



STUDY OF ASSOCIATION BETWEEN THROMBOCYTOSIS AND LOWER RESPIRATORY TRACT INFECTION IN CHILDREN LESS THEN 5 YEARS OF AGE

Medical Science

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ABSTRACT

Background: Thrombocytosis is a marker of inflammatory reaction with various clinical outcomes. Primary or essential thrombocytosis in children is very rare but reactive thrombocytosis occurs in children and respiratory tract infection is the commonest cause. The study aimed to determine the association of thrombocytosis with severity of lower respiratory tract infection; and the association of degree of thrombocytosis with severity of pneumonia. **Materials and methods:** This observational study was conducted in the Department of Paediatrics of Nalanda Medical College, Patna. This study was done on 240 children aged between 2 months and 5 years who were admitted with lower respiratory tract infection and classified according to WHO guidelines. Complete general physical examination and systemic examination with special orientation towards respiratory system was done. Complete blood count was performed with automated system sysmex xs800i cell counter. Thrombocytosis was noted and severity of thrombocytosis was classified. **Results:** Among 240 cases of lower respiratory tract infections, 96 children had thrombocytosis. 26 (48.1%) children with very severe disease, 58 (46.1%) children with severe pneumonia and 12(20%) children with pneumonia had thrombocytosis. Thus it was seen that there was significant association between platelet count and severity of pneumonia (p value=0.018). Two children had severe thrombocytosis (9.01-10.00L/mm³) and both of them had very severe disease. It indicates that degree of thrombocytosis increases as severity of pneumonia increases. **Conclusion:** There is a significant relationship between thrombocytosis and severity of pneumonia. Also degree of thrombocytosis increases as severity of pneumonia increases. The current study indicated that children with lower respiratory tract infection frequently had associated thrombocytosis. The duration of hospital stay and severity of pneumonia were clearly higher in the group with high thrombocyte count. Thrombocyte count can be used as a predictor for the severity of the disease in children less than 5 year old with pneumonia to prioritize them.

KEYWORDS

Thrombocytosis; Lower Respiratory Tract Infection; Pneumonia; Severe Pneumonia

INTRODUCTION

Every year, ARI in young children is responsible for an estimated 3.9 million deaths worldwide. Hospital based studies have reported that 20 – 40% of admissions in under- fives are due to acute respiratory infections (ARI) [1]. In India during 2018, about 41,996 cases of ARI were reported with 3,740 deaths. Same year 9,28,485 cases of pneumonia were reported with 4,213 deaths [2].

Platelets play a major role in antimicrobial host defense, the induction of inflammation and tissue repair [3]. Primary thrombocytosis is very uncommon in children; but infections at any body part are the common causes of reactive thrombocytosis. There are many studies that suggest platelet count as indicator of serious bacterial infection. A study revealed respiratory tract infection as the most common cause of infectious etiology of reactive thrombocytosis [4]. Another study observed that respiratory infection (28.3%) was the main cause among infections causing increased platelet count [5].

Primary or essential thrombocythemia is extremely rare in the pediatric age group, but infections at any part of the body including meninges are the common causes of reactive thrombocythemia in children. Besides acute infections, chronic inflammation and chronic hemolytic states are the other causes of pediatric thrombocytosis [6]. Reactive thrombocytosis of 6% to 15% was reported among hospitalized children [7]. Fauzas et al., studied re-active thrombocytosis in febrile young infants with serious bacterial infection and suggested that thrombocyte count can be a predictor for the severity of infection [8]. Ozcan described upper respiratory tract infection as the most common cause of reactive thrombocytosis followed by pneumonia [5]. Subramaniam et al., indicated that respiratory infection was the predominant (28.3%) infectious cause of reactive thrombocytosis [4]. Hadidopoulou found reactive thrombocytosis in children with viral respiratory tract infection [9]. However, Wolach et al., found thrombocytosis in children with pneumonia and empyema [10]. Similarly, Atef et al., evaluated platelet count in hospitalized patients with the community-acquired pneumonia and found that platelet count may be more informative to predict poor outcome than abnormal leukocyte count [11]. With the wide spread availability of automated analyzer in the field of hematology, platelet count is often taken as a component of routine hematology work-up of every patient. As total platelet count is a part of complete blood count, thrombocytosis is frequently encountered in day to day practice. Elevated level of thrombopoietin (TPO), interleukin (IL)-6, IL-3, IL-11, and catecholamines play major roles in

