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Anemia: A Risk Factor for Acute Lower Respiratory Tract Infection in Children under 5 years of age

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Abstract
Background: *Anemia in children with Lower tract respiratory infection (LRTI) is a common phenomenon that have crucial role on outcome and quality of life. Proving the observation in our country context, the present study was designed to evaluate the role of anemia as a risk factor among children <5 years along with LRTI.*
Methods: *The case-control study was conducted among 59 childrenaged <6 years and were admitted in Dhaka Shishu (Children) Hospital for the period of June 2019 to November 2019. They study population was divided into two groups where case was defined as- children with LRTI and controls were apparently healthy children. Age and sex matched were done. The study protocol conformed to the ethical guideline of the current Declaration of Helsinki and was approved by local ethics committee. All parents gave consent before participation. Data analysis was done by Statistical Package for Social Science (SPSS) version 22.0.*
Observation and Results:*Both case and control group were similar in terms of socio-demographic profile eg. age, sex, residence and socioeconomic status (p value >0.5 for all). Children with LRTI had significantly more anemia than control (83.18 vs 0.09%, p<0.001). Further analysis revealed that anemia is a predictor of LRTI (OR 323.272, 95% CI 19.910-5248.798; p=.001)*
Conclusion:*Anemia was significantly found to be associated with acute lower respiratory tract infections in children under five years of age. Prevention of anemia, irrespective of etiology, early diagnosis and treatment is important to reduce the incidence of lower respiratory tract infections in children.*
Key words:*Anemia, Bronchiolitis, Lower tract respiratory infection, Risk factors.*

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I. Main Body:

Background

Acute Lower Respiratory Tract Infections (LRTI) is one the major causes of childhood mortality under the age of 5 years in developing countries (1). Per year, children under age of 5 are affected by 5 to 6 episodes of LRTI (2). It is responsible for 21% of all deaths in children younger than five years in Southeast Asia (3). AcuteLRTI includes croup syndromes, bronchitis, bronchiolitis and pneumonia. Several risk factors increase the risk of development of LRTI like- lack of breast feeding, overcrowding, under nutrition, delayed weaning, and pre-lacteal feeding. Other associated conditions are PEM, infectious diseases, and secondary bacterial infections (4).

Anemia is a major public health problem commonly found among pregnant women and young children (mostly 0-5years of age). It affects approximately 30% of children all over the world (5). Global prevalence of anemia is around 47% among preschool children (2). In Bangladesh, most of the people are lower middleclass

and low-income group. So, anemia prevalence is high (6). Along with others risk factors, low hemoglobin is also associated with ALRTI. Anemia can result in an abnormal immune response leading to increased incidence of LRTI (7). Moreover, nutritional factors such as iron, zinc, vitamin A and others are closely related to the body's resistance to infection and decrease of this are responsible for development of infection (8). Evidence suggest thatlow hemoglobinlevel is significantly associated with LRTI (5). Study in Egypt (8) and India (9) also agreed with the preceding evidence. Iron-deficiency anemia is commonly found with LRTI. It has been suggested that preventive effect against infections is supported by iron supplementation in children under 5 years of age (10). Anemic children are 3.59 times more susceptible to lower respiratory tract infections found by Yogesh Avhad et al (2). In other study these patients are found to be 4.6 times more susceptible to LRTI (11).
Both anemia (mainly iron deficiency) and acute LRTI are more common in developing countries like Bangladesh. The cost-effective prevention of LRTI by correction of anemia may reduce incidence of morbidity and mortality of under 5 children.Adequate nutritional supplementation and food fortification may also improve the immunity and develop resistance power against infections. Therefore, the study aimed to determine if anemia is a risk factor for lower respiratory tract infections in children under age of 5.

II. Materials and Methods:

Patients and Methods:

This case–control study was conducted at department of paediatric respiratory medicine (pulmonology), Dhaka Shishu (Children) Hospital in the period from June 2019 to December 2019.For the convenient of the study, the study participants were divided into two groups: group I (cases) included 37infants and children under 5 years of age admitted into the study site with LRTIs, whereas group II included 22 apparentlyhealthy infants and children (<5 years) without anyrespiratory problems as a control group, from the attendance of vaccination.Children with diagnosis of LRTI within the age range 6 months-up to 5 years of age were included into the study. LRTI was defined by the presence of fever, cough, increased respiratory rate for age, chest indrawing, and rhonchi or crepitation on auscultation (12). On the other hand, children with presence of any otherknown risk factors for LRTIs, including prematurity,congenital chest wall malformations, passive smoking,intake of iron supplements, and severe systemic illnesse.g. malnutrition, congenital heart disease, andtuberculosis were excluded from the study. Moreover, the parents who did not provide consent to the participation were also excluded from the study.

