

Significance of thrombocytosis in lower respiratory tract infections

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Abstract

Background and Objective: Infections of the respiratory tract are perhaps the most common human ailment. Its incidence in developing countries range between 20 and 30 percent. Pneumonia is one of the leading causes of mortality among under five children in most developing countries, accounting for almost 18 percent of under five deaths. Platelets have long been recognized for their importance in maintaining hemostasis and for their contribution to wound healing. However, platelets have historically been underappreciated for their contributions to antimicrobial host defense. The objective of this study was to determine the association of thrombocytosis with severity of clinical manifestations, complications and outcome of lower respiratory tract infections in children aged between 2 months and 5 years. **Methods:** The present study was a prospective study done over a period of 12 months on 220 children hospitalised with lower respiratory tract infections in the age group of 2 months to 5 years. In accordance with the platelet count, they were divided into children with thrombocytosis and children without thrombocytosis. Severity of lower respiratory tract infection, complications and outcome of the children with thrombocytosis and without thrombocytosis were analysed. **Results:** 70% percent of children were in the age group of 2 months to 12 months. Severity of pneumonia was more in infancy and common among low socioeconomic status. 35% of study population had thrombocytosis, out of which 68.8% of the children were in the age group of 2 months to 12 months. Association of thrombocytosis and leukocytosis with severity of pneumonia was significant. 83.3% of cases with pleural effusion had thrombocytosis. Mean duration of hospital stay was 4.52 days. There was significant association of thrombocytosis with prolonged hospital stay. Mortality was seen in 3.2% of cases and its association with thrombocytosis was not statistically significant. **Conclusion:** Thrombocytosis is a common finding among children with lower respiratory tract infection, especially in infancy. Children with thrombocytosis have more severe clinical condition and longer hospitalization. Platelet count increases as the severity of pneumonia increases. Importantly, thrombocytosis occurs almost exclusively in children with pleural effusion. Platelet count may be used as useful marker associated with severity of lower respiratory tract infection and its complications.

Keywords: Lower respiratory tract infection; Pneumonia; Thrombocytosis; Severity; Pleural effusion.

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INTRODUCTION

Acute respiratory infection (ARI) is defined as acute onset of respiratory symptoms including cough, rhinorrhea, fast or difficulty in breathing; chest wall in drawing and wheeze of less than 14 days duration.¹ ARI

is often classified depending upon the site of infection as – Upper respiratory tract infection and Lower respiratory tract infection. LRIs are the most common cause of illness and death in children. With an estimated 146-159 million new episodes per year in developing countries, pneumonia is estimated to cause approximately 4 million deaths among children.² While the incidence of lower respiratory tract infections in developed countries may be as low as 3-4%, its incidence in developing countries range between 20% and 30%. In India, in the states and districts with high infant and child mortality rates, ARI is one of the major causes of death. Up to 13% of inpatient deaths in pediatric wards are due to ARI. Lower respiratory tract infections include epiglottitis, laryngitis, laryngotrachietis, bronchitis, bronchiolitis and pneumonia.³ Pneumonia is one of the leading causes of morbidity and mortality in children under five years of

age. Recent estimates from the World Health Organization suggest that pneumonia is responsible for 20% of deaths in the above age group, leading to 3 million deaths per year. Of these deaths, two thirds occur during infancy and more than 90% occur in the developing countries.^{4,5} In India, recent estimates in under-fives suggest that 13% of deaths and 24% of National Burden of Disease is due to pneumonia.⁶ Hospital based studies have reported that 20 – 30% of admissions in under-fives are due to pneumonia. Case fatality rates in hospitalized children are reported to be between 8.7% and 47%.^{7,8}

