Aims and Objectives :-To assess the utility of platelet count as a potential predictor of serious bacterial infection**. Material and Methods:-**The study was conducted in the Postgraduate Department of Pediatrics, G.B. Pant hospital, an associated hospital of Govt. Medical College Srinagar, which is a referral tertiary care hospital for the children of Kashmir valley .The study was a prospective non-randomized study conducted from April 2011 to March 2012 **.** All infants of age 30-89 days admitted in hospital with rectal temperature > 38◦C/100.4◦F without an apparent focus of infection on history and clinical examination were included in the study. **Results:-** Total of 149 patients fulfilled the inclusion criteria .Only 39 out of 149 (26.2%) had SBI (serious bacterial infection). Mean platelet count (lakh/mm^3 ± 1SD) in our study was 5.1±1.1 in SBI versus 3.9±1.6 in Non-SBI which was statistically significant in SBI, p value < 0.05. Combination of four tests TLC ≥ 15000 / mm3 ,Pyuria ,CRP≥2mg/dl and PLT ≥ 4.5 lakh /mm3 may help in early prediction of febrile young infants at risk of serious bacterial infection.**Conclusion :-** In our study a combined high-risk criterion of platelet count of ≥450,000 mm/3 ,TLC ≥15,000/mm3, Pyuria > 5 WBC/hpf and CRP≥ 2mg/dl resulted in misclassification of only 2(5.1%) patients out of 39 SBI, so this combination help in early prediction of patients at risk of SBI.

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Introduction:-

Thrombocytosis or elevation in the peripheral blood platelet count to values > 400,000/ μL is common in infancy and childhood, occurring in 3 to 13% of children [(1)] .Thrombopoietin (Tpo) is the key regulator of platelet production in humans, and is primarily expressed in the liver, and to a lesser extent the kidney, bone marrow and other organs [(2)]. Thrombocytosis is of two types, Primary thrombocytosis which is divided into familial and essential. [(3– 4),] Secondary thrombocytosis also known as reactive thrombocytosis in childhood results from increased thrombopoiesis , as a reactive process due to causes[(5 –8)] like, Infections (e.g., of the respiratory tract, gastrointestinal tract, central nervous system, skeleton and others), Iron deficiency anemia, hemolytic anemia, bleeding, Connective tissue diseases, malignancies, drugs, trauma, burns, and intense exercise.

Reactive thrombocytosis seems to affect up to 15% of hospitalized children [(1, 9, 10)]. It is more common in neonates, particularly premature ones and up to 2 years of age and less common in older children. In most children with reactive thrombocytosis, platelet counts are modestly elevated up to 700,000/μL. Moderate thrombocytosis (platelets between 700,000 and 1,000,000/μL) occur in 6–8 % of children with reactive thrombocytosis ,while platelets > 1,000,000/μL occur in less than 2% of Children with reactive Thrombocytosis[(5)], but may be more common in critically ill children[(10)] . Infections, both viral and bacterial, are by far the most common cause of secondary thrombocytosis in childhood. Presently, infections of the respiratory tract account for 60-80 % of cases of secondary

thrombocytosis in children[5,9,11], followed by infections of the urinary[12] and gastrointestinal tracts , and of the bones [5,6 ,13].

Sick infants less than 3 months of age present a management challenge , as many of these have no identifiable source of fever, and the prevalence of serious bacterial infection (SBI) in this age group is high[14-17]. The most commonly suggested strategy for the febrile neonates admitted to a hospital is to undergo full sepsis work up [16-17]. The objective of our study was to assess the utility of platelet count as a potential predictor of serious bacterial infection.

Review of literature:-

Thomas GA et al. (1986) a retrospective study of thrombocytosis in children with Hemophilus influenza meningitis was performed. Their results documented that thrombocytosis was common finding among children with H. influenzae meningitis[18].

Chan KW et al. (1989) In a 12-month period, 100 episodes of marked thrombocytosis were found among 94 children. These patients were young. All but one episode of marked thrombocytosis occurred as a phenomenon secondary to a variety of disease states. Infections, especially those involving the central nervous systems were the commonest cause of an elevated platelet count in this series. [19].