Data collection methods: parents of the selected children (in according to the inclusion and exclusion criteria)were first approached following providing details of the study including objectives, and study procedure. Then written informed consent was ensured for each child. The data collection was done by NA along with a pre-formed questionnaire. The interview duration was in an around 30 minutes. In case of any interruption, the interview session was stopped and subsequently contacted with the parents. All of the study population were independent of giving necessary information during study and there were no financial benefits other than usual management. Ethical measures were followed in accordance to the Helsinki declaration and ethical clearance was taken from the Ethical Review Committee (ERC) of the study place. Privacy and confidentiality of all patients were maintained strictly throughout the procedure.

Validation and preparation of the study instrument: A preformed questionnaire was used to assess the patients and relevant data were also collected by clinical history taking, clinical examination and relevant investigations. The questionnaire was made from the insight of the previous study of this topic. The questionnaire was pre-tested in the arena of the Dhaka Shishu (Children) hospital (total sample size was 10) and from the experience of the pre-testing, sufficient modification was done and final questionnaire was prepared.

Ethic statement: The study team was aware of the ethical measures whole over the study period and formal ethical approval was taken from the Dhaka Shishu Hospital before commencement of the study.

Statistical analyses:

After collection of all the required data, these were checked, verified for consistency and then tabulated into the computer using the Package for Social Sciences (SPSS Inc., Chicago, IL,version 20.0 for Windows). Normality of data was first checked by measures of Kolmogorov–Smirnov tests of normality. For normally distributed data, means was compared using Student's t-test for two groups. Qualitative or categorical variables was described as frequencies and proportion and proportion was compared using Chi square test. Moreover, regression analysis was done to find out the factors responsible for anemia. All statistical tests was two-sided and performed at a significance level of $p =<0.05$.

III. Results:

Age group of study population varied from 1 month to 6 years old. Of all, mean age was 14.51±11.89 (SD) months. In both group- cases and controls, majority children were in age group 7-10 months (32.4%, n=12 in cases and 31.8%, n=7 in controls). Among cases, male population was 54.1% (n=20) and female population

was 45.9% (n=17). Among controls, female population was 63.6% (n=14) and male population was 35.4% (n=8). About 51.4% (n=19) patients in case group and 45.5% (n=10) in control group were from rural area. Regarding socio economic class, 40.54% (n=15) among cases and 13.63% (n=3) among controls belonged to lower socio economic class while 45.95% (n=17) among cases and 63.63% (n=14) among controls belonged to middle socio economic class. About 13.48% (n=4) from cases and 22.74% (n=6) from controls belonged to upper socio economic class. No statistical difference was noted between cases and controls regarding age, sex, residence and socio economic class (p>.05).

Regarding obstetric variables, 67.56% (n=25) mothers were primigravida among cases and 63.63% (n=14) were primigravida among controls. In both groups majority children were term babies (83.79%, n=31 in cases and 81.81%, n=18 in controls). About 43.25% (n=16) children born in health care facilities among cases while 54.55% (n=12) children born in health care facilities among controls. Rest of both group born in home. Rate of vaginal delivery was 64.86% (n=24) and rate of LSCS was 35.14 (n=13) among cases. Rate of vaginal delivery was 77.27% (n=17) and rate of LSCS was 22.73 (n=5) among controls. No statistical difference was noted between two groups regarding parity of mother, gestational age, place of delivery and mode of delivery (p>.05).

Presenting clinical features were fever 89.19% (33), cough, 94.59% (n=35), breathlessness 35 (94.59%), indrawing of intercostal space 22 (59.45%), running nose 29.72% (11), history of repeated attack of RTI 43.24% (16), vomiting/diarrhea 18.91% (7), failure to thrive 29.72 (11) and poor feeding 78.37% (29).

Mean haemoglobin level among cases was 8.21±2.19 gm/dl and among controls was 12.06±.82 gm/dl. haemoglobin level was found significantly low among cases in compare to controls revealed by student t test (p<.001). Mean serum ferritin level was 11.89±1.77ng/ml among cases and 13.04±.78ng/ml. About 24.32% (n=9) children among cases had low serum ferritin level than normal value while among control only 9.09% (n=2) had low level of serum ferritin. The difference was not significant (p>.05). Among cases, 89.18% (n=33) children had anemia and among controls 9.09% (n=2) children had anemia. Peripheral blood smear showed that, among all anemic children 88.57%'s (n=31) Red Blood Cell was of microcytic hypochromic type and 11.43%'s Red Blood Cell was of normocytic normochromic (n=4).