Role of platelets in infections

Platelets play a major role in antimicrobial host defence, the induction of inflammation and tissue repair.⁹ Activation of platelets by agonists enhances platelet interactions with complement proteins and humoral immune components, as well as leukocytes and endothelial cells. They are capable of binding, aggregating and internalizing micro organisms, which enhances the clearance of pathogens from bloodstream and also participate in antibody dependent cell cytotoxicity functions to kill protozoal pathogens by releasing array of potent antimicrobial peptides. Inflammatory thrombocytosis is related to increased levels of several cytokines such as thrombopoietin, interleukin-6, interleukin-1alpha, interleukin-8 and tumour necrosis factor alpha.¹⁰ Severe community acquired pneumonia is associated in the literature with significant increment of plasma levels of the inflammatory cytokines TNF- α , IL-1b, IL-6, IL-8. The TNF- α , IL-1b and IL-6 were also elevated in the bronchoalveolar lavage fluid of patients with community acquired pneumonia.^{11,12}

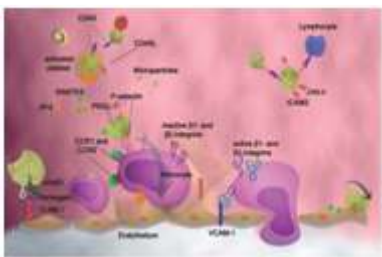


Figure 1: Interactions of platelets with different leukocyte subtypes regulate vascular inflammation. A multitude of molecular mechanisms and platelet derived components mediate and regulate platelet-induced leukocyte infiltration including chemokine deposition and mononuclear and endothelial cell activation

Thrombocytosis

Normal platelet counts range between 150000/mm³ and 450000/mm³.¹³ Thrombocytosis or elevation in the peripheral blood platelet count to values >500,000/mm³ is common in infancy and childhood, occurring in 3 to 13%

of children.⁹ Reactive thrombocytosis has an estimated incidence of 6–15% among hospitalized children. Bacterial or viral infections (acute or chronic) are the most common cause for reactive thrombocytosis (37–78%) at any age during childhood. Within this group, infections of the respiratory tract account for 60–80% of reactive thrombocytosis, followed by infections of the gastrointestinal and urinary tract.^{14,15} Regarding infections of the respiratory tract, thrombocytosis is a common finding among patients with LRI, being particularly prominent in those with pleural effusions or empyema. In some studies, children admitted for lower respiratory tract infection with thrombocytosis had more severe presentation at admission and had a severe and protracted clinical course resulting in longer duration of hospitalization.¹⁶ Those findings most likely indicate that the excessive platelet production is closely associated with the degree of tissue inflammation. Thrombocytosis can be a useful marker associated with more severe infection of the lower respiratory tract.

OBJECTIVES

To determine association of thrombocytosis with

- Severity of clinical manifestations,
- Complications and outcome

of lower respiratory tract infections in children aged between 2 months and 5 years.

METHODOLOGY

A prospective study was done on thrombocytosis in children admitted with lower respiratory tract infections aged between 2 months and 5 years at Cheluvamba Hospital attached to Mysore Medical College and Research Institute, Mysore, Karnataka. It is a teaching hospital and also tertiary care centre, constitutes largest referral centre in Mysore District. The patient population comprises, mainly of low income group from rural areas, urban slums, referred patients from surrounding rural areas, private clinics and adjacent district hospitals.

Study Design: Descriptive study

Period of Study: July 2012 - June 2013 (12 months)

INCLUSION CRITERIA

All children from 2 months to 5 years admitted to Cheluvamba Hospital attached to MMCRI, Mysore, with lower respiratory tract infections meeting the criteria in ARI control programme (WHO).³

EXCLUSION CRITERIA

Children <2 months and >5 years and Children with associated anaemia (Hb<11g/dl), neuroinfections, connective tissue disorders, or congenital heart diseases. 220 children admitted to Cheluvamba Hospital with lower respiratory tract infections in the age group of 2 months to 5 years were included in the study. In accordance with