Vora A J et al.(1993) conducted a study to estimate the incidence and causes of secondary thrombocytosis in children, a 12 month study of all patients attending a children's hospital. Of 7916 children who had platelet counts during the study period, 36 (0.5%) produced a value>800x 109/l; there were 19 boys and 17 girls. There was a preponderance of young infants. Twenty seven of the 36 had some sort of associated infection, bacterial in 18 and viral in nine. So they noted that secondary thrombocytosis was not rare and was most frequently seen in very young infants after infections [7].

Yohannan M D et al. (1994) studied 663 children with thrombocytosis prospectively for etiology. The causes of thrombocytosis were infection (30.6%), hemolytic anemia (19.3%), tissue damage (15.2%), rebound thrombocytosis (14.8%), chronic inflammation (4.1%), renal disorders (4.1%), and malignancy (2%). Among all patients with infections, osteomyelitis and septic arthritis were associated with higher platelet counts than other infections (P<.0001). Thrombocytosis secondary to infections was significantly more common in children under 5 years of age, where as chronic inflammation, malignancy, and renal disorders were more common causes over 5 years of age. Thrombocytosis was a frequent finding in children [9].

Heng JT et al. (1998) found that 135 cases out of 10,288 admissions had raised platelet count. Majority were less than 1 year old. 78% had associated infections of which 2/3rd were due to bacteria, Pneumonia was the most common bacterial infection associated with thrombocytosis whilst gastroenteritis was the most common cause for non-bacterial infection and Kawasaki's disease constituted the majority of the non-infective etiology. Cases with platelet count > 900x10(9)/l, 73.3% were due to bacterial infection [6].

Vlacha V et al. (2006) a total of 102 pediatric patients hospitalized with lower respiratory tract infection during a period of 30 months were studied. Forty nine (48%) of those patients had platelet counts >500x10(9)/L. The patients with thrombocytosis had more serious illness. This was indicated by three factors: more severe clinical condition on admission, presence of respiratory distress and longer hospitalization .So thrombocytosis was a common finding among patients with lower respiratory tract infection. Thrombocytotic patients had a more severe clinical condition. [11].

S Fouzas et al. (2010) from the Department of paediatrics, University hospital of Patras, Greece studied 408 infants, 103 (25.2%) had SBI. Platelet count was significantly higher in infants with SBI compared to those without (median 513000/mm3 versus median 398000/mm3; P value <0.001). Thrombocytosis had only moderate ability in predicting SBI (area under the curve: 0.74, 95% CI0.70-0.79).Thrombocytosis ≥ 450,000cells/mm3, in combination with leucocytosis > 15000/mm3, elevated CRP ≥ 2mg/dl and pyuria > 10WBC/HPF, may help in early recognition of febrile young infants at risk for SBI [20].

Material & Methods:-

The study was conducted in the postgraduate Department of Pediatrics G.B. Pant hospital, an associated hospital of Govt. Medical College Srinagar, which is a referral tertiary care hospital for the children of Kashmir valley.
The study was a prospective non-randomized study conducted from April 2011 to March 2012.

Inclusion Criteria:-

All infants of age 30-89 days admitted in hospital with rectal temperature > 38◦C/100.4◦F without an apparent focus of infection on history and clinical examination.

Exclusion Criteria:-

Infants having fever more than 72 hours, and who had received antibiotics or vaccination within 48 hours of presentation.

Approach:-

All patients who had fulfilled, the inclusion criteria, underwent sepsis screening including WBC count, platelet count, blood culture, urine microscopy and culture and CRP. Lumbar puncture for cerebrospinal fluid (CSF) analysis and culture, pleural tap for pleural fluid analysis and culture 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 (Bac T/ALERT 3D). Urine was obtained by urethral catheterization using a sterile technique. A careful urinalysis, on a fresh urine sample, can identify children with a high likelihood of UTI to enable presumptive treatment while awaiting results of urine culture, the WBC in the urine were quantified by standard microscopic examination and expressed as WBC >5 leukocytes / high power field in a centrifuged sample or >10 leukocytes / mm^3 in an uncentrifuged sample[21]. The urine, CSF, pleural fluid and stool cultures were monitored using standard laboratory techniques. Normal CSF was defined as, clear in colour, WBCs up to 5/mm^3, proteins 10 to 40mg/dl, glucose content about 60% of the blood glucose level in a healthy child and polymorphonuclear cells were always taken abnormal in all patients[22].