Bivariate logistic regression analysis of risk factors revealed that presence of anemia and low socio economic condition are significant risk factors for lower respiratory tract infection with LRTI [313.599 OR , 95% CI (26.626-3261.255); p=<.001] and [4.250 OR , 95% CI (1.050-17.202); p=.043] respectively. Multivariate logistic regression analysis of risk factors revealed that presence of anemia is a significant risk factors for lower respiratory tract infection with LRTI [323.272 OR, 95% CI (19.910-5248.728); p=<.001].

IV. Discussion

LRTI is a group of infections with different etiology, risk factors, pathogenesis, clinical presentations and outcomes. The etiology, epidemiology and clinical features vary with age, gender, risk factors, season, place and environment. Typically, LRTI are affected by certain factors which are modifiable by simple interventional measures like lack of breast feeding, overcrowding, under nutrition, delayed weaning and prelacteal feeding but some associated conditions like PEM, infectious diseases, secondary bacterial infections make children vulnerable for mortality and morbidity (13). The etiological microorganisms of LRTI are viral, bacterial in origin or both combined together (14). Anemia is a clinical condition which occurs due to decrease in the level of hemoglobin below the level insufficient to meet the body's physiologic need. Anemia is a major health hazard in all age groups, but the prevalence is higher in children and pregnant women. Children up to 5 years are in age group where infections, most commonly pneumonia and gastroenteritis are more frequent (15). Identifying risk factors and implementing preventive measures has always been a mainstay for long term disease management, control and prevention.

In this study, mean haemoglobin level among cases was 8.21±2.19 gm/dl and among controls was 12.06±.82 gm/dl where haemoglobin level was found significantly low among cases (p<.001). Among LRTI patients, 89.18% (n=33) children had anemia and only 9.09% (n=2) children had anemia among healthy children with statistical difference. Bivariate logistic regression analysis of risk factors revealed that presence of anemia and low socio economic condition are significant risk factors for lower respiratory tract infection with LRTI [313.599 OR , 95% CI (26.626-3261.255); p=<.001] and [4.250 OR , 95% CI (1.050-17.202); p=.043] respectively. Multivariate logistic regression analysis of risk factors revealed that presence of anemia is a significant risk factors for lower respiratory tract infection with LRTI [323.272 OR, 95% CI (19.910-5248.728); p=<.001].

Anemia was also found as risk factor for LRTI by Rashad et al. (16) and Abdel Maksoud et al. (17).Maurad et al. stated that there was statistical significant difference of between both anemic group and hospitalized cases when compared with non-anemic group and healthy controls regarding history of recurrent chest infections, as it was higherin children with anemia (37.5% vs 14.5%) than non-anemic children and they concluded that when anemia was present, children were two times more susceptible to have LRTI (5). Roma et

al. did a study on 100 cases with ALRTI and 100 controls and found that 72% of cases and 34% of controls were anemic, with an OR of 4.99 and 95% CI: 2.73–9.1 and concluded that children with anemia when compared with control group were found to be 4.99 times more susceptible to ALRTI (18).
In this study, about 40.54% (n=15) among cases and 13.63% (n=3) among controls belonged to lower socio economic class while 45.95% (n=17) among cases and 63.63% (n=14) among controls belonged to middle socio-economic class. Savitha et al. found that low socioeconomic status was significantly associated with ALRI. Similar results were found by Cunha AL et al even after adjusting for other risk factors like nutritional status(19). Low Socio Economic Status leads to less access to social, human and material resources and this facts lead to less awareness regarding health care facilities and importance of seeking early consultation for illness of their children. Another associated co condition is overcrowding which contributes to the transmission of infections through respiratory droplets hence more prevalence of LRTI.

Mean age of study population was 14.51±11.89 (SD) months with a majority in age group 7-10 months (32.4%, n=12 in cases and 31.8%, n=7 in controls). Acute lower respiratory tract is one of the leading cause of mortality in the children under 5 years of age worldwide, accounting to 16% of deaths under 5 years of age (15). The prevalence is even prominent in the developing countries. Shakya et al. found the most common affected age group was 3 months to 23 months. Malla T et al. (20) and Ashraf M et al. (21) also found the commonest age group was 3 months to 23 months. Male population was predominant among case (54.1% n=20) and while vice versa was noted among controls with 45.9% (n=17) female population. No significant association with gender was found as among various studied populations (20-23). The higher number of male children might be attributed to gender biasness for early admissions hospitals seen in our society. No statistical difference was noted between cases and controls regarding age, sex, residence and socio economic class ($p>.05$).