the platelet count, the study population was divided into children with thrombocytosis and children without thrombocytosis. Severity of lower respiratory tract infection was graded according to ARI classification (WHO) as pneumonia, severe pneumonia and very severe pneumonia. The clinical condition at admission, course in the hospital, complications and outcome of the children with thrombocytosis and children without thrombocytosis were analysed. Children without thrombocytosis included those with normal platelet count (1.50-4.50Lakhs/mm³) and low platelet count (<1.50Lakhs/mm³). Children with platelet count from 4.51-4.99 Lakhs/mm³ were also included in this group, as according to definition, thrombocytosis in children is >5.00 Lakhs/mm³. Thrombocytosis was further divided as mild (5.00-7.00Lakhs/mm³), moderate (7.01-9.00Lakhs/mm³), severe (9.01-10.00Lakhs/mm³) and extreme (>10.00Lakhs/mm³) thrombocytosis.¹³ A predesigned proforma was used to collect information regarding age, sex, socio demographic profile, presenting complaints like duration of fever, cough, hurried breathing, chest in drawing, decreased feeding, lethargy, convulsions. Complete general physical examination, systemic examination with special orientation towards respiratory system like Respiratory Rate, SpO₂, capillary refilling time, chest in drawing, stridor, grunting, crepitations, rhonchi were noted. Routine and relevant investigations such as Hb%, Total leukocyte count, ESR, Platelet count and Chest X-ray were done. Complications like parapneumonic effusion/empyema, pneumatoceles, septic shock and respiratory failure were noted. Number of deaths were also noted.

STATISTICAL METHOD USED

Descriptive statistics, SPSS for windows (version 16.0), Chi square test.

RESULTS AND ANALYSIS

70% (154) of the cases were in the age group of 2 months to 12 months, and rest 30% (66) of the cases were in the

age group of 13 months to 60 months (5 years). 50% (110) of the cases were severe pneumonia, 26.4% (58) were very severe pneumonia and 23.6% (52) were pneumonia. (Table: 1)

Table 1: Severity of pneumonia

LRI	Number
Pneumonia	52 (23.6)
Severe pneumonia	110 (50)
Very severe pneumonia	58 (26.4)
Total	220 (100)

Out of 154 cases in the age group of 2 months to 12 months, majority of the cases were admitted with severe pneumonia (80 children) followed by very severe pneumonia (43 children), whereas in the age group of 13 months to 60 months majority were admitted with severe pneumonia (30 children) and pneumonia (21 children). This indicates that severity of pneumonia is more in infancy. Severity of pneumonia was more in class IV socioeconomic status (85%). Severity of pneumonia increases as the birth weight decreases and was more in children of birth weight <1.5 kgs (P-value 0.024). 130 (59%) cases were undernourished and 90 (41%) cases had adequate nutrition. Severity of pneumonia increased significantly (P-value<0.001) in children with under nutrition as compared to children with adequate nutrition. Among very severe pneumonia, 82.7% of the children were undernourished and remaining 17.3% had adequate nutrition. Thrombocytosis was found in 77 (35%) children. Out of total 77 cases, 53 children were in the age group of 2 months to 12 months. This shows that thrombocytosis was more common in infancy. Significant association between platelet count and severity of pneumonia was seen (P-value 0.017). Among 4 children with severe thrombocytosis (9.01-10.00 L/mm³), 3 had very severe pneumonia and 1 had severe pneumonia. It indicates that platelet count increases as the severity of pneumonia increases. (Table 2)

Table 2: Relationship between platelet count and severity of pneumonia

Platelet count (lakhs/cumm)		Pneumonia	Severe Pneumonia	Very Severe Pneumonia	Total	P-value
Without thrombocytosis	<1.5	3 (16.6)	6 (33.3)	9 (50)	18 (100)	0.017
	1.50-4.99	38 (30.4)	64 (51.2)	23 (18.4)	125 (100)	
	5.00-7.00 (mild)	10 (19.6)	26 (50.9)	15 (29.4)	51 (100)	
	7.01-9.00 (moderate)	1 (4.7)	12 (57.1)	8 (38.1)	21 (100)	
With thrombocytosis	9.01-10.00 (severe)	0 (0.0)	1 (25)	3 (75)	4 (100)	
	>10.00 (extreme)	0 (0.0)	1 (100)	0 (0.0)	1 (100)	
	Total	52 (23.2)	110 (50)	58 (26.4)	220 (100)	