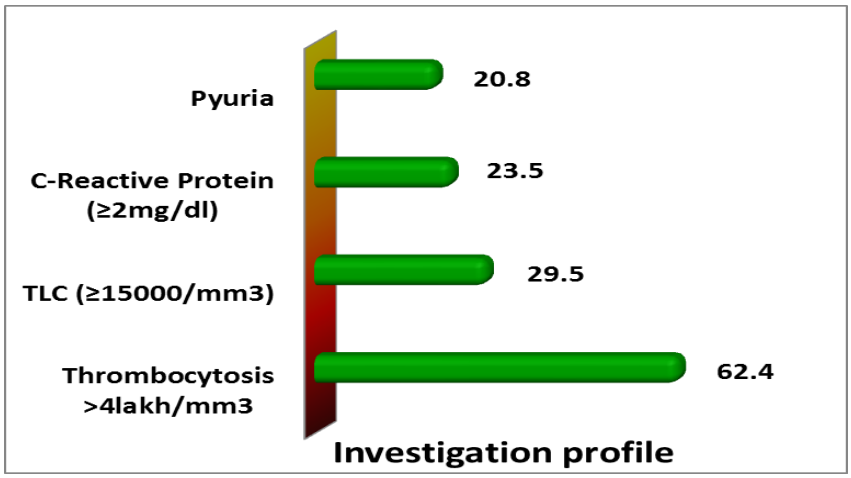
Serious Bacterial Infection:-

Was defined as occult bacteremia, urinary tract infection (UTI), bacterial meningitis, pneumonia. Isolates such as Staphylococcus epidermidis in the blood culture were considered contaminants unless they were isolated from more than two consecutive cultures. Urinary tract infection was defined as growth of single known pathogen on urine culture with≥100,000 cfu/mL of urine obtained by urethral catheterization. Confirmation of the diagnosis on urine culture is necessary [21]. Definite pneumonia was defined as consolidation on chest radiograph plus any of the following signs: a positive blood culture for a pathogenic organism or culture of a pathogenic organism from pleural fluid sample. Probable pneumonia was defined as consolidation alone[23]

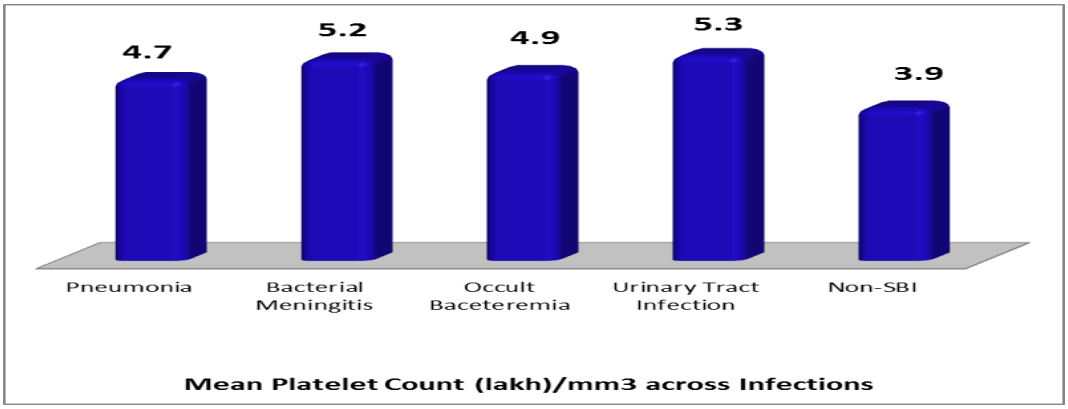
Occult bacteremia was defined as a pure growth of a single pathogenic micro-organism on blood culture of a febrile young infant without any apparent focus of infection on history and clinical examination. Probable bacteremia was defined as the growth of two or more types of bacteria [23].Definite bacterial meningitis was defined as isolation of organism on CSF culture. Probable bacterial meningitis was defined as abnormal CSF on analysis with sterile CSF culture [22]. Only patient with definite bacterial infection, was taken as serious bacterial infection.