In a human body hemoglobin performs significant physiological role such as regulating oxygen and carbon dioxide transport and carrying and inactivating nitric oxide (24). So, quantitative and/or qualitative reductionin hemoglobin adversely affect the normal physiological functions. Alveolar macrophages obtain iron primarily from the metabolism of RBC and from plasma pool (25). So, function of alveolar macrophages might be hampered during anemia and creates a vulnerable environment for LRTI.

V. Conclusion:

In conclusion, this study clearly highlighted that presence of anemia is a significant risk factor of LRTI in children <5 years of age. Prevention and early diagnosis of anemia seems to be important to reduce the incidence of lower respiratory tract infection. Further research needs to be considered to consolidate this significance and other risk factors.

Limitations: The present study was a hospital-based study and hospitalized cases may not represent full entity of LRTI cases in the community as this needs an extensive population-based research including health care facilities at community level, primary, secondary and higher health care institutes. Another limitation of this study was small sample size.

Declarations:

Ethical consideration

This study was approved by the ethical committee of the DSH. Moreover, the researchers were duly concerned about the ethical issues and the ethical issues were maintained in according to the current Declaration of Helsinki.

Consent of Publication: Not applicable.

Availability of data and material: Data and materials supporting study findings in the manuscript will not be shared. It was not in accordance with participants' written informed consent. However, it can be shared with the reviewer team on request.

Competing Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Supplementary Materials: Available on request.

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Tables and Figures:

Table 1: Distribution of respondents by socio-demographic features (n=59)

Age Group	Cases[§] (n=37) n (%)	Control[§] (n=22) n (%)	Total (n=59) n (%)	p value*
<3 months	1 (2.7)	1 (4.5)	2 (3.4)	
3-6 months	5 (13.5)	3 (13.6)	8 (13.6)	
7-10 months	12 (32.4)	7 (31.8)	19 (32.2)	.905[ns]
11-14 months	9 (24.3)	4 (18.2)	13 (22)	
15-18 months	3 (8.1)	2 (9.1)	5 (8.3)	
>18 months	7 (18.9)	5 (22.7)	12 (20.3)	
Mean (months) ± SD	14.81±12.76	14±10.51	14.51±11.89	.56[nsβ]
Sex				
Male	20 (54.1)	8 (36.4)	28 (47.5)	.188[ns]
Female	17 (45.9)	14 (63.6)	31 (55.5)	
Residence				
Rural	19 (51.4)	10 (45.5)	29 (49.2)	.433[ns]
Urban	18 (48.6)	12 (54.5)	30 (50.8)	
Socio Economic Status				
Poor				
Lower Class	15 (40.54)	3 (13.63)	18 (30.50)	.130[ns]
Middle Class	17 (45.95)	14 (63.63)	31 (52.55)	
Upper Class	4 (13.48)	6 (22.74)	10 (16.95)	

* Data were expressed as frequency and percentage and p value was determined by chi-square test
β Data were expressed as frequency and percentage and mean±SD and p value determined by student t test
§Cases: Children with acute lower respiratory tract infection
§Controls: Children without acute lower respiratory tract infection

Table 2: Distribution of respondents by obstetric variable (n=59)

	Cases (n=37) n (%)	Controls (n=22) n (%)	Total (n=59) n (%)	p value*
Parity				
Primi	25 (67.56)	14 (63.63)	39 (66.10)	.529^{ns}
Multi	12 (32.44)	8 (36.37)	20 (33.89)	
Gestational age				
Preterm (<37 weeks)	4 (10.81)	2 (9.09)	6 (10.16)	.509^{ns}
Term (38-42 weeks)	31 (83.79)	18 (81.81)	49 (83.05)	
Post term (>42 weeks)	2 (5.4)	2 (9.1)	4 (6.79)	
Place of delivery				
Health care facility	16 (43.25)	12 (54.55)	28 (47.45)	.195^{ns}
Home	21 (56.75)	10 (45.45)	31 (52.55)	
Mode of delivery				
Vaginal Delivery	24 (64.86)	17 (77.27)	37 (62.71)	.915^{ns}
Caesarian section	13 (35.14)	5 (22.73)	18 (30.29)	

* Data were expressed as frequency and percentage and p value was determined by chi-square test
β Data were expressed as mean±SD and p value determined by student t test
§Cases: Children with acute lower respiratory tract infection
§Controls: Children without acute lower respiratory tract infection

Table 3: Distribution of respondents by clinical presentation (n=37)

