

# Hyponatremia As A Predictor Of Adverse Outcome In Children With Severe Lower Respiratory Tract Infection In Tribhuvan University Teaching Hospital (Tuth), Nepal

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## Research article

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# Abstract

**Background** Lower respiratory tract infection (LRTI) is one of the major causes of mortality in children with estimated 1 million deaths every year. Hyponatremia is the most common electrolyte abnormality seen in LRTI.

**Objective** To find association of hyponatremia (serum sodium < 135 meq/l) with severe LRTI.

**Design** Prospective cross sectional study

**Settings** Pediatric Emergency, Ward and Pediatric Intensive Care Unit of Tribhuvan University Teaching Hospital (TUTH)

**Subjects** Children between 2 months to 16 years presenting with cough for less than 3 weeks, fast breathing and chest indrawing.

**Methods** Children between 2 month to 16 years of age having cough, fast breathing and chest indrawing admitted in emergency, ward or PICU of TUTH were screened and among them, children having pediatric respiratory severity score of 4-5 were enrolled in the study. Serum sodium was sent during admission and collected within 2 hours. Daily follow up was done to find need of respiratory support, duration to resolve hypoxia, total duration in hospital and final outcome of patient. Statistical test applied were Chi-square test and Fisher exact test.

**Results** 47.5% of study population had hyponatremia, of whom 65.79% had mild hyponatremia 26.31% had moderate and 7.89% had severe hyponatremia. Association of hyponatremia with need of non rebreathing face mask ( $p=0.001$ ), ventilator ( $p=0.009$ ), duration of hospital stay ( $p=0.047$ ) were significant. The study also found the association of severity of hyponatremia with need of non rebreathing facemask ( $p=0.001$ ), ventilator ( $p=0.01$ ), outcome ( $p=0.001$ ), duration of stay (0.002). Mean time to resolve hypoxia in children with hyponatremia (4.5 days) was longer compared to normal sodium (2.58 days). Four patients died during the study period and all of them had hyponatremia.

## Background

Lower respiratory tract infection (LRTI) is infection below the level of the larynx and it includes bronchiolitis, pneumonia and empyema. It is inflammation of the airways/pulmonary tissue, commonly due to viral, bacterial or fungal infection(1).

ARIs are the major cause of mortality among children aged less than 5 years especially in developing countries. Worldwide, 1 million (16%) mortality among children aged less than 5 years is attributed to respiratory tract infections predominantly pneumonia associated. Southeast Asia stands first in number for ARI incidence accounting for more than 80% of all incidences together with sub-Saharan African countries(2, 3). Children with ARI account for 30% to 50% of the children attending outpatient clinics and 20% to 40% of admissions into hospitals(4).

According to Nepal demographic health survey 2016, prevalence of symptoms of ARI among children under age 5 in Nepal fell from 5% in 2011 to 2% in 2016. Prevalence of symptoms of ARI was the highest among children age 6-11 months and age 12-24 months (4% each), followed by children age 24-35 months (2%)(5).

LRTI comprises bronchiolitis, pneumonia and empyema. Bronchiolitis is one of the common childhood illness and Respiratory syncytial virus is the most common etiologic agent. Hospitalization due to bronchiolitis is required in approximately 1% of affected children, primarily because of associated dehydration, inadequate oral intake, or respiratory insufficiency. Among those admitted, 10-15% requires intensive care due to impending respiratory failure(6).

Pneumonia is a form of acute respiratory infection that affects the lungs Pneumonia is usually preceded by upper respiratory tract infection, which promote invasion of lower respiratory tract by virus, bacteria or other pathogens that trigger an immune response. (7).

Empyema is defined as collection of pus in pleural cavity. Common pathogens are Streptococcus pneumoniae, Staphylococcus aureus and Streptococcus pyogenes. Empyema starts as moderate to large exudative parapneumonic effusion, which can progress to being loculated with further development of a fibrinous peel. This can be associated with fever, fast breathing and respiratory distress(8).

LRTI can be complicated as lung abscess, pneumatocele, pneumothorax, apnoea, hyperinflation, atelectasis, respiratory failure. Complications beside respiratory include sepsis, meningitis, pericarditis, endocarditis, osteomyelitis, septicarthritis, and electrolyte imbalance(9, 10).

