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THROMBOCYTOSIS AS A PREDICTOR OF SEVERITY OF LRTI IN CHILDREN AGED 2 MONTHS TO 5 YEARS

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Abstract
Background: Platelets play a major role in antimicrobial host defences, the induction of inflammation and tissue repair. The present study aimed at determining the prevalence of thrombocytosis and its significance in predicting the severity of clinical manifestations in children with LRTI aged between 2 months to 5 years. **Methods:** This was an observational cross-sectional study with purposive sampling technique conducted in the Department of Paediatrics and Department of Emergency Medicine in a tertiary care hospital from Western India between 2018 and 2019. The study included children aged two months to 60 months admitted with lower respiratory tract infection. The sample size was estimated to be 358 with 95% confidence. **Results:** Majority (62.0%) were between 2 months and 12 months. Nearly two thirds (62.6%) were males. We found that 16.2% children aged two months to 60 months had pneumonia; 55.3% had severe pneumonia; and 28.5% had very severe pneumonia. While 72.6% children between two months and 60 months had no malnutrition, we noted that 15.6% children had Grade 1, 8.4% had Grade II, 2.8% had Grade III, and 0.5% had Grade IV malnutrition. Chest indrawing, grunting, severity of pneumonia, total leucocyte count, and duration of stay were significantly ($p<0.05$) associated with thrombocytosis. **Conclusion:** The findings suggest that thrombocytosis may be a useful marker of disease severity in this population and highlight the importance of monitoring platelet count in the management of LRTI in children.
Keywords: Thrombocytosis, lower respiratory tract infection, children, pneumonia, India

Introduction

Acute onset of respiratory symptoms, such as cough, rhinorrhoea, rapid and/or difficult breathing, lower chest wall indrawing, and wheezing, lasting shorter than 14 days is referred to as an acute respiratory infection (ARI).(1, 2) Upper respiratory tract infection (URTI) and lower respiratory tract infection are two common classifications for ARI based on the site of illness (LRTI).(3) Infections in the lower respiratory tract include pneumonia, bronchitis, and bronchiolitis.(4) The main cause of lower respiratory tract infections (LRTI), which can result in pneumonia and bronchiolitis in young children, is respiratory syncytial virus (RSV).(5)
One of the main causes of illness and mortality in children under the age of five is pneumonia. Pneumonia is the most severe ARI complication and the leading infectious killer of children, taking the lives of over 800,000 children under the age of five year, or over 2,200 per day.(6)

In the world, there are more than 1,400 cases of pneumonia per 100,000 children, or 1 case per 71 kids, with South Asia having the highest frequency (2,500 cases per 100,000 kids), followed by West and Central Africa (1,620 cases per 100,000 children).(7) ARI is one of the leading causes of death in India's states and districts with high rates of newborn and child mortality.(8, 9) Recent estimates from the World Health Organization suggest that pneumonia is responsible for 20% of deaths in the under-five years of age, leading to 3 million deaths per year.(10) Of these deaths, two thirds occur during infancy and more than 90% occur in the developing countries like India. The risk factors for pneumonia vary between countries, regions and communities.(11) Frequently studied factors are young age, low birthweight, under nutrition, anaemia, lack of parental education, overcrowding, indoor air pollution, lack of exclusive breast feeding, lack of measles immunization, co-morbidities such as congenital heart diseases and other congenital anomalies. Other associated conditions like PEM, infectious diseases, and secondary bacterial infections make the child more vulnerable to mortality and morbidity.(12) Platelets play a major role in antimicrobial host defences, the induction of inflammation and tissue repair.(13) Secondary, or reactive thrombocytosis is a common occurrence in children.(14) It has been reported to occur in 6.0 to 15.0% of hospitalized children, with variations based on age. Bacterial or viral infections (acute or chronic) are the most common cause for reactive thrombocytosis (37.0 to 78.0%) at any age during childhood.(15) LRTI is not a single disease entity, but a group of infections with different aetiology, risk factors, pathogenesis, clinical presentations, and outcomes. Within this group, infections of the respiratory tract account for 60.0 to 80.0% of reactive thrombocytosis.(16, 17) Importantly, thrombocytosis occurs almost exclusively in children with pleural effusion. Therefore, platelet count may be used as a marker associated with severity of lower respiratory tract infection and its complications.

The availability of information related to implications of thrombocytosis in children with lower respiratory tract infection, especially from a developing country like India is limited. Against this background, the present aims to determine the prevalence of thrombocytosis and its significance in predicting the severity of clinical manifestations in children with LRTI aged between 2 months to 5 years.