reactive thrombocytosis due to infection. Platelets play a vital role in antimicrobial host defense mechanism, by inducing inflammation and tissue repair. Activated platelets bind aggregate and internalize microorganisms, which hasten the clearance of pathogenic organism from the blood stream. They also take part in antibody-dependent cell cytotoxicity to kill pathogens. Severe community-acquired pneumonia is associated with increased plasma level of inflammatory mediators such as tumor necrosis factor (TNF)-alpha, IL-1B, IL-6, and IL-8. Also, the level of TNF-alpha, IL-1B, and IL-6 increased in the bronchoalveolar lavage fluid of the same patients. Normal thrombocyte count varies from 150000 to 450000/mm³; platelet count more than 500 000/mm³ is observed in 3% to 13% of pediatric population [12]. Respiratory tract infections constitute 60% to 80% of reactive thrombocytosis among the systemic infections, which can lead to complications such as pneumonia.

This study primarily aimed at finding out the association between severity of pneumonia and degree of thrombocytosis, and secondary aimed at evaluating whether a simple test such as platelet count can be used to predict complications and outcomes of pneumonia in the targeted age group to prioritize them in a poor resource setting, similar to the current study.

MATERIALS AND METHODS

The current prospective observational study was conducted in the department of paediatrics, NMCH, Patna, Bihar over a period of 1 year from January 2022 to December 2022. All patients within the age range of 2 to 60 months admitted with a clinical diagnosis of lower respiratory tract infection were studied. Patients were classified as per world health organization (WHO) criteria in acute respiratory infection (ARI) control programme guidelines [12]. Children with lower respiratory tract infection, associated with connective tissue disorders, congenital heart diseases, and anemia (hemoglobin (Hb) < 10 mg/dL) were excluded from the study. After signing the written consent by the parents, the demographic profile, clinical data, and laboratory testing results of each participant were collected. Complete blood count (CBC) was performed with automated Sysmex, a 6 part analyzer (XN Series), and differential count was performed by a hematologist for any abnormality. Chest radiographs were assessed by the radiologist. As per ARI control programme, tachypnea was defined as respiratory rate more than 50/minute in children aged 2 to 12 months and more than 40/minute in children aged 12 to 60 months. Presence of tachypnea, retraction of chest, or SpO₂ < 94% in room air was considered as respiratory distress. Clinical severity of the disease was

classified as pneumonia, severe pneumonia, or very severe pneumonia. The duration of hospitalization and radiological findings were noted. Thrombocytosis was considered when peripheral blood platelet count was $> 500000/\text{mm}^3$. Thrombocytosis is further divided as mild if platelet count ranges 500000 to 700000/ mm^3 , moderate if ranges 700000 to 900000/ mm^3 , and severe if ranges 900000 to 1000000/ mm^3 . Extreme thrombocytosis was defined as platelet count $> 1000000/\text{mm}^3$. All the patients were classified into 2 groups on the basis of platelet count; ie, patients with or without thrombocytosis.

Statistical analysis was performed using the online tool openepi [7]. Data has been presented with descriptive methods, and between group difference was analyzed with chi-squared test for test of significance, and chi-squared test for trend as applicable. P-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 240 cases of lower respiratory tract infection were recruited for the study. 168 (70%) children were aged between 2 months and 12 months and 72 (30%) children were aged between 13 months and 60 months. 152 (63.3%) children were male and 88 (36.7%) were female. 60 (25%), 126 (52.5%), 54 (22.5%) children had pneumonia, severe pneumonia and very severe disease respectively.

Among total 240 cases of lower respiratory tract infections, 96 cases had thrombocytosis and 144 cases were without thrombocytosis. 20%, 46.1% and 48.1% of children with pneumonia, severe pneumonia and very severe disease respectively had thrombocytosis. Significant association between platelet count and severity of pneumonia was seen (p value=0.018). Among 54 cases of very severe disease, 26 (48.1%) cases had thrombocytosis. Data of relationship between platelet count and severity of pneumonia is given in table 1.

Table 1: Relationship between platelet count and severity of pneumonia.

