ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/pediatr.2021-83974

Factors Affecting Acute Respiratory Rate Change Among Under-Five Children Hospitalized with Severe Pneumonia: A Longitudinal Study

Ağır Pnömoni Nedeniyle Hospitalize Edilen Beş Yaş Altındaki Çocuklarda Akut Solunum Hızı Değişikliğini Etkileyen Faktörler: Boylamsal Bir Çalışma

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ABSTRACT Objective: About one-third of all childhood deaths are due to Pneumonia with high respiratory rate/acute respiratory infections. Respiratory rate is used as a preliminary health indicator in the diagnosis and progression of Pneumonia. The current study was conducted to identify factors associated with tachypnea. **Material and Methods:** Quasi-Poisson modeling using generalized linear mixed-effects (GLM) and multiple logistic regressions models were used to analyze the study variable. The data were extracted from each patient's hospital chart. Parameter estimation was conducted using penalized quasi-likelihood estimation. **Results:** Four-hundred, fifty-three Pneumonia patients under-five years of age were included in the study. From the main effects, body temperature (adjusted rate ratio (ARR= 1.01, p<0.001), length of hospital stay (ARR=0.92, p<0.001), previous cough history (ARR= 1.03, p=0.0135), and season (summer: ARR= 0.98, p=0.0021; autumn: ARR=0.99952, p=0.0032; spring: ARR= 0.90, p=0.02) had a significant effect on variation of acute respiratory rate in Pneumonia patients. Interaction effects that were significant for the variable of interest included visiting times with family disease history, age with breast feeding history, and length of hospital stay with previous disease history. **Conclusion:** Certain groups of Pneumonia patients (those with high temperature, previous disease history, and family disease history) need special intervention to reduce the risk of acute respiratory rate in Pneumonia patients. Parents should be educated to follow up their children for health checks whenever breathing rate becomes fast or increases. Special attention should be given to patients with a previous disease history, family disease history, and those hospitalised during the winter season.

Keywords: Acute respiratory rate; generalized linear mixed model; pneumonia; under-five children; Ethiopia

ÖZET Amaç: Tüm çocukluk ölümlerinin yaklaşık üçte biri yüksek solunum hızlı pnömoni/akut solunum yolu enfeksiyonları nedeniyle meydana gelmektedir. Solunum hızı, pnömoninin tanısı ve ilerlemesi için bir ön sağlık göstergesi olarak kullanılmaktadır. Bu çalışma, Kuzey-Batı Etiyopya'daki Felege Hiwot Başvuru Hastanesinde pnömoni ile hastaneye yatırılan beş yaşın altındaki çocuklarda takipne ile ilişkili faktörleri belirlemek amacıyla yapılmıştır. **Gereç ve Yöntemler:** Çalışma değişkenini analiz etmek için genelleştirilmiş doğrusal karışık etkiler ve çoklu lojistik regresyon modelleri kullanan Quasi-Poisson modellemesi kullanılmıştır. Veriler, hastaların hastane kayıtlarından elde edilmiştir. Parametre tahmini, penalize yarı-olabilirlik tahmini kullanılarak yapılmıştır. **Bulgular:** Çalışmaya 5 yaşın altında 453 pnömoni hastası alınmıştır. Ana etkilerden vücut ısısı [ayarlanmış hız oranı (ARR)=1.01, p<0.001], hastanede kalış süresi (ARR=0.92, p<0.001), önceki öksürük öyküsü (ARR=1.03, p=0.0135) ve mevsim (yaz: ARR=0.98, p=0.0021; sonbahar: ARR=0.99952, p=0.0032; ilkbahar: ARR=0.90, p=0.02) pnömoni hastalarında akut solunum hızı varyasyonu üzerinde anlamlı bir etkiye sahipti. İlgilenilen değişken için anlamlı olan etkileşim etkileri arasında aile öyküsü ile ziyaret süreleri, emzirme öyküsü ile yaş ve önceki hastalık nedeniyle hastanede kalış süresi yer almaktadır. **Sonuç:** Bazı pnömoni hasta grupları (yüksek ateşi, önceki hastalık öyküsü ve ailede hastalık öyküsü olanlar) akut solunum hızı riskini azaltmak için özel müdahaleye ihtiyaç duyarlar. Anne-babalar, solunum hızı hızlandığında veya arttığında çocuklarını sağlık kontrolleri için takip etmeleri konusunda eğitilmelidir. Daha önce hastalık öyküsü olan, ailesinde hastalık öyküsü olan ve kış mevsiminde hastaneye yatırılan hastalara özel dikkat gösterilmelidir.

Anahtar Kelimeler: Akut solunum hızı; genelleştirilmiş doğrusal karma model; pnömoni; beş yaşından küçük çocuklar; Etiyopya

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Peer review under responsibility of Turkiye Klinikleri Journal of Pediatrics.

Received: 23 Apr 2021 ***Received in revised form:*** 14 Jan 2022 ***Accepted:*** 24 Jan 2022 ***Available online:*** 27 Jan 2022

Childhood acute respiratory illness constitutes a major health problem for which families seek medical advice, and account for 30% of pediatric hospitalizations.[1] High number of breaths per minute (tachypnea) for children hospitalized with pneumonia is an important clinical indicator for severity of pneumonia in children.[2] The contribution of fast-breathing pneumonia to family stress and school non-attendance is substantial, but difficult to estimate. A high proportion of young children hospitalized with high respiratory rates have pneumonia as the discharge diagnosis, and increased respiratory rate is significantly associated with morbidity and mortality globally.[2] One of the important severity indicators in pneumonia is inflammation of the lung parenchyma which results in disrupted gas exchange and elevated respiratory and heart rates.

Pneumonia is one of the leading causes of illness globally, and is a leading cause of death in children under-5 years of age.[3-6] Approximately, about 2 million children die because of pneumonia in lower-middle income countries.[7] Pneumonia is also a leading cause of childhood deaths in sub-Saharan Africa.[8] In Ethiopia, fast-breathing pneumonia consistently causes approximately 8,000 (20%) of the 40,000 under-5 years old annually.[9] These deaths are largely preventable and treatable through the use of basic interventions, including immunization, nutritional support, exclusive breastfeeding, hand washing and access to antimicrobials.[9]

Fast breathing pneumonia influences all age groups, but certain age groups are more at risk for severe. Risk factors for fast-breathing pneumonia in children include parental smoking, nutritional status, socio-economic factors, number of siblings under-5 years of age in the household, lack of basic health services (including immunization), lack of awareness and overcrowding.[10] Infants, children under-5 years, and the elderly, especially those with comorbidities including human immunodeficiency virus-infection, measles, or Malaria are more at risk for developing fast-breathing pneumonia.[11]

The World Health Organization (WHO) criteria used for diagnosis of childhood pneumonia requires a history of cough or difficulty breathing and determination of age-specific respiratory rate per minute.[12] Fast breathing pneumonia (tachypnea) is defined as ≥60 breaths per minute (bpm) for children less than 2 months, ≥50 bpm for children aged 2-11 months, and ≥40 bpm for children aged 1-5 years. Fast breathing pneumonia in children ranges from mild to severe to fatal. Even in non-fatal cases, fast breathing pneumonia poses a significant economic burden on health care systems.

There are inconsistencies regarding pneumonia risk factors between studies, many of which did not evaluate interaction effects between potential covariates.[2,13-15] One way of clarifying these factors is use of appropriate models which use respiratory rate, not pneumonia, as the outcome variable of interest. The aim of this study was to identify factors that were associated with age specific fast breathing (tachypnea) among children under-5 years old, hospitalized with pneumonia. The study variable (age specific fast breathing pneumonia) is one of the criteria used by the WHO for diagnosis of childhood pneumonia. The study variable in current investigation also categorized as tachypnea and non-tachypnea to check the consistency of results obtained by the 2 models namely generalized linear mixed (GLM)-effects and multiple logistic regression models.

MATERIAL AND METHODS

Study design and settings: We conducted a retrospective longitudinal study design among severe pneumonia patients aged under-5 years at Felege Hiwot Teaching and Specialized Hospital, Amhara region, North-West Ethiopia. The study was conducted from July 01, 2018 to June 30, 2020. The hospital is the largest health facility in the region, located at an altitude of 1,800 (5,906 feet) meters above sea level and treating more than 400 pneumonia patients per week.[16]

Sample size and selection procedures: The sample size was determined using single proportion formula with the following assumptions: estimated proportion of pneumonia patients 60% (p=0.60), 95% confidence interval (CI): ($Z_{\alpha/2}$=1.96), and a 5% margin of error (d=0.05).[17,18] The final sample size was 453 pneumonia patients selected randomly using

stratified random sampling, considering their residence as strata. The investigation used secondary data, collected by well-trained health service providers.[19] In sampling procedures, children hospitalized with pneumonia were serially measured their respiratory rates over time during the course of the hospitalization episode. This assures that the children were being assessed during the same pneumonia episode.

Quality of data: The quality of data was controlled by data controllers at the pediatric emergency department, specialized and teaching hospital. The data extraction tools as well as variables included in the study were tested for consistency of understanding and their completeness of data items on 45 randomly selected patients. Necessary amendments were made on the final data collection sheet.

Inclusion criteria: Children under-5 years of age, hospitalized with pneumonia that complied with the WHO cut-offs for tachypnea bay age-group (as mentioned above) were included. Only children that required repeat assessment during the study period were included: all participants had at least 2 visits, and some had a maximum of 14 visits. The sampling strategy was used to ensure repeated observations on the same individual during the course of the same pneumonia episode.[20-22]

Data collection tools and procedures: The study objectives were presented to health care providers at the hospital. Data were extracted using a data extraction form developed by the investigators in consultation with health service providers. All important information related to predictor and response variables were recorded by health care service providers whenever patients visited the hospital for treatment. Data were extracted from participant charts into dedicated case record formats, and digitized. The data were retrieved using unique participant registration numbers which were recorded in the electronic database.

Variables included under investigation: The response or outcome variable for this study was age-specific respiratory rate recorded in breaths per minute (bpm). The variable of interest was collected in a standardized manner throughout the study period. Hence, a UNICEF respiratory rate time (number of breaths per minute) was used in all respiratory rate determinations.

Explanatory variables were: Sex; age (in months); weight (kilograms); body temperature (degrees celsius); residence (urban versus rural); family disease history: asthma (yes, no), tuberculosis (yes, no); seasonal variation (autumn, spring, summer, winter); cough history (yes, no); previous disease history such as: asthma (yes, no), tuberculosis (yes, no), malaria (yes, no), diarrhea (yes, no); vaccination history of the child (yes, no); treatment type (amoxicillin, ampicillin, ceftriaxone, gentamicin, penicillin); vomiting status (yes, no); breast feeding [exclusive (B), complimentary (C), both (B and C)]; number of follow-up visits; and length of hospital stay (in days) if hospitalized.[20-23]

Analysis: We used SAS version 9.2 (SAS Institute Inc.) for data analysis. Missing observations were inferred using multiple imputations. Outliers and influential observations were tested using Cook's distance. The response variable was evaluated as both as count and dichotomous form. GLM effect and multiple logistic models were used to investigate predictors of the variable of interest (respiratory rates). Eligible predictors were included in multivariate analysis applying forward selection procedures. Non-eligible predictors were excluded using backward elimination. Deviance and Pearson chi-square divided by the degrees of freedom were used to detect whether or not the distribution was over- or under-dispersed. Values greater than 1 was an indicator of over-dispersion, that is, true variance larger than the mean, whereas values less than 1 indicated under-dispersion, that is, true variance smaller than the mean. Evidence of under-dispersion or over-dispersion indicated inadequate fit of the Poisson model. Multiple logistic regression model was also used to check the consistency of results analyzed by the 2 models.[17,24]

ETHICAL CONSIDERATION AND CONSENT TO PARTICIPATION

Ethical clearance was obtained from the Institutional Review Ethical Board of Science College, Bahir Dar University (date: October 20, 2019, no: PRCSVD/23/2012). Permissions were also obtained from the

ethics committee of the hospital administration. As this was a retrospective study using secondary data, informed consent from the caregivers of individual patients was not obtained. Names and unique identification numbers were not included in the study.

RESULTS

Of 1,572 pediatric pneumonia patients attended during the study period, 45 were not included due to death (n=45), transfer to another healthcare facility (n=350) and other reasons (n=468). From the remaining 754 pneumonia patients, 453 were randomly selected. Among the selected pneumonia patients, 252 (55.6%) of which were male, visited on at least 2 occasions during the course of the same pneumonia episode and were eligible for inclusion in the study. Three-hundred, twenty (70.6%) of the 453 children included in the analysis were assessed on 14 occasions, and 130 (28.7%) were hospitalized for at least 6 days. Eighty-four (18.5%) patients were treated as outpatients.

Underlying medical conditions included diarrhea (n=63, 13.9%) and asthma (n=42, 9.3%). Three-hundred, fifty (77.3%) children were fully vaccinated according to the WHO criteria. Clinical and epidemiologic characteristics associated with the 453 included pneumonia cases are shown in Table 1.

EXPLORATORY DATA ANALYSIS

Goodness of fit and tests of dispersion were conducted using the mean variance relationship for the response variable.[17,25] Negative binomial did not converge to a specific value, but quasi-Poisson converged; hence, quasi-Poisson was considered as preferable for data analysis (Supplementary Table 1).[26] Information criteria, the mean-variance relation and comparison of the cut-off point and mean of respiratory rate were also used to compare the negative binomial and quasi-Poisson models.[27] These comparisons confirmed that the quasi-Poisson model was superior to the negative binomial model in the current analysis.

In descriptive analysis, the variance was twice the mean and the distribution was over-dispersed.

SUPPLEMENTARY TABLE 1: Goodness of fit statistics (comparison of quasi-Poisson and negative Binomial models for fitting the data).

Model	Fit Statistics	
Quasi-Poisson	-2 Res Log Likelihood	5606.06
	AIC	5546.06
	AICC	5545.36
	BIC	5369.14
	CAIC	5339.14
	HQIC	5482.07
	Generalized Chi Square	2955.38
	Generalized Chi Square / DF	1.10
Negative binomial	Did not converge	-------

The quasi-Poisson regression analysis with the over-dispersion parameters were used to identify the basic determinants for the risk factors of acute respiratory rate per minute on pneumonia patients of under-5 years of age. GLM model for main effects were used to identify predictors of respiratory rate of pneumonia patients of under-5 years of age. Similarly, multiple logistic regression model was also used by categorized the variable of interest as tachypnea and non-tachypnea.

In univariate linear mixed model with quasi-Poisson regression, potentially significant variables that were associated with respiratory rate at a significance level of ≤0.25 (i.e., with a p≤0.25) were considered for inclusion in the multivariate model. Sex and a history of vomiting were excluded from the multivariate model as these characteristics were not associated with respiratory rate to the required significance level (Table 2).

After generating univariate results in Table 2, all significant variables were put on the generalized linear mixed effect model (GLMMX) procedure analyzed using SAS version 9.2. The fitted model based on univariate analyses was presented in supplementary materials.

The final GLM effect and logistic regression models for reparatory rate per minute for children hospitalized with pneumonia is given in Table 3. This is the final model done using quasi-Poisson regression model under the GLM effect model and multiple logistic regression models.

TABLE 1: Baseline socio-demographic and clinical characteristics of the pneumonia patients (n=453).

Characteristics	Level	Median (Q1, Q3)	n (%)
Respiratory rate		49.35 (24, 84)	
Age in months		13.91 (6, 48)	
Weight in kg		7.83 (2, 18)	
Number of days admitted in hospital for each visit		3.5 (2, 5)	
Visiting times for hospital		6.5 (3.5, 9.4)	
Temperature (°C)		37.1 (38.5, 40.4)	
Sex	Female		201 (44.4)
	Male		252 (55.6)
	Asthma		42 (9.3)
	Diarrhea		63 (13.9)
Previous disease history	Malaria		10 (2.2)
	Tuberculosis		20 (4.4)
	No		318 (70.2)
Vaccination status	Yes		350 (77.3)
	No		103 (22.7)
	Exclusive breast (B)		159 (35.1)
Breast feeding	Complementary (C)		24 (5,3)
	B&C		159 (59.6)
	Amoxicillin		40 (8.9)
	Ampicillin		15 (3.4)
	Ceftriaxone		184 (40.7)
	Gentamicin		25 (5.6)
Treatment type	Penicillin		149 (32.9)
	Gent&Amp		34 (7.5)
	Gent&Cef		4 (0.9)
	Autumn		143 (31.6)
Season of the year	Summer		118 (26.1)
	Spring		81 (17.8)
	Winter		111 (24.5)
Vomiting status	Yes		232 (51.1)
	No		221 (48.9)
Residence of a patient	Rural		229 (50.6)
	Urban		224 (49.4)
Cough status of a patient	Yes		331 (73)
	No		122 (27)
Family disease history	Asthma		54 (11.9)
	Tuberculosis		42 (9.3)
	No		357 (78.8)

Holding all other variables constant, each additional degree celcius increase in body temperature was associated with a 0.01 bpm increase in respiratory rate (β=0.01387, 95% CI: 0.0098, 0.0179; p<0.001). Furthermore, holding all other variables constant, each month increase in patient age was associated with a 0.003 bpm reduction in respiratory rate (β=-0.00245, 95% CI: -0.0082, -0.0011; p=0.0035). Length of hospitalization was also significantly associated with reductions in respiratory

TABLE 2: Type 3 tests for fixed effects.

Covariates	DF	F value	Pr>F
Sex	1	1.03	0.311
Age	1	27.98	<0.001
Weight	1	7.42	0.007
Temperature	1	320.89	<0.001
Waiting days in hospital	1	1926.17	<0.001
Previous disease history	4	4.11	0.003
Vaccine	1	0.18	0.055
Breast feed	2	6.02	0.003
Treatment type	7	2.10	0.046
Seasonal variation	3	1.05	0.045
Vomiting	1	139.03	0.257
Residence area	1	3.72	0.045
Cough history	1	152.84	<0.001
Family disease history	2	1.49	0.0271

rate, with a 0.08 bpm (β=-0.084, 95% CI: -0.1062, -0.0617; p=0.0001) for each additional day of hospitalization (Table 3).

Other patient characteristics that were significantly associated with reductions in respiratory rate included: season in which the child developed pneumonia (autumn, spring and summer were each associated with significantly lower respiratory rates compared to winter); each additional hospital visit was also associated with significant reductions in respiratory rate, with a 0.03 bpm (β=-0.03, 95% CI:-0.2794,-0.0122; p=0.003); Table 3.

Factors that were significantly associated with increased respiratory rate included residence in a rural setting [which increased the respiratory rate by 0.01 bpm (95% CI: 0.0062, 0.0536; p=0.0135) relative to children that resided in urban settings)]; history of cough (p=0.014); and past medical history of diarrhea (p=0.018); Table 3.

Additionally, Table 3 presents the result of multiple logistic regression analysis of significant variables in the univariate analysis. As age increased by one month, the odds of a child having tachypnea was decreasing by 37%, keeping the other covariates constant [adjusted odds ratio (AOR) 0.630; p=0.001].

Weight and body temperature of a child had a positively and statistically significant effect for a child being tachypnea (AOR=1.142; p=0.001 and AOR=1.516; p=0.001). On the other hand, repeated visiting time of a hospital was less likely for a child to develop tachypnea (AOR=0.472; p=0.001); the season in which the child developed pneumonia (autumn) was associated with lower respiratory rates compared to winter (AOR=0.606; p=0.001); treatment types (gentamicin with ampicillin and gentamicin with ceftriaxone were each associated with lower respiratory rates compared to penicillin).

The odds of a child whose treatment type amoxicillin having tachypnea was increased by 47.4% as compared to those whose treatment type is penicillin, keeping the other things constant (AOR=OR 1.474; p=0.001). The odds of a child whose treatment type is gentamicin having tachypnea was increased by 60.6% as compared to whose treatment type was penicillin (AOR=1.606; p=0.047).

The odds of a child whose family disease history, asthma having tachypnea was increased 7,727 times as compared to whose with a family disease history, tuberculosis, keeping the other things constant (AOR=7.727; p<0.0001). Similarly, the odds of a child whose residence area, rural having tachypnea was increased by 77.3% as compared to whose residence area, urban keeping the other things constant (AOR=1.773; p<0.001). Similar to main effects, the interaction effects was described based on GLM model as follows.

Interaction effects between waiting days and disease history of parents: There were significant reductions in respiratory rate as the number of days since first assessment during the course of respiratory illness increased; however, rates of decline in respiratory rate differed in association with family history of illness (Table 3). Rate of decline in respiratory rate was greatest in children without a family history of illness (β=-0.09 bpm, 95% CI: -0.0120, -0.0239; p=0.0418), and slowest in those with a family history of diarrhea (β=0.0198 bpm, 95% CI: 0.0034, 0.0362; p=0.018) (Figure 1).

TABLE 3: Parameter estimation using quasi-Poisson under generalized linear mixed model.

	Generalized linear mixed model						Logistics regression	
Effect	**Model parameter β**	**Standard error**	**Adjusted rate ratio (ARR) [exp (β)]**	**95% CI for ARR**		**p value**	**AOR (SE)**	**p value**
Intercept	3.5124	0.127	33.6031	26.1	43.1	<0.0001		
Age	-0.00245	0.003	0.997551	0.99	0.10	0.0035*	0.630 (0.039)	<0.0001*
Weight	0.003518	0.012	1.003526	0.98	1.03	0.0774	1.142 (0.33)	<0.0001*
Body temperature	0.01387	0.003	1.013976	1.01	1.02	<0.0001*	1.516 (0.071)	<0.0001*
No of days admitted in hospital (waiting time)	-0.08396	0.011	0.919419	0.89	0.94	<0.0001*	0.472 (0.194)	<0.0001*
Treatment type (reference=Pen)								
Amo	-0.01574	0.011	0.984373	0.96	1.01	0.1590	1.474 (0.761)	0.069
Amp	-0.00800	0.014	0.992027	0.97	1.02	0.5597	1.206 (0.701)	0.535
Cef	-0.00033	0.006	0.99967	0.99	1.01	0.9537	1.206 (2.023)	0.130
Gent	0.005091	0.012	1.005107	0.98	1.03	0.6755	1.606 (0.580)	0.047*
Gent&Amp	-0.03835	0.026	0.962353	0.91	1.01	0.1468	0.574 (0.159)	0.033*
Gent&Cef	0.05085	0.065	1.052199	0.93	1.19	0.4329	0.273 (0.182)	0.021*
Gent&Pen	-0.03059	0.051	0.969854	0.88	1.08	0.5473	1.474 (2.102)	0.069
Family disease history (reference=TB)								
Asm	0.03465	0.032	1.03528	1.97	1.10	0.0253*	7.727 (0.761)	<0.0001*
No	-0.05626	0.026	0.945293	0.92	0.97	0.0304*	0.623 (0.701)	<0.0001*
Residence area (reference=urban)								
Rural	0.012998	0.032	1.030361	1.01	1.06	0.0135*	1.773 (0.114)	<0.0001*
Seasonal variation (reference=winter)								
Summer	-0.001512	0.017	0.978706	0.67	1.00	0.0021*	1.175 (0.152)	0.274
Autumn	-0.00050	0.019	0.99952	0.45	1.00	0.0032*	0.606 (0.156)	<0.0001*
Spring	-0.001512	0.017	0.901514	0.75	1.00	0.0213*	0.887 (0.171)	0.470
Cough history (reference=no)								
Yes	0.02989	0.012	1.030361	1.01	1.06	0.0135*	1.710 (0.130)	0.006*
Visiting times	-0.03242	0.021	0.9681	0.76	0.99	0.0034*	0.472 (0.194)	<0.0001*
Visiting times* family disease history (reference=TB)								
No of days* Asm	-0.01838	0.006	0.981776	0.97	0.99	0.0043*	1.940 (0.194)	0.755
No of days* no	-0.01632	0.005	0.983802	0.97	0.99	0.0016*	0.566 (0.154)	0.004*
Age* breast feeding [reference=complementary feeding, (C)]								
Age* breast feeding (B)	-0.00969	0.003	0.990351	0.98	1.00	0.0005*	0.738 (0.041)	<0.0001*
Age* B&C	-0.00797	0.003	0.992057	0.99	1.00	0.0019*	0.795 (0.040)	<0.0001*
No of days waiting in hospital* previous disease history (reference=TB)								
Asm	0.01769	0.009	1.017859	1.00	1.04	0.0404*	1.138 (0.185)	0.587
Dia	0.01982	0.008	1.02003	1.00	1.04	0.0180*	0.877 (0.181)	0.559
Mal	0.00927	0.012	1.009322	1.00	1.03	0.0480*	0.683 (0.441)	0.371
No	-0.008951	0.008	1.008997	0.98	0.99	0.0418*	0.976 (0.153)	0.907

Model information *Refers significant at 95%; CI: Confidence interval; AOR: Adjusted odds ratio; SE: Standard error; Amo: Amoxicilin; Amp: Ampicillin; Cef: Ceftriaxone; Gent: Gentamicin; Pen: Penicilin; TB: Tuberculosis; Asm: Asthma; Dia: Diarrhea; Mal: Malaria.

Interaction between age and feeding type: Rates of decline in respiratory rate decreased significantly with age, but at different rates depending on type of feeding choice that was given to the child (Table 3). Breastfed children had a more rapid decline in respiratory rate as they aged (β=-0.001 bpm, 95% CI: -0.0152, -0.0042; p=0.001) than children that received breastfeeds mixed with complementary feeding (β=-0.008 bpm, 95% CI: -0.0130, -0.0029; p=0.002) (Table 3, Figure 2).

Interaction plot between number of follow-up visits and previous disease history: Using a history of previous tuberculosis as the referent indicator, the interaction between the number of clinic visits during the pneumonia illness episode and other pre-existing co-morbidities was associated with significant differences in the rate of change of respiratory rate over time (Table 3, Figure 3). Rate of decline in respiratory rate was lowest in children with a prior history of diabetes.

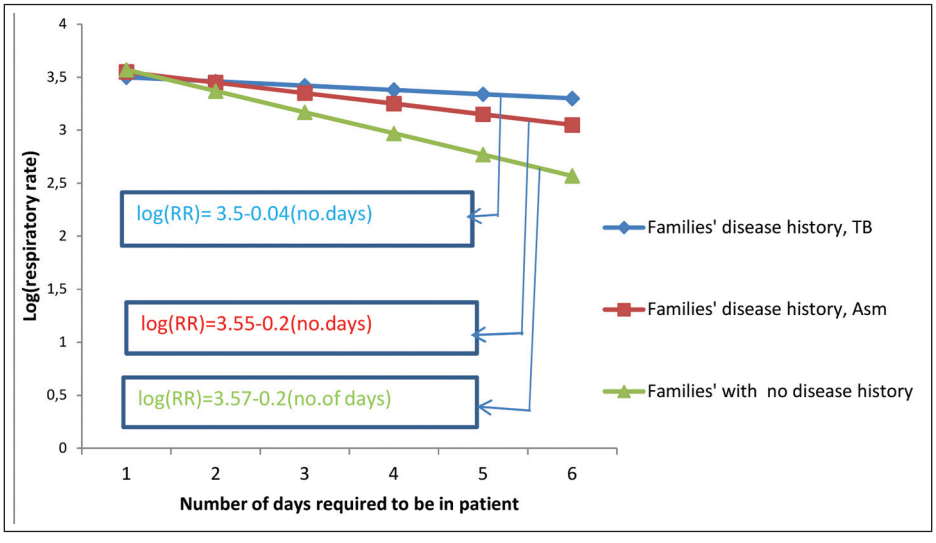

FIGURE 1: Plot of interaction effect between visiting time and disease history of parents.
Log(RR): logarithem of Respiratory Rate/the response variable; RR: Rate ratio; TB: Tuberculosis; Asm: Asthma.

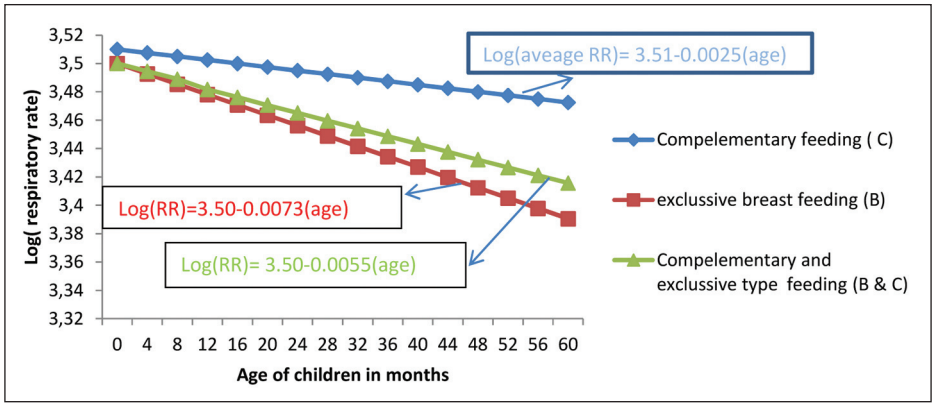

FIGURE 2: Plot of interaction effect between age and feeding type.
Log(RR): logarithem of Respiratory Rate/the response variable; RR: Rate ratio.

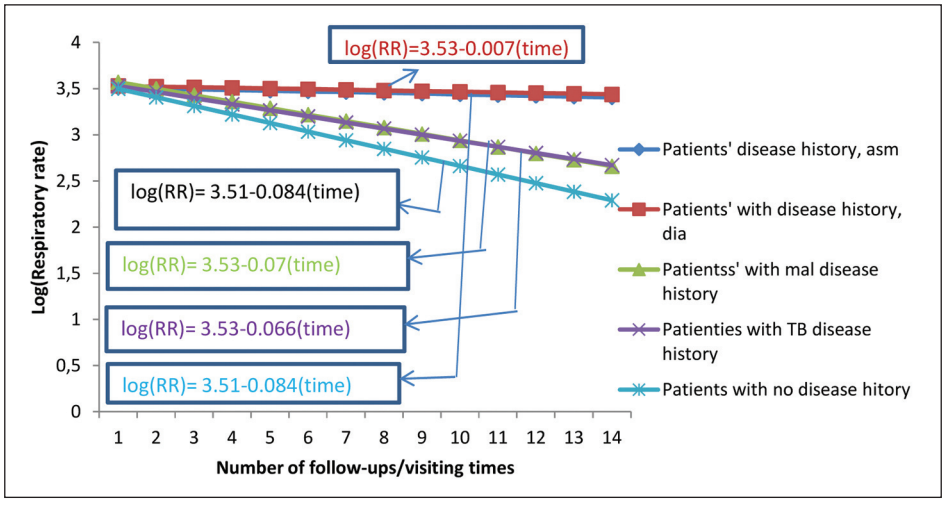

FIGURE 3: Plot of interaction effect between follow-up visits and parents' disease histories.
Log(RR): logarithem of Respiratory Rate/the response variable; Asm: Asthma; Dia: Diarrhea; RR: Rate ratio; TB: Tuberculosis.

DISCUSSION

The focus of the current study was to identify factors that affect the acute respiratory rate of pneumonia patients of under-5 years of age. We identified numerous patient characteristics that were significantly associated with fast breathing pneumonia over time in children treated for pneumonia in-hospital and as outpatients in a busy referral hospital in Ethiopia. Previous studies have identified environmental, nutritional, behavioral, socioeconomic and demographic risk factors for pneumonia in children, but few have interrogated potential interactions between covariates in longitudinal analyses.

We demonstrate that body temperature, repeated consultations during the course of the pneumonia illness episode, cough history, length of hospital stay and residence area (rural versus urban) were significantly associated with fast breathing pneumonia for hospitalized children under-5 years of age.

We also identified two-way interaction effects that were associated with statistically significant differences in rates of decline in respiratory rate through our analysis, namely: number of visits and family illness history, age and type of feeding, and number of visits and previous disease history.

Fever is a well-known driver of fast breathing pneumonia, so our finding that abnormally fast breathing pneumonia (tachypnea) with increasing body temperature is not surprising.[28,29] Length of hospitalization, with clinical improvement during the course of supportive, empiric and targeted treatment, was found to be associated with significant reductions in fast breathing pneumonia in our study. This finding has been described in previous studies.[30,31]

Our finding on breast feeding was associated with the most rapid declines in fast breathing pneumonia, is important. This result suggests that breastfeeding has greater advantage in the recovery stage of a child hospitalized with pneumonia over complementary or mixed feeding. The advantages of breastfeeding in promotion of child lung health have been described in other studies.[32]

CONCLUSION

A history of previous or pre-existing illness is also important. In our study, children with a previous history of tuberculosis had slower resolution of their respiratory rate over time compared to those with no prior disease history; however, children with asthma or diabetes had slower rates of decline in their respiratory rates compared even to children with a prior history of diarrheal. These findings emphasize the need to ensure good control of underlying chronic disease processes, through reinforcement of instruction and education to caregivers

of young children, in order to optimize the health status of their children.

This study is not without limitations. Although, we demonstrated important associations between feeding type and respiratory rate, we did not evaluate the nutritional status of the study participants. Malnutrition is an important risk factor for pneumonia, and would be expected to impact on respiratory rate. We also did not evaluate the effect of household air pollutant exposure, including cigarette smoke exposure, on resolution of respiratory rate in children that were treated for pneumonia. Ours was a single-center study, and so the findings may not be generalizable to other settings. Further studies would be expected to complement and consolidate the findings from our study.

RECOMMENDATION

The current study shows that fast breathing pneumonia decreased as length of hospital stay increased, as well as with each additional outpatient evaluation during the course of a child's pneumonia illness episode. Special attention should be given to patients with a history of previous disease, as well as to those with a family history of illness. Health education should be given to parents to emphasize the importance of exclusive breast feeding and adherence to management of chronic childhood diseases including asthma and diabetes. Interventions should also target families that reside in rural areas, to recognize the signs of respiratory illness (fever and increased respiratory rate) in children, so that presentation to health care facilities is not delayed.

Acknowledgement

Felege-Hiwot Teaching and referral Hospital and all health staffs, is gratefully acknowledged for the data they supplied for our health research.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Muluwerk Ayele Derebe;* ***Design:*** *Muluwerk Ayele Derebe;* ***Control/Supervision:*** *Muluwerk Ayele Derebe;* ***Data Collection and/or Processing:*** *Muluwerk Ayele Derebe, Awoke Seyoum Tegegne, Haile Mekonnen Fenta;* ***Analysis and/or Interpretation:*** *Muluwerk Ayele Derebe, Awoke Seyoum Tegegne, Haile Mekonnen Fenta;* ***Literature Review:*** *Muluwerk Ayele Derebe, Awoke Seyoum Tegegne, Haile Mekonnen Fenta;* ***Writing the Article:*** *Muluwerk Ayele Derebe, Awoke Seyoum Tegegne, Haile Mekonnen Fenta;* ***Critical Review:*** *Muluwerk Ayele Derebe, Awoke Seyoum Tegegne, Haile Mekonnen Fenta;* ***References and Fundings:*** *Muluwerk Ayele Derebe;* ***Materials:*** *Muluwerk Ayele Derebe.*

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