Fluids and electrolytes are the main pillars in the maintenance of body homeostasis. Most important among electrolytes is sodium which is the abundant cation of the extracellular fluid. Hyponatremia is the most common electrolyte abnormality seen in the intensive care unit (ICU), with an incidence as high as 30% in some reports(11, 12).

Hyponatremia is defined as serum sodium (Na) concentration of less than 135mEq/L (9-10).A major consequence of hyponatremia is influx of water into the intracellular space, resulting in cellular swelling that can lead to cerebral edema and encephalopathy. The clinical manifestations of hyponatremia are primarily neurologic and related to cerebral edema caused by hypo- osmolality(13).

Hyponatremia associated with pediatric pneumonia is most commonly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This syndrome is characterized by hyponatremia and hypo-osmolality. It results from the inappropriate and continued secretion and/or action of antidiuretic hormone despite normal or increased plasma volume (14, 15).

Hyponatremia associated with bronchiolitis is due to hyperinflation of lungs. Hyperinflation reduces blood flow to the right atrium and stimulates the release of vasopressin(AVP)from the posterior pituitary causing accumulation of intravascular fluid leading to dilutional hyponatremia(16).

In a study done by Shingi S et.al to determine the frequency of electrolyte disturbance in pneumonia in 264 hospitalized children in Chandigarh, India found hyponatremia in 71(27%) children with pneumonia. It was associated with two fold increase in complications and 3.5 times higher mortality(17).

Single-center retrospective cohort study was done in Children's Hospital Colorado, USA comprising children age 1 month to 2 years admitted to the PICU between January 2009 and April 2011. Study was done to characterize the relationship between hyponatremia and clinical outcome in bronchiolitis. One hundred and two children with bronchiolitis were enrolled. Twenty-three patients (22%) were diagnosed with hyponatremia. Mortality (13% vs 0%;  $P = .011$ ), ventilator time ( $8.41 \pm 2$  days vs  $4.11 \pm 2$  days;  $P = .001$ ), duration of stay in the PICU ( $10.63 \pm 2.5$  days vs  $5.82 \pm 2.09$  days;  $P = .007$ ), and noninvasive ventilator support (65% vs 24%;  $P = .007$ ) were significantly different between subjects with Hyponatremia than those without (18).

Acute respiratory tract infection is one of the serious health problems leading to hospitalization and mortality. In developing countries, 7 out of 10 deaths happen due to ARI in under 5-year age group(19).

Acute respiratory infection is classified by World Health Organization (WHO) as no pneumonia(child presenting as cough and cold), pneumonia(child with cough and fast breathing and or chest indrawing) and severe pneumonia or very severe disease( child with cough, fast breathing, chest indrawing and danger signs like unable to drink, convulsions, stridor)(20).

In Nepal, according to the most recent Annual Health Report by Department of Health Services (DOHS), in fiscal year 2073/74, a total of 1,810,722 ARI cases were registered, out of which 10.5% were categorized as pneumonia cases and 0.29% were severe pneumonia cases. The incidence of pneumonia at national level was 66 per 1000 under five children(21).

## **Pneumonia**

Pneumonia is a form of acute respiratory infection that affects the lungs. (7). The physiological intrapulmonary shunting of de-oxygenated blood and ventilation perfusion mismatch following these pathological changes results in hypoxemia(22).

Causes of pneumonia in children are Bacteria- Escherichia coli, Group B Streptococcus, Listeria monocytogenes in birth to 20 days, Bacteria-Chlamydia trachomatis, Streptococcus pneumoniae, Viruses Adenovirus, Influenza, Parainfluenza virus 1,2,3 from 3 weeks to 3 months, Bacteria-Chlamydia pneumoniae, Mycoplasma pneumoniae, Streptococcus pneumoniae from 4 months to 5 years and from 5 years to adolescence Bacteria-Chlamydia pneumoniae, Mycoplasma pneumoniae, Streptococcus pneumoniae(23) Etiology of Bronchiolitis(24): Respiratory syncytial virus(50% cases), Rhinovirus, Adenovirus, Influenza, Parainfluenza, Human metapneumovirus, Human Bocavirus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia trachomatis.