Materials and methods

This was an observational cross-sectional study with purposive sampling technique conducted in the Department of Paediatrics and Department of Emergency Medicine in a tertiary care hospital from Western India between 2018 and 2019. The study included children aged two months to 60 months admitted with lower respiratory tract infection. However, we excluded children with secondary thrombocytosis due to any of the reasons including, anaemia (Hb less than 11 gm/dl), neurological infections, connective tissue disorders, chronic systemic diseases, malignancies, and hypersplenism/post splenectomy. We also excluded children for whom prior consent from parents could not be obtained.

Existing literature evidence highlights that 37.0% children with lower respiratory trat infection had thrombocytosis. Considering the prevalence to be 37.0% (and therefore q = 63.0%), with an absolute precision of 5.0%, the estimated minimum required sample size was 358 with 95% confidence. We enrolled children fulfilling the prespecified inclusion and exclusion criteria. A purpose designed, pretested questionnaire was used to collect data on basic socio-demographic

profile, clinical features and examination findings, routine and relevant lab investigations such as Hb%, total leucocyte count, ESR, platelet count, CRP and chest X-ray. The severity of LRTI was graded according to ARI classification (WHO) as pneumonia, severe pneumonia and very severe pneumonia. Also, based on platelet count, the study population was divided into children with thrombocytosis and children without thrombocytosis – normal platelet count (1.50 to 4.50 lakhs/mm3); low platelet count (<1.5 lakhs/mm3); and children with thrombocytosis as mild (5.00 to 7.00 lakhs/mm3), moderate (7.01 to 9.00 lakhs/mm3), severe (9.01 to 10.00 lakhs/mm3) and extreme (>10.00 lakhs/mm3).

The data collected was entered in Microsoft Excel and analysed using Software for Statistics and Data Science (Stata) v16. Descriptive analysis was presented using numbers and percentages. Chi square test of significance (two-sided) was applied to test for association (where data was not normally distributed Fischer's Exact test was used) between thrombocytosis and independent variables. Statistical significance was considered at $p<0.05$.

Results

The present study included 358 children aged two months to 60 months admitted with lower respiratory tract infection. Majority (62.0%) were between 2 months and 12 months. Nearly two thirds (62.6%) were males. We found that 16.2% children aged two months to 60 months had pneumonia; 55.3% had severe pneumonia; and 28.5% had very severe pneumonia. We also grouped the study participants based on socioeconomic status – 3.9% were of class I, 8.4% were of class II, 19.0% were of class III, 29.1% were of class IV and 39.7% were of class V socioeconomic status. Based on birthweight, 10.1% children were between 1 to 2 kilograms, 58.7% were between 2.1 to 3 kilograms, 30.7% were between 3.1 to 4 kilograms, and 0.5% were between 4.1 to 5 kilograms.

The nutritional status was categorised according to the grades of malnutrition. While 72.6% children between two months and 60 months had no malnutrition, we noted that 15.6% children had Grade 1, 8.4% had Grade II, 2.8% had Grade III, and 0.5% had Grade IV malnutrition. Of the laboratory investigations performed, platelet count was of importance. We found that 40.2% children had platelet counts less that 4.99 lakhs, 48.0% had between five to seven lakhs, 10.1% had between 7.01 to 9 lakhs and 1.7% had between 9.01 and 10 lakhs.

We assessed the association between independent study variables and severity of thrombocytosis. We found that nasal flaring, stridor, and ESR were not associated with thrombocytosis. However, chest indrawing, grunting, severity of pneumonia, total leucocyte count, and duration of stay were significantly ($p<0.05$) associated with thrombocytosis – a statistically significant association.

Discussion

The present study was an observational cross-sectional study that aimed at determining the prevalence of thrombocytosis and its significance in predicting the severity of clinical manifestations in children with LRTI aged between 2 months to 5 years. The study enrolled a total of 358 children (based on sample size estimated) in accordance with prespecified inclusion and exclusion criteria.

Existing literature highlights that case fatality rates tend to be high among infants and young children.(18) The results of the study revealed that the majority (62.0%) of the participants

were between 2 months to 12 months of age, which indicates that this age group may be more susceptible to LRTI. Additionally, a higher proportion of males (62.6%) were included in the study population. The study findings indicated that 16.2% of the children aged two months to 60 months had pneumonia, and out of those, 55.3% had severe pneumonia, and 28.5% had very severe pneumonia. These results highlight the high burden of pneumonia in children and its potential severity, indicating that prompt diagnosis and treatment are crucial for positive clinical outcomes.(19, 20)