Results:-

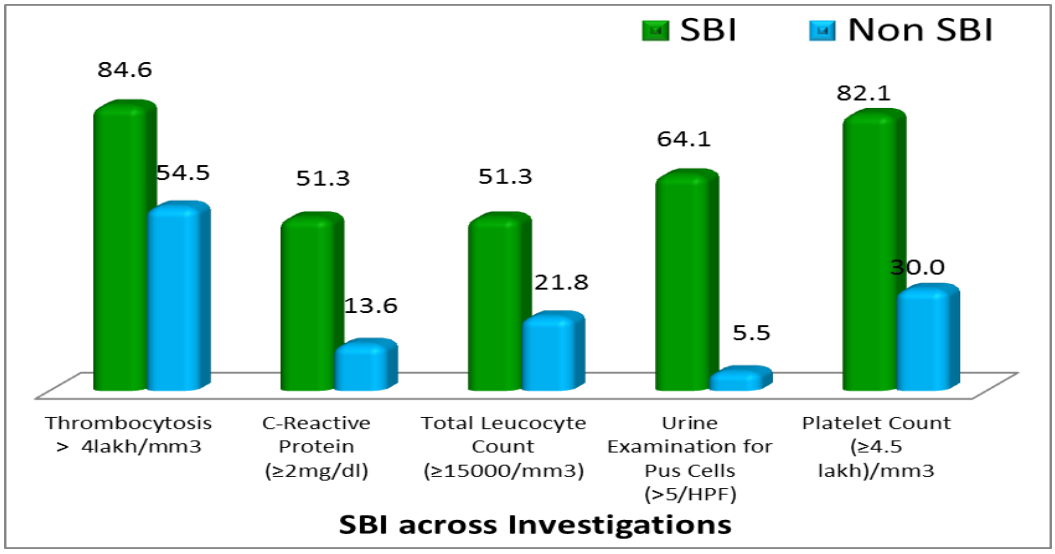
Total number of patients with fever without an apparent focus of infection on history and clinical examination, admitted to hospital was 180 . Total number of patients fulfilling the inclusion criteria was 149. 31 patients out of 180 were excluded out of the study, as among these, 12 had fever for more than 72 hours, 3 had received vaccination, 16 were treated with antibiotics within 48 hours of presentation .Total number of males were 50.3% and females was 49.7%, p value was not significant.



Graph 1: Depicting the % positivity of each investigation across febrile young infants. Other investigations Urine Culture 16 (10.7%) , CXR for Bacterial Pneumonia and Pleural Fluid Analysis / culture for separation of pathogen responsible for bacterial pneumonia were in 9 (6%) , CSF Culture was positive in 6 (4%) and Stool culture was positive in nil , in one patient Escherichia Coli was isolated in both urine culture and blood culture .Blood culture was positive in 9 SBI patients ,urine culture in 16 , CSF culture 6, chest X-ray suggestive of bacterial pneumonia and Pleural fluid analysis /culture for isolation of pathogen responsible for bacterial pneumonia in 9 .



Graph 2 : Showing mean platelets in lakh/mm^3 across SBI and Non-SBI.



Graph 3: Depicting investigation across SBI and Non-SBI .