Bronchiolitis is a common cause of illness and is the leading cause of hospitalization in infants and young children. RSV infection is common in children older than two years(25).

Hypoxia, co-morbid condition such as diarrhea, age below 1 year, inability to feed, presence of loose stools and severe malnutrition are known factors for adverse outcome in children with lower respiratory tract infection. These factors increases duration of stay at hospital and if not managed properly can lead to death (26, 27).

## Hyponatremia

**Table 1: Severity of hyponatremia**

Severity of Hyponatremia	Sodium(mEq/L)
Mild	131-135
Moderate	126-130
Severe	<125

Hyponatremia is defined as serum sodium (Na) concentration of less than 135 mEq/L. The effect of ADH on plasma osmolality depends on intact kidney function, which is required for appropriate retention or excretion of free water. (28).

SIADH syndrome is characterized by hyponatremia and hypoosmolality and results from the inappropriate and continued secretion and/or action of antidiuretic hormone despite normal or increased plasma volume presumably due to inflammatory cytokines, such as interleukin-6 (29), stress, and hypoxemia(30, 31). Hyperinflation of the lungs, a hallmark of the bronchiolitis, wheezing, reduces blood flow to the right atrium and stimulates the release of vasopressin(AVP)from the posterior pituitary causing accumulation of intravascular fluid leading to dilutional hyponatremia(32).

## Pediatric Respiratory Severity Score (PRESS score)

This score was devised for a study done in National Hospital Organization Yokohama Medical center, an urban emergency hospital in Japan, in 2010-2011 to establish and examine the utility for assessing severity in children with respiratory symptoms (33).

The World Health Organization has suggested that children suspected of having infective illnesses and presenting not only with drowsiness, feeding difficulties, vomiting, convulsion but respiratory complains as dyspnoea should be hospitalized quickly(34). For calculating the score, objective signs such as respiratory rate, wheezing, retraction (accessory respiratory muscle use), SpO<sub>2</sub>, and feeding difficulties are assessed with each component given a score of 0 or 1, and total scores classified as mild (0–1), moderate (2–3), or severe (4–5). Using PRESS score, hospitalization rate was higher in moderate to

severe cases and duration of oxygen therapy was significantly longer in severe cases compared with mild and moderate cases.

**Table 2 : Pediatric Respiratory Severity Score ( PRESS ) (33)**

Score component	Operational definition		0 or 1
Respiratory rate	Month	RR	
	< 12	>60	
	12- 36 months	>40	
	>36 months	> 30	
Wheezing/ Crepitations	Based on auscultation		
Accessory muscle use	Subcostal retraction, intercostal recession, suprasternal recession		
Spo2	Less or more than 95 %		
Feeding difficulties	Refusing feedings or not		

## Methodology

**Research Design:** Prospective Cross sectional Study

**Research Method:** Quantitative

**Type of study:** Observational study

**Study Population/Sampling Frame:** Children of age 2 month to 16 years with severe lower respiratory tract infection admitted in TUTH during duration of data collection.

**Study site:** Emergency, ward and PICU of Tribhuvan University Teaching Hospital.

**Sampling Method:** Purposive sampling technique was used to select patient with lower respiratory tract infection admitted in emergency, Pediatric ward and PICU of Tribhuvan University Teaching Hospital.

**Sample size:** 80

**Inclusion criteria**

- Children 2 months to 16 years admitted at TUTH with cough(<3 weeks), fast breathing and chest indrawing.
- PRESS score 4-5

**Duration of the Study:** 1 year

### **Data Management and Statistical Analysis**

Data were entered in Microsoft Excel and converted into SPSS 20 version for statistical analysis. The descriptive data were expressed in frequency, percentage, mean, standard deviation, median etc. along with graphical and tabular presentation. Descriptive statistics was used to analyse data like mean, median and mode and standard deviation (SD).

Inferential statistics i.e. Chi square test, Fisher exact test were used at 95% confidence interval where p value<0.05 was considered statistically significant to assess association of hyponatremia with selected outcome variables and to assess association of socio-demographic variables.

