RESEARCH PAPER

Risk Factors for the Development of Pneumonia and Severe Pneumonia in Children

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Objective: To identify the risk factors for pneumonia and severe pneumonia in children.

Design: Prospective cohort study.

Setting: Five tertiary-care teaching hospitals in India .

Participants: Children 2 to 59 months of age suffering from acute respiratory infection (ARI).

Main outcome measures: Risk factors for the development of WHO defined pneumonia and severe pneumonia.

Result: A total of 18159 children screened, and 7026 (39%) children with ARI were enrolled. According to the WHO criteria, 938 (13.4%) and 6088 (86.6%) of the enrolled children had pneumonia and no pneumonia, respectively. Out of 938 children with pneumonia, 347 (36.9%) had severe pneumonia. On univariate analysis, younger age, male gender and low weight for height, were significant risk factors for pneumonia. On multivariate analysis, one-unit increase in age in months (OR = 0.97; 95% CI: 0.97-0.98) and weight for height *z*-score (OR = 0.76; 95% CI: 0.72-0.79) had a protective effect.

Conclusions: Young age and undernutrition (low weight for height/length) in children are significant independent risk factors for pneumonia.

Keywords: *Acute respiratory infection treatment unit, Under nutrition.*

Acute respiratory infections (ARI) are the most common cause of morbidity and mortality in children under five years of age. WHO estimate indicates 156 million new cases of pneumonia occurring annually worldwide in under-five children, with 95% of these occurring in developing countries [1,2]. Pneumonia accounts for 15% of all deaths in under-five children globally [3].

It is important to understand the risk factors of pneumonia at the global, regional, and national levels. Identification of risk factors is important for enhancing insight into the etiology of pneumonia, prevention, and adequate and timely diagnosis [4,5].

There is a wide variation in the risk factors for pneumonia in the published studies. Most of the studies for risk factors of pneumonia were hospital-based and represented only a small proportion of pneumonia cases. Few studies had focused on the risk factors that were associated with progression to severe or very severe pneumonia [6-8].

The identified risk factors for childhood pneumonia are undernutrition, incomplete immunization, use of solid fuels in the household, over-crowding, lack of exclusive breastfeeding, low degree of maternal education, and limited access to secondary care. These risk factors are characteristics of low socioeconomic status and are inter-related. However, due to the linear relation of these risk factors, it is difficult to estimate their individual risk [9]. To study this problem, we conducted a large multi-center prospective study to determine the risk factors for the development of pneumonia and severe pneumonia in under-five children.

METHODS

This multi-centric study was part of a large prospective cohort study that was designed to develop acute respiratory infection treatment units (ATUs) and assess their utility in improving healthcare and research in pneumonia-related morbidity and mortality in India. The study was carried out at the following five different sites in India: *i*) Sher-e-Kashmir Institute of Medical Sciences (SKIMS), Srinagar; *ii*) All India Institute of Medical Sciences (AIIMS), Jodhpur; *iii*) All India Institute of Medical Sciences (AIIMS), Bhubaneswar; *iv*) Karnataka Institute of Medical Sciences (KIMS),

Hubbali; and *v*) MP Shah Medical College, Jamnagar. All India Institute of Medical Sciences, New Delhi, was the coordinating center for the study. Ethical clearance was taken from the institutional ethical committees from all the study sites.

Previously healthy children of either gender, 2 months to 59 months of age attending the Pediatrics outpatient department were recruited over 24 months (June, 2016 to May, 2018), with ARI – defined as any cough and/or breathing difficulty, for less than 2 weeks [10]. Children with any of the following were excluded from the study, *a*) Patients with chronic respiratory diseases (such as asthma, cystic fibrosis, bronchopulmonary dysplasia, airway anomalies), diagnosed in a health care facility; *b*) Patients with congenital heart disease (suspected based on the history of the suck-rest-suck cycle and cyanosis) – confirmed by echocardiography or presence of murmur; *c*) Patients with GER/ recurrent aspirations (based on the history of choking or coughing while feeding or barium swallow/GER scan); *d*) Known or suspected HIV positive/ immunocompromised patient – based on the history of recurrent, documented multisite infection or on immunosuppressive therapy; *e*) Place of residence outside the city where the study site is based; *f*) Unable to attend follow up; *g*) History of radiologically confirmed pneumonia in the last 2 months; *h*) Terminally sick children - impending respiratory failure, cyanosis at room air and shock.