Platelet count	Pneumonia N (%)	Severe pneumonia	Very Severe disease	Total	Statistics
Without Thrombocytosis	48 (80)	68(53.9)	28(51.8)	144(60)	P value=0.035
With Thrombocytosis	12 (20)	58(46.1)	26(48.1)	96(40)	
Total	60(100)	126(100)	54(100)	240 (100)	

All values are in no. (%).

As seen in table 2, out of 4 children who had severe thrombocytosis (platelet count 9.01-10.00 L/mm^3), both (100%) had very severe disease. Only 2 case was found to have extreme thrombocytosis (platelet count $>10\text{L}/\text{mm}^3$) and it (100%) had severe pneumonia. On the other hand, most (78.5%) of the cases with moderate thrombocytosis and almost half (54.8%) of the cases with mild thrombocytosis had severe pneumonia. Thus it is seen that with the increase in degree of thrombocytosis the severity of pneumonia increases (P=0.035).

Table 2: Relationship between severity of thrombocytosis and severity of pneumonia.

Platelet count Lakhs / cumm.		Pneumonia	Severe pneumonia	Very severe Disease	Total
Without thrombocytosis	<5.00	48(33.3)	68(47.2)	28(19.4)	144(100)
With thrombocytosis	5.00-7.00 (mild)	10(16.1)	34(54.8)	18(29.1)	62(100)
	7.01-9.00 (moderate)	2(7.1)	22(78.5)	4(14.2)	28(100)
	9.01-10.00 (severe)	0(0.0)	0(0.0)	2(100)	4(100)
	>10.00 (extreme)	0(0.0)	2(100)	0(0.0)	2(100)
	Total	60(25)	126(52.5)	54(22.5)	240(100)

Mild thrombocytosis has almost 2.6 times probability of severe

pneumonia/very severe disease compared to pneumonia without thrombocytosis, while the same probability increases to 6.5 when thrombocytosis is 'moderate'. Comment cannot be made about 'severe' and 'extreme' thrombocytosis as the number of pneumonia cases are nil, in this group and hence OR could not be calculated.

Table 3: Chi-square for trend analysis for severity of thrombocytosis and severity of pneumonia.

Thrombocytosis	Severe pneumonia and very severe disease (Cases)	Pneumonia (Controls)	Total	Odds ratio
< 5.00	96	48	144	2
5.00-7.00 (mild)	52	10	62	5.2
7.01-9.00 (moderate)	26	2	28	13
9.01-10.00 (severe)	4	0	4	'undefined'
>10.00 (extreme)	2	0	2	'undefined'
Total	180	60	240	

Out of the total 240 cases of lower respiratory tract infection, majority i.e. 168 (70%) children were aged between 2 to 12 months while 36 (30%) children were aged between 13 to 60 months. Out of the 168 cases in the age group of 2 months to 12 months, almost half i.e. (52.3%) of the cases were admitted with severe pneumonia followed by very severe disease in 42 (25%) children. Whereas, in the age group of 13 months to 60 months almost half i.e. 38 (52.7%) children were admitted with severe pneumonia and 22 (30.5%) children were admitted with pneumonia. 42(25%) children in the age group of 2 to 12 months had very severe disease while 12 (16.6%) children in the age group of 13 to 60 months had very severe disease. Thus it is seen that severity of pneumonia is more in infancy.

DISCUSSION

Though platelets play a vital role in antimicrobial host defense, the exact mechanism of reactive thrombocytosis is unknown yet. During respiratory tract infection, the level of inflammatory cytokines increases, which heighten the production of thrombocyte. Lower respiratory tract infections are the leading cause of mortality in children less than 5 years old. Mortality rate and the severity of disease are usually high in young infants and young children.

In present study, among total 240 cases of lower respiratory tract infections, 96 (40%) cases had thrombocytosis and 144 (60%) cases were without thrombocytosis. 20%, 46.1% and 48.1% of children with pneumonia, severe pneumonia and very severe disease respectively had thrombocytosis. This study revealed significant association between thrombocytosis and severity of pneumonia (p value of 0.018). In a study by Vlachas et al., 48% of total admission with LRTI had thrombocytosis which is similar to this study. They also found that children with thrombocytosis had more serious illness (p value <0.001). Unsal et al., noted that the severity of symptoms in patients with thrombocytosis is more than in patients with normal platelet count (p value=0.004) [12]. Choudhury and Rath also found similar results in their study where there was significant association between platelet count and severity of pneumonia (p <0.05) [13]. In contrast to this study, Prina et al., found that 8% cases of lower respiratory tract infection had thrombocytosis and 90% had normal platelet count [14].