## **Results**

The study was conducted over a period of 12 month from September 1<sup>st</sup> 2017 to September 1<sup>st</sup> 2018. Total 90 cases were screened, 10 cases were excluded. Among the excluded case 5 cases were of congenital heart disease, two patients came after receiving IV fluids , 2 cases had cough for more than 3 weeks and 1 patient had PRESS score of less than 4. Total 80 children were enrolled. Thirty eight patients had hyponatremia at presentation. Patients were admitted in pediatrics ward or pediatric ICU. Serum sodium was sent during IV cannulation after stabilizing the patients, patients were followed till discharge or mortality. Outcome evaluated were need of non invasive and invasive respiratory support, time taken for hypoxia to resolve, discharge of the patient or mortality

**Fig 1: Flow chart of screened and enrolled cases in the study**

### **Sociodemographic variable of study population**

**Fig 2: Age of study population**

Figure 2 shows age of study population. Out of 80 children, majority of the children were infant accounting for 41.3% followed by toddler and preschool children.

**Fig 3: Sex of study population**

Figure 3 shows the sex distribution in study population. Out of 80 children 66.25% were boys and rest were girls.

**Table 3: Sociodemographic variable of study population n=80**

Variables	Characteristic*	Frequency	Percentage (%)
<b>Age of study population</b> (mean±SD)=(2.3± 1.4) years			
<b>Father's education</b>	Lower secondary	18	22.5
	Secondary	23	28.8
	Higher secondary	11	13.8
	University level	28	35
<b>Mother's education</b>	Lower secondary	18	22.5
	Secondary	27	33.8
	Higher secondary	14	17.5
	University level	21	26.3
<b>Father's occupation</b>	Technical/professional	26	32.5
	Sales/service	26	32.5
	agriculture	4	5
	labor	8	10
	abroad	16	20
<b>Mother's occupation</b>	Technical/professional	10	12.5
	Sales/service	6	7.5
	agriculture	1	1.3
	labor	1	1.3
	housewife	62	77.5

\*Characteristics of parent's education and occupation according to NDHS 2016

Above table 3 depicts sociodemographic variable of study population, about one third of father had university level education followed by 28.8% in secondary level. Among mothers about one third that is 33.8% mothers had education upto secondary level followed by 26.3% university level. Occupation of most of the fathers was technical/ profession and sales/service each 32.5% and 77.5% of the mothers were housewife.

**Table 4: Clinical characteristics of study population**

**n=80**

Characteristics	Frequency	Value	Percentage (%)
Cough (mean±SD)	80	5.15 ( ± 2.89)days	
Fast breathing (mean±SD)	80	2.687( ± 1.24) days	
Chest indrawing (mean±SD)	80	1.74 ( ± 0.97)days	
Refusal to feed	15		18.7
Fever	54		67.5
Respiratory rate(mean)			
· Infant	33	(64.69±5.62)/min	
· Toddler	15	(58.33±10.96)/min	
· Preschool	14	(36.28±3.22)/min	
· School going	9	(47.22±15.98)/min	
· Adolescent	9	(44.22±12.46)/min	
Temperature(mean±SD)	80	(99.13±1.63) F	
Oxygen saturation(mean±SD)	80	(88.5± 7.17)%	
Hypoxia*	31		38.75
Wheeze on auscultation	31		38.75
Crepitation on auscultation	49		62.25
Respiratory support	Need of nasal prongs	70	87.5
	Need of simple facemask	61	76.25
	Need of non rebreathing face mask	16	20
	Need of CPAP	7	8.75
	Need Ventilator	6	7.5

\*Hypoxia defined by WHO as oxygen saturation <90%

The above table shows clinical characteristics of study population. Mean duration of cough was 5.15 (± 2.89) days , mean duration of fast breathing was 2.687( ± 1.24) and mean duration of chest in drawing was 1.74 ( ± 0.977). Among 80 children 18.7% had refusal to feed during the illness meanwhile 67.5% children presented with fever. Mean duration of fever was 3.36 days (± 3.34). Thirty one children were hypoxic at presentation. Examination of chest revealed crepitation in 61.25% and 38.75% had wheeze. All study population required oxygen support. Mean time required for weaning oxygen was 4.22 days and mean time for complete discontinuation was 4.93 days. Among the eighty patient 87.5% required nasal

prongs and 76.25% children required simple facemask. CPAP was given in 8.75% children and 7.5% children required mechanical ventilation.

**