The study was initiated after clearance by the respective Ethics Committees of all five study sites. All children who fulfilled the case definition of ARI [10], were enrolled in the study after written informed consent from parents or legally authorized representative. Children were assessed for a history of cough or breathing difficulty by counting respiratory rate and presence of chest indrawing by a trained study staff nurse under the supervision of the doctor. A detailed clinical history and examination findings of the enrolled patient were recorded on a pre-designed case record form before any radiological investigation. An *X*-ray film of the chest was obtained in every fifth child assessed to have ARI.

The outcome variable was the diagnosis of pneu-monia defined by WHO criteria [11] as cough or difficulty breathing and age-specific tachypnea (>60 breaths per minute for children less than 2 months of age, >50 breaths per minute for children 2-11 months of age and >40 breaths per minute for children 1-5 years of age). Severe pneumonia was defined as oxygen saturation <90%, severe respiratory distress, inability to drink or breastfeed or vomiting everything, altered consciousness, and convulsions [11]. Variables examined as risk factors were age, gender, nutritional status, and immunization status.

Statistical analysis: Data were recorded on a pre-designed proforma and managed on an Excel spread-sheet. All the entries were double-checked for any possible typographical error. Data analysis was performed using STATA 11.0 (STATA Corp). Categorical variables were analyzed using both absolute and relative frequencies; continuous variables were analyzed based on the median. Pearson chi-square and Fisher exact tests were used to compare the categorical variables. Numerical variables were analyzed using the nonparametric Mann-Whitney U test. The odds ratio with 95% CI were calculated for risk factor for pneumonia which were identified as those with $P \leq 0.05$ in the univariate analysis. They were selected for inclusion in a stepwise forward logistic regression model to determine the significant independent risk factors for pneumonia. *z*-scores for weight and height for age were calculated using WHO Anthroplus software [12].

RESULTS

A total of 18159 children were screened, and 7026 (39%) children (4251 boys) with ARI were enrolled. Among them, 938 (13.4%) and 6088 (86.6%) had 'pneumonia' and 'no pneumonia', respectively, and 347 of the 938 (36.9%) children had severe pneumonia. The median (IQR) age of the enrolled children was 23 (10,40) months with baseline characteristics shown in (**Table I**).

The risk factors for pneumonia were evaluated as seen in (**Table II**). On multivariate analysis one-unit increase in age in months (OR = 0.97; 95% CI: 0.97-0.98) and weight for height (OR = 0.76; 95% CI: 0.72-0.79) led to a decreased odds of developing pneumonia. Therefore, younger age and low weight for height were considered as an independent risk factor for pneumonia. In the case of Hib vaccination, positive vaccination history increased the odds of developing community acquired pneumonia.

The risk factors for developing severe pneumonia were evaluated in univariate analysis (**Table III**).

Table I Baseline Demographic and Clinical Characteristics of Enrolled Children (*N*=7026)

Characteristics	*Values*
Weight for age, *z*-score[a]	-0.69 (-1.83, 0.35)
Height/length for age, *z*-score[a]	-0.76 (-2.36, 0.77)
Weight for-height, *z*-score[a]	-0.29 (-1.14, 0.53)
Mid-upper arm circumference, *z*-score[a]	-1.47 (-2.13, -0.8)
Cough	6995 (99.6)
Fever	3998 (56.9)
Audible wheeze	512 (7.3)
Fast breathing[b]	715 (10.2)
Chest indrawing	478 (6.8)

All values are n (%) or [a]median (IQR). [b]as per WHO criteria.

DISCUSSION

In this multi-center prospective cohort study across five sites in India, younger age and low weight-for-height *z*-score were independent determinants of pneumonia.

Younger children were more prone for pneumonia possibly because of a relatively immature immune system in younger children [13,14]. Male gender was found to be significantly associated with pneumonia in univariate analysis, but not in multivariate analysis. Similar findings were reflected in the earlier study [15,16]. It may be because males are more vulnerable to pneumonia and are given more preference for hospitalization. Females may have a greater resistance due to their enhanced Th1 immune response [17]. Undernutrition is a significant risk factor for the development of pneumonia in children [18] as also seen by us. Undernutrition is associated with secondary immune deficiency and an increase in the risk of infections, including pneumonia [19,20].

Vaccination with Hib reduces the incidence of pneumonia in children [21], unlike the results of the present study. The possible reason may be the higher number of viral pneumonia than bacterial pneumonia in the present study as the etiology of pneumonia was not investigated. Pneumococcal and influenza vaccines are also associated with a decrease in the incidence of pneumonia [22,23]. In view of very few children immunized with these vaccines in this study, we were not able to find any significant association with these vaccines.

The major strength of this study was that it was a multi-centric study and conducted in the different geographic areas of the country with large sample size. This study has several limitations. First, children who did not have ARI were not compared. Second, some potential risk factors like exposure to smoking, indoor environment, use of cooking fuel were not studied. Moreover, *X*-ray chest was not done in all enrolled patients.

We conclude that younger and malnourished children are at increased risk of developing pneumonia. Further studies are required from developing countries considering host factors, etiology, including viral causes, and the effect of vaccination to understand the risk factors for pneumonia and severe pneumonia in children. At the same time, it is also important to address undernutrition in children, to reduce pneumonia-related mortality, and ensure their growth and development.

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Ethics clearance: Permission number AIIMS/IEC/2017/301; date 15/09/2017.

Contributors: JPG, PK: involved in data collection and manuscript writing; AM, RL: involved in development of protocol, supervision of study, data analysis; RRD, JIB, VR, BV: data collection, manuscript review and final approval of study.

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Table II Risk Factors Associated With Development of Community-Acquired Pneumonia

Characteristics	*No pneumonia n=6088*	*Pneumonia n=938*	*P value*[a]	*OR (95%CI)*	*P value*[b]
Age (mo)[c]	24 (11, 42)	15 (8, 25)	<0.001	0.97 (0.97,0.98)	<0.001
Boys, *n* (%)	3655 (60.0)	596 (63.5)	0.04	1.12 (0.97, 1.29)	0.13
Weight for height/length *z*-score[c]	-0.24 (-0.99, 0.56)	-0.77 (-1.96, 0.3)	<0.001	0.76 (0.72, 0.79)	<0.001
Vaccination, n=5687					
Influenza, *n* (%)	15 (0.31)	4 (0.48)	0.51		
Pneumococcal, *n* (%)	15 (0.31)	6 (0.72)	0.07		
H. influenzae, *n* (%)[b]	3781 (77.9)	681 (81.7)	0.01	1.81 (1.53, 2.13)	<0.001

Community-acquired pneumonia defined as per World Health Organization guideline. [a]Univariate analysis; [b]Multivariate analysis.

Table III Risk Factors Associated With Severe Community-Acquired Pneumonia

Characteristics	*Pneumonia n=591*	*Severe pneumonia n=347*	*P value*[a]	*OR (95%CI)*	*P value*[b]
Age, mo	16 (8,28)	12 (7, 24)	0.001	0.99 (0.98, 0.99)	0.04
Male, *n* (%)	374 (63.8)	222 (63.9)	0.83	1.03 (0.78, 1.36)	0.82
Weight for height/length *z*-score	-0.98 (-2.2, 0.26)	-0.46 (-1.48, 0.33)	0.001	1.12 (1.04, 1.21)	0.002

Values are median (IQR) unless specified. [a]Univariate analysis; [b]Multivariate analysis.

WHAT IS ALREADY KNOWN?

- Undernutrition, younger age, lack of immunization are well-known risk factors for community-acquired pneumonia

WHAT THIS STUDY ADDS?

- Risk factors for community-acquired pneumonia are reiterated through a large multi-centric study.

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ANNEXURE I

Acute Respiratory Infection Treatent Unit Study Group:

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