In present study, 40% had thrombocytosis. Among children with thrombocytosis, 64.5% had mild thrombocytosis, 29.1% had moderate thrombocytosis, 4.16% had severe thrombocytosis and 2.08% had extreme thrombocytosis. This is comparable to studies done by Sutor et al., Yohannan et al., Heng and Tan, where mild thrombocytosis was seen in 72-86%, moderate thrombocytosis in 6-8%, severe thrombocytosis in 3%, and extreme thrombocytosis in 0.5%.

In this study, out of 4 children with severe thrombocytosis (9.01-10.00 L/mm^3), both (100%) had very severe disease. Only one case was found to have extreme thrombocytosis (platelet count >10 lakhs/ mm^3) and it (100%) had severe pneumonia. On the other hand, most (78.5%) of the cases of moderate thrombocytosis and almost half (54.8%) of the cases with mild thrombocytosis had severe pneumonia; while none had very severe disease. The critically ill children had more severe thrombocytosis. Unsal et al., concluded that the symptoms were more severe in patients with thrombocytosis, compared with the ones with

normal thrombocyte count (12). Thus it was seen that, degree of thrombocytosis increased with increase in severity of pneumonia. Choudhury and Rath had similar findings. They found that all the 4 children with very severe thrombocytosis also had very severe pneumonia which indicated an association between severity of pneumonia and degree of thrombocytosis [13].

A study by Mirsaedi et al., found significant association between thrombocytosis and the 30-day mortality, but no association between leukocytosis and the 30-day mortality in children. They suggested that thrombocytosis was a better prognostic indicator than leukocytosis. They also found a significant association between high thrombocyte count and pleural effusion (14).

They opined an association between thrombocytosis and very severe pneumonia as well as pro-longed hospitalization, which was similar to the results of the current study. The current study found that the majority of the cases with radiological evidence of pneumonia or pleural effusion also developed thrombocytosis, which was similar to the results of the study by Prina et al. (20). They concluded an association between thrombocytosis in patients with the community-acquired pneumonia and pleural effusion, empyema, and poor outcome.

In this study, out of 168 infants, 88 (52.3%) and 42 (25%) infants had severe and very severe disease respectively and out of 72 children in the age group of 13 to 60 months, 38 (52.7%) and 6 (16.6%) children had severe pneumonia and very severe disease respectively. This showed that severity of pneumonia was more in infants than in children aged in between 13 to 60 months age group. Choudhury and Rath also had similar findings where they found that out of 170 infants, 80, 52 and 38 had very severe pneumonia, severe pneumonia and pneumonia respectively and in 12 to 60 months age group, out of 60 children, 32, 16 and 12 had very severe pneumonia, severe pneumonia, and pneumonia respectively. Kiyawat et al., also had similar findings where severity of pneumonia was higher in infancy than in children aged 12 to 72 months old children [15]. However, Guven and Kislal found that there was no statistically significant difference in age between severe and mild groups ($p > 0.05$) [16].

The study was done in low sample size. A large sample size would be more beneficial in arriving at a conclusion about relationship between degree of thrombocytosis and severity of pneumonia.

CONCLUSION

Increased thrombocyte count was commonly associated with pneumonia in children. Children with thrombocytosis usually develop severe illness and complications resulting in prolonged hospital stay. Degree of thrombocytosis is directly correlated with severity of illness. Thrombocyte count may be considered as a simple and useful tool to assess priority in patients in the developing countries such as India.

Percentage of cases with thrombocytosis increases with severity of pneumonia. Also degree of thrombocytosis increases with increase in severity of pneumonia. Hence, platelet count may be used as a useful marker associated with severity of lower respiratory tract infection. Increased severity of pneumonia is found to be more in infancy. In agreement with other studies, the current study concluded that thrombocytosis was a useful indicator for the severity of the disease and complications in children with lower respiratory tract infection.

Small sample size was a limitation of the current study, and the results should be validated in a larger cohort.

Authors' Contribution:

AR: study design, abstracting and analysing data, statistical analysis and interpretation, writing the manuscript; SV: study design, abstracting and analysing data, statistical analysis and interpretation, writing the manuscript.

Conflicts of interests

Authors declare no conflicts of interests.

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