C/F	n (%)
Fever	33 (89.19)
Cough	35 (94.59)
Breathlessness	35 (94.59)
Chest indrawing	22 (59.45)
Running nose	11 (29.72)
H/O repeated attack of RTI	16 (43.24)
Vomiting/Diarrhoea	7 (18.91)
Failure to thrive	11 (29.72)
Poor feeding	29 (78.37)

Table 4: Arthrometric measurement of study population (n=59)

	Cases (n=37)	Controls (n=22)	p value$^{\beta}$
Height (mean±SD) cm	67.73±16.48	98.36±135.01	.194^{ns}
Weight (mean±SD) kg	8.46±2.24	10.25±3.24	.785^{ns}
MUAC (mean±SD) cm	114.67±3.38	111±1.46	.471^{ns}

β Data were expressed as mean±SD and p value determined by student t test

Table 5: Distribution of respondents by serum hemoglobin and serum ferritin level (n=59)

	Cases (n=37) n (%)	Controls (n=22) n (%)	p value*
Haemoglobin (mean) ± SD gm/dl	8.21±2.19	12.06±.82	<.001^{s}
Hb (<10 gm/dl)	33 (89.18)	2 (9.09)	<.001^{s}
Hb (≥10 gm/dl)	4 (10.82)	20 (90.91)	
Serum Ferritin (mean) ± SD ng/ml	11.89±1.77	13.04±.78	.237n^{s}
Serum Ferritin (<12 ng/ml)	9 (24.32)	2 (9.09)	.146^{ns}
Serum Ferritin (>12 ng/ml)	28 (75.68)	20 (90.91)	

* Data were expressed as frequency and percentage and p value was determined by chi-square test
β Data were expressed as mean±SD and p value determined by student t test
§Cases: Children with acute lower respiratory tract infection
§Controls: Children without acute lower respiratory tract infection

Figure 1: Pattern of peripheral smear of anemic patients among study population (n=59)

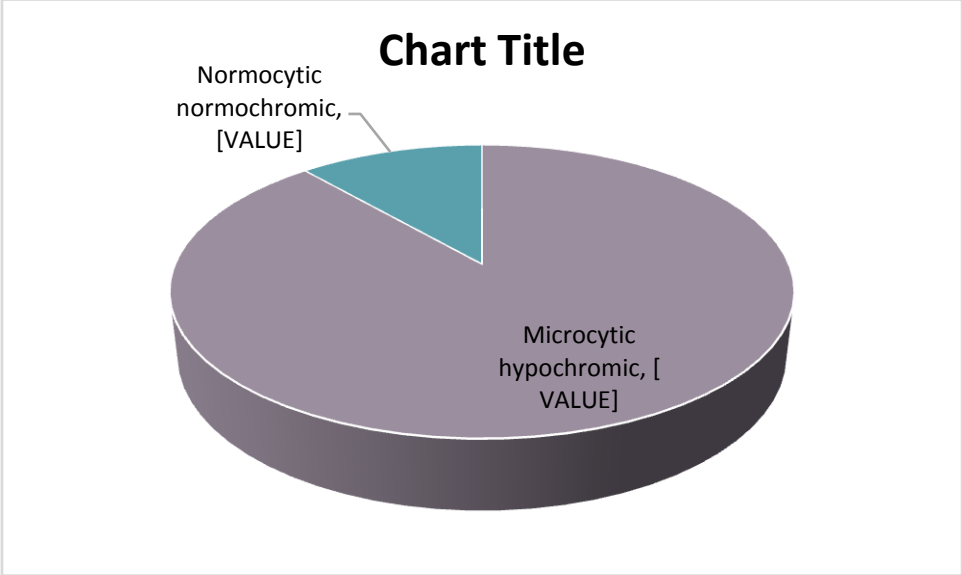

Table 6: Bivariate relationship between patient characteristics and Lower Respiratory Tract Infection

Variables	OR	95% CI		p value[µ]
		Lower limit	Upper Limit	
Age (months)	.994	.950	1.041	.799[ns]
Sex (female)	.486	.164	1.434	.191[s]
Socio Economic Condition (lower socio economic class)	4.250	1.050	17.202	.043[s]
Anemia	313.599	26.626	3261.255	<.001[s]

µ p value determined by regression analysis

Table 7: Multivariate relationship between patient characteristics and Lower Respiratory Tract Infection

Variables	OR	95% CI		p value[µ]
		Lower limit	Upper Limit	
Anemia	323.272	19.910	5248.798	<.001[s]
Socio Economic Condition Class	6.978	.336	145.101	.210[ns]

µ p value determined by regression analysis

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