According to test characteristics for different platelet count thresholds we came to know that platelet count of ≥4.5 lakh/mm3 carried the best accuracy of 73.2%, odds ratio of 10.7, sensitivity 82.1% ,specificity 70.0%, Negative predictive value 91.7% and Positive Predictive Value 49.2% than any other platelet thresholds, 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

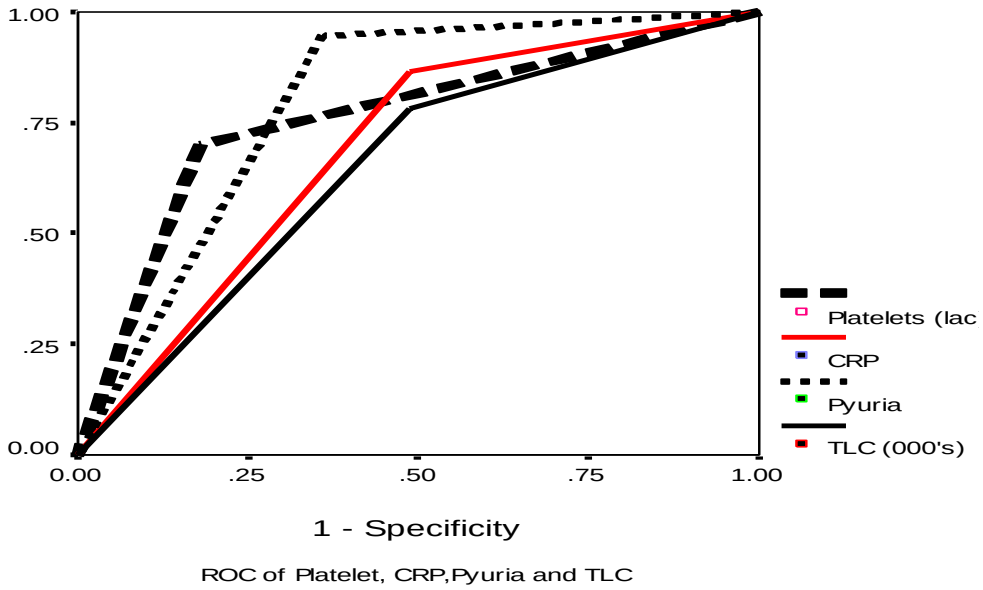
Platelets in lakh/mm^3	N (39)	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	OR
Platelet (≥ 4.0 lakh/mm^3)	33	84.6	45.5	35.5	89.3	55.7	4.6
Platelet (≥ 4.5 lakh/mm^3)	**32**	**82.1**	**70.0**	**49.2**	**91.7**	**73.2**	**10.7**
Platelet (≥ 5.0 lakh/mm^3)	20	53.8	70.0	38.9	81.1	65.8	2.7
Platelet (≥ 6.0 lakh/mm^3)	8	20.5	90.0	42.1	76.2	71.8	2.3

Table1 : Test characteristics for different platelet count thresholds.(NPV:Negative predictive value ; PPV:Positive predictive value; OR:Odds ratio;N:Total no of SBI 39 out of 149 Febrile young infants.)

A combined high-risk criterion of two tests (≥15,000 /mm3 for TLC and > 5 WBC/hpf for pyuria) led to the misclassification of 17.9% of the SBI (7 infants), while 26 infants were falsely classified as high-risk out of Non-SBI . Further combination of three (TLC ≥15000 /mm3, pyuria >5 WBC /hpf, and CRP ≥2 mg/dl) led to the misclassification of 4 infants out of SBI (10.2% of SBIs), whereas 35 infants without bacterial infections(Non-SBI) were falsely classified as high-risk .The addition of platelet count of ≥450,000 / mm3 to the above combination of three tests (now combination of four tests) , resulted in misclassification of only 2 SBI infants (5.1%) with improvement in picking up of 2 new patients (5.15% out of SBI) over combination of three tests ,with final pickup of 37 out of 39, thus the combination of four tests TLC ≥ 15000 / mm3 ,Pyuria ,CRP≥2mg/dl and PLT ≥ 4.5 lakh /mm^3 may help in early prediction of febrile young infants at risk of serious bacterial infection (with Sensitivity: 94.9%; Specificity : 53.6% ; NPV:96.7%; PPV:42.0%; OR:21.4 best among all combinations).