Socioeconomic status (SES) is an important factor that can significantly impact a child's health outcomes.(21) In this study, the participants were grouped based on SES, with 39.7% belonging to the class V SES, indicating a higher proportion of lower SES individuals. These results suggest that low SES may be associated with a higher risk of LRTI and its severity, potentially due to poor living conditions, inadequate nutrition, and limited access to healthcare. Birthweight is another important factor that can influence a child's health outcomes. The study found that the majority (58.7%) of the children had a birth weight between 2.1 to 3 kilograms. It is well established that low birth weight is associated with an increased risk of various health problems, including respiratory infections.(22, 23) However, the proportion of children with birth weights less than 2.5 kg was not reported in the study, which limits the interpretation of the findings. The study also investigated the prevalence of thrombocytosis and its association with clinical outcomes in children with LRTI. Thrombocytosis is a condition characterized by an abnormally high platelet count and has been linked with increased inflammation and disease severity in various conditions. The present study found that thrombocytosis was present in 19.4% of the children with LRTI. Overall, the study provides valuable insights into the prevalence of LRTI and its severity in children, highlighting the need for early diagnosis and prompt treatment. The study findings also underscore the importance of considering socio-economic factors and birth weight in assessing the risk and severity of LRTI in children.(24, 25) However, further research is needed to fully explore the significance of thrombocytosis in predicting clinical outcomes in children with LRTI.

The results showed that malnutrition was present in a significant proportion of children, with 15.6% having Grade 1 malnutrition, 8.4% having Grade II, 2.8% having Grade III, and 0.5% having Grade IV malnutrition. This finding is of particular concern as malnutrition is a major risk factor for infection and can contribute to increased morbidity and mortality.(26, 27) The study also investigated the importance of platelet count in predicting clinical outcomes in children with LRTI. The results showed that 40.2% of children had platelet counts less than 4.99 lakhs, 48.0% had platelet counts between five to seven lakhs, 10.1% had platelet counts between 7.01 to 9 lakhs, and 1.7% had platelet counts between 9.01 and 10 lakhs. Thrombocytosis, or an abnormally high platelet count, was not reported in the study. However, the results suggest that platelet count may be an important marker of disease severity in children with LRTI, as lower platelet counts were associated with more severe clinical manifestations. The study findings also indicated that the majority (72.6%) of children between 2 months to 60 months had no malnutrition. This is a positive finding, as it suggests that the majority of children in this age group have adequate nutrition, which is crucial for good health outcomes. However, the high prevalence of malnutrition in the study population indicates that there is a need for interventions to improve nutrition in at-risk populations. The study provides important insights into the prevalence of malnutrition and platelet count in children with LRTI, and their

potential significance in predicting disease severity. These findings underscore the importance of nutritional status and platelet count in the management of LRTI in children and highlight the need for further research in this area.

The results of tests of association are consistent with previous studies that have shown an association between thrombocytosis and disease severity in various infectious and non-infectious conditions, including sepsis, pneumonia, and cancer (Lippi et al., 2011; Levi et al., 2018).(28) Thrombocytosis has been proposed as a biomarker of inflammation and infection and has been shown to be associated with poor outcomes in critically ill patients (Levi et al., 2018). The association between thrombocytosis and severity of pneumonia is particularly noteworthy, as pneumonia is a common and serious complication of LRTI in children. Thrombocytosis may be a useful marker of disease severity in this context and may help guide clinical management and decision-making.(29, 30)

The study has some limitations, including its cross-sectional design and small sample size. Further research is needed to confirm the findings and explore the mechanisms underlying the association between thrombocytosis and disease severity in children with LRTI. In conclusion, the study provides important insights into the association between thrombocytosis and clinical and laboratory parameters in children with LRTI. The findings suggest that thrombocytosis may be a useful marker of disease severity in this population and highlight the importance of monitoring platelet count in the management of LRTI in children.

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Table 1: Distribution of study variables

Study variables		**Number (n)**	**Percentage (%)**
Age (in months)	2 to 12	222	62.0
	13 to 60	136	38.0
Gender	Female	134	37.4
	Male	224	62.6
LRTI	Pneumonia	58	16.2
	Severe pneumonia	198	55.3
	Very severe pneumonia	102	28.5
Socioeconomic status	I	14	3.9
	II	30	8.4
	III	68	19.0
	IV	104	29.1
	V	142	39.7
Birth weight (in kgs)	1 to 2	36	10.1
	2.1 to 3	210	58.7
	3.1 to 4	110	30.7
	4.1 to 5	2	0.5
Nutritional status (malnutrition)	No malnutrition	260	72.6
	Grade I	56	15.6
	Grade II	30	8.4
	Grade III	10	2.8
	Grade IV	2	0.5
Platelet count (in lakhs)	Less than 4.99	144	40.2
	5 to 7	172	48.0
	7.01 to 9	36	10.1

	9.01 to 10	6	1.7
LRTI, lower respiratory tract infection			

Table 2: Tests of association

Thrombocytosis		**No**	**Mild**	**Moderate**	**Severe**	**p value**
		n (%)	**n (%)**	**n (%)**	**n (%)**	
Chest indrawing	Present (n = 290)	60 (20.7)	194 (66.9)	30 (10.3)	6 (2.1)	0.001*
	Absent (n = 68)	36 (52.9)	26 (38.2)	4 (5.9)	2 (2.9)	
Nasal flaring	Present (n = 230)	54 (23.5)	154 (67.0)	20 (8.7)	2 (0.9)	0.211
	Absent (n = 128)	42 (32.8)	66 (51.6)	14 (10.9)	6 (4.7)	
Grunting	Present (n = 106)	12 (11.3)	76 (71.7)	14 (13.2)	4 (3.8)	0.008*
	Absent (n = 252)	84 (33.3)	144 (57.1)	20 (7.9)	4 (1.6)	
Stridor	Present (n = 8)	0 (0.0)	4 (50.0)	4 (50.0)	0 (0.0)	0.127
	Absent (n = 350)	96 (27.4)	216 (61.7)	30 (8.6)	8 (2.3)	
Severity of pneumonia	Pneumonia (n = 56)	34 (60.7)	20 (35.7)	2 (3.6)	0 (0.0)	<0.001*
	Severe (n = 204)	56 (27.5)	136 (66.7)	10 (4.9)	2 (0.1)	
	Very severe (n = 98)	6 (6.1)	64 (65.3)	24 (24.5)	4 (4.1)	
Total leucocyte count	<5000 (n = 6)	4 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	0.049*
	5000 to 15000 (n = 230)	68 (29.6)	144 (62.6)	14 (6.1)	4 (1.7)	
	>15000 (n = 122)	24 (19.7)	76 (62.3)	18 (14.8)	4 (3.3)	
ESR	Less than 20 (n = 58)	24 (41.4)	26 (44.8)	8 (13.8)	0 (0.0)	0.225
	More than 20 (n = 300)	72 (24.0)	194 (64.7)	26 (8.7)	8 (2.7)	
Hospital stay	Less than a week (n = 140)	60 (42.9)	70 (50.0)	10 (7.1)	0 (0.0)	0.024*
	More than a week (n = 218)	56 (25.7)	130 (59.6)	24 (11.0)	8 (3.7)	

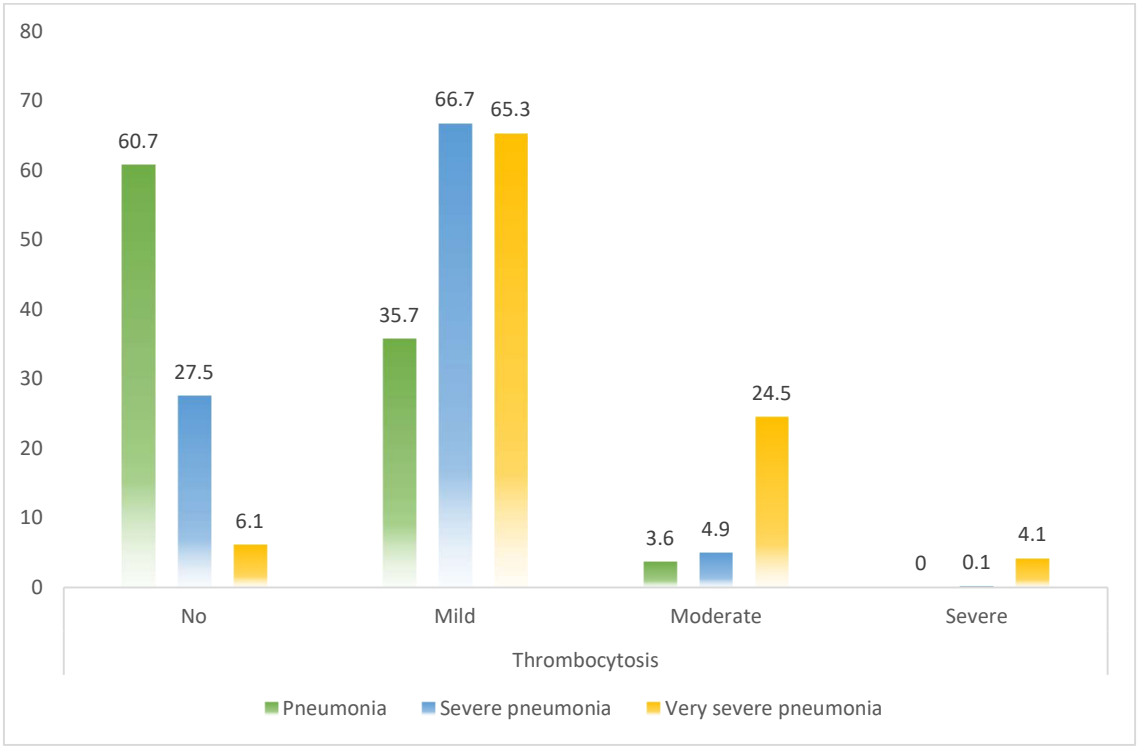

Figure 1: Association between severity of pneumonia an thrombocytosis