Significant association between Total Leukocyte Count and the severity of pneumonia was seen (P-value 0.004). Among 58 cases of very severe pneumonia, 55.2% had

TLC between 5000-15000/mm³, 41.4% cases had TLC >15000/mm³ and 3.4% had TLC <5000/mm³.(Table:3)

Table 3: Relationship between TLC and severity of pneumonia

TLC(/mm ³)	Pneumonia	Severe Pneumonia	Very Severe Pneumonia	Total	P-Value
< 5000	1 (1.9)	3 (2.7)	2 (3.4)	6 (2.72)	0.004
5000 - 15000	46 (88.5)	80 (72.8)	32 (55.2)	158(71.8)	
>15000	5 (9.6)	27 (24.5)	24 (41.4)	56 (25.4)	
Total	52 (100)	110 (100)	58 (100)	220 (100)	

All 4 cases of severe thrombocytosis (9.01-10.00 Lakhs/mm³) and 1 case of extreme thrombocytosis (>10.00 Lakhs/mm³) had TLC >15000/mm³. With increase in Total Leukocyte Count, the Platelet count also increases. Significant association of thrombocytosis and

leukocytosis with increasing severity of pneumonia was noted (P-value 0.004). Majority of children with Chest X-ray showing lobar pneumonia and pleural effusion had severe pneumonia and very severe pneumonia.

Table 4: Relationship between platelet count and chest x ray findings

Platelet count	Chest X –Ray				P-value
	Normal	BPI	LP	PE	
Without thrombocytosis	18 (75)	113 (64.2)	11 (78.6)	1(16.7)	0.004
With thrombocytosis	6 (25)	63 (34.8)	3 (21.4)	5 (83.3)	
Total	24 (100)	176 (100)	14 (100)	6 (100)	

*BPI: Bronchopulmonary infiltrates, LP: Lobar pneumonia, PE: Pleural effusion.

Significant association was seen between thrombocytosis and pleural effusion (P-value 0.004). Out of six children with pleural effusion, 83.3% (5 cases) had thrombocytosis. In children with Chest X-ray feature

suggestive of bronchopulmonary infiltrates and lobar pneumonia, majority had platelet count within normal range. Mean duration of stay was 4.52 days.

Table 5: Relationship between platelet count and duration of hospital stay

Platelet count	Duration of hospital stay				Total	P-value
	1-3 days	4-6 days	7-9 days	≥10 days		
Without thrombocytosis	54 (76)	71(59.2)	14(73.7)	4 (40)	143 (65)	0.010
With thrombocytosis	17 (24)	49(40.8)	5 (26.3)	6 (60)	77 (35)	
Total	71(100)	120(100)	19 (100)	10(100)	220(100)	

Significant association of thrombocytosis with duration of hospital stay was noted (P-value 0.010). Children admitted with LRI having thrombocytosis had longer duration of hospital stay, which indirectly indicate more severity of pneumonia. Mortality was more common in children with thrombocytosis, but this association of thrombocytosis with mortality was not statistically significant.

DISCUSSION

Acute respiratory infections (ARI) may cause inflammation of respiratory tract anywhere from nose to alveoli, with a wide range of combination of symptoms and signs. ARI is often classified by clinical features depending on site of infection as upper respiratory tract infections and lower respiratory tract infections. **Upper respiratory tract infections include:** common cold, pharyngitis and otitis media. **Lower respiratory tract infections include:** epiglottitis, laryngitis,

laryngotrachietis, bronchitis, bronchiolitis and pneumonia. Case fatality rates tend to be high in young infants and young children. They are affected more often with more severity.³ In present study, out of 220 subjects, 154 (70%) were in age group of less than 12 months. This is comparable to study done by Karalanglin Tiewsoh *et al* in 2008 at AIIMS, New Delhi, where cases under the age group of 12 months were 71%.¹⁷ Severity of illness was more in infancy. In a study done by Sehgal V *et al* (1997) in New Delhi, severity of pneumonia and case fatality rate was more in children less than one year.⁷ He also stated that age less than 1 year was a independent risk factor for mortality. In the present study, 85% (187) of the cases were from class IV socioeconomic status which correlates with other studies^{17,18} Severity of pneumonia increased significantly (P-value<0.001) in children with under nutrition as compared to children with adequate nutrition. Among very severe pneumonia 82.7% of the children were undernourished. Similar finding was noted