Table 2: Depicting combined high-risk criterion of TLC ≥15000/ mm^3, Pyuria>5 WBC/HPF, CRP ≥2mg/dl and Platelet ≥4.5lakh/mm^3 in early prediction of patients of SBI.

Variable	N (39)	Sensitivity %	Specificity %	PPV %	NPV %	OR
Total Leucocyte Count (000's)	20	51.3	78.2	45.5	81.9	3.8
Pyuria >5WBC/hpf	25	64.1	94.5	80.6	8.1	30.9
C-Reactive Protein	20	51.3	86.4	57.1	83.3	6.7
Platelet Count (≥4.5lakh)/mm^3	32	82.1	70.0	49.2	91.7	10.7
TLC+Pyuria	32	82.1	76.4	55.2	92.3	14.8
TLC+Pyuria+CRP	35	89.7	68.2	50.0	94.9	18.7
TLC+Pyuria+CRP+Platelet (>=4.5lakh/mm3)	**37**	**94.9**	**53.6**	**42.0**	**96.7**	**21.4**



Graph4:- Depicting Receiver operating characteristic curves (ROC) for PLT,WBC,CRP and Pyuria predicting serious bacterial infection in febrile young infants Area under the curve (AUC) for TLC was 0.647; For CRP was 0 .688; Pyuria was 0 .793 and PLT was 0.760, The AUC for TLC was significantly lower as compared to the AUC for pyuria (Pvalue < 0.05). No statistically significant differences were found between the AUCs of the other parameters, thus PLT with 0.760 AUC carry moderate ability in predicting patients with SBI.

Discussion:-

Total number of admissions during period was 25640 .Total number of patients with fever without apparent focus of infection on history and clinical examination, admitted during this period was 180.Finally total number of patients fulfilling the inclusion criteria was 149 . The purpose of this study was to assess the utility of platelet count as a potential predictor of serious bacterial infection.

In this study, platelet count was significantly higher in febrile infants with documented bacterial infection, particularly in those with UTI, occult bacteremia and pneumonia. However, due to a substantial overlap, it was difficult to identify threshold value that could clearly differentiate infants with SBI from other febrile infants. platelet count of ≥4.5 lakh/mm^3 carried the best accuracy of 73.2%,odds ratio 10.7, sensitivity 82.1%, specificity 70.0%, Negative predictive value 91.7% and Positive Predictive Value 49.2% than any other platelet threshold in differentiating infants with SBI . The overall ability of platelet count to identify infants with SBI was moderate (AUC 0.76), but comparable to the other parameters on receiver operating characteristics curve. The fact that

platelets can behave like an acute phase reactant is well recognized. Stimulation of platelet production is triggered by interleukin-6 which enhances megakaryopoiesis directly and indirectly by stimulating hepatic thrombopoietin production .In this study, platelet count was significantly higher in infants with SBI compared to those without, and this was So, reactive thrombocytosis in combination with WBC, CRP and pyuria seems to be a useful tool in predicting early the risk of SBI in young febrile patients . Hence , thrombocytosis in febrile young infants could be used as a quick inexpensive diagnostic tool for predicting SBI.

Conclusion:- Mean WBC count in our study was significantly higher in SBI 14915 ± 4998 versus 10948 ± 4586 in non-SBI, p value < 0.05 . C –Reactive Protein ,pyuria and platelet count were noted statistically significant in SBI than in non SBI. The mean platelet count (lakh / mm^3 ± 1SD) was 5.1±1.1 in SBI versus 3.9±1.6 in Non-SBI which was statistically significant in SBI, p value < 0.05.In our study a combined high-risk criterion of platelet count of ≥450,000 /mm^3 ,TLC ≥15,000/mm3, Pyuria > 5 WBC/hpf and CRP≥ 2mg/dl resulted in misclassification of only 2(5.1%) patients out of 39 SBI, so this combination help in early prediction of patients at risk of SBI .

Research need:-

More trials are required to be done for further confirmation of early utility of platelet count in prediction of serious bacterial infection .Sample size in our study was small ,so study over a larger sample is required to be done , before including platelet count in septic screen for early detection of serious bacterial infection in febrile young infant.

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