in a study done by R Nantanda *et al* (2008) where P-value was 0.002.¹⁹ Thrombocytosis was noted in 35% of the study population, among which 68.8% of the children were in the age group of 2 months to 12 months. In study conducted by Vlachia *et al* in 2006, thrombocytosis was observed in 34.5% of the children aged <12months.¹⁶ In our study, significant association was noted between platelet count and severity of pneumonia (P-value 0.017). As the severity of pneumonia increases, platelet count also increases. In present study, 8.2% had low platelet count, 56.8% had normal platelet count and 35% had thrombocytosis. Among children with thrombocytosis, 66.2% had mild thrombocytosis, 27.3% had moderate thrombocytosis, 5.7% had severe thrombocytosis and 1.3% had extreme thrombocytosis. This is comparable to studies done by Sutor *et al* (1999), Yohannan *et al* (1994), Heng and Tan (1998), where mild thrombocytosis was seen in 72-86%, moderate thrombocytosis in 6-8%, severe thrombocytosis in 3%, and extreme thrombocytosis in 0.5%.^{14,15,20} Study done by Vlachia V *et al* (2006), 48% of total admission with LRI had platelet count >5.00Lakhs/mm³ and children with thrombocytosis had more serious illness (P-value<0.001).¹⁶ Study by Unsal E *et al* (2005) noted severe symptoms in patients with thrombocytosis than in patients with normal platelet count (P-value 0.004).²¹ Among total 220 cases, 2.72% of the cases had TLC<5000/mm³, 71.8% of the cases had TLC between 5000-15000/mm³ and 25.4% of the cases had TLC >15000/mm³. This is comparable to a study conducted by Purcell K *et al* (2007), where 3% of the cases had TLC <5000/mm³, 73.2% had TLC between 5000- 15000/mm³, and 22.2% had TLC >15000/mm³.^{3,22} All 4 cases of severe thrombocytosis and 1 case of extreme thrombocytosis, had Total Leukocyte Count >15000/mm³. This shows that, with increase in total leukocyte count, platelet count also increases (P-value<0.001). Study done by Mirsaedi M *et al* (2009), on community acquired pneumonia showed that platelet count was strongly associated (P-value 0.009) with 30 day mortality, whereas no association was observed for leukocyte count (P-value 0.5114) and concluded that an abnormal platelet count is a better predictor of outcome than an abnormal leukocyte count.²³ Significant association was seen between thrombocytosis and pleural effusion (P-value 0.004). Out of six children with pleural effusion, 83.3% (5 cases) had thrombocytosis which is comparable to many studies.^{16,24,25} Significant association of thrombocytosis with duration of hospital stay was noted (P-value 0.010). Children admitted with LRI having thrombocytosis had longer duration of hospital stay, which indirectly indicate more severity of pneumonia. Similar finding was noted in a study done by Vlachia V *et al* in 2006, where the association of

thrombocytosis with length of hospital stay was significant (P-value 0.03).¹⁶ Another study in 2012 by Prina E *et al* also shows similar results with P-value of 0.004.²⁵ Association of thrombocytosis with outcome of children having LRI was not statistically significant (P-value 0.354) in the present study. But studies done by Prina E *et al* in 2012 and Mirsaedi M *et al* in 2009 concluded that there was a significant association of thrombocytosis with outcome (30 day mortality) with P-value<0.001 and 0.009 respectively.^{23,25}

CONCLUSION

Thrombocytosis is a common finding among children with lower respiratory tract infection, especially in infancy. Children with thrombocytosis have more severe clinical condition and longer hospitalization. Platelet count increases as the severity of pneumonia increases. Importantly, thrombocytosis occurs almost exclusively in children with pleural effusion. Platelet count may be used as a useful marker associated with severity of lower respiratory tract infection and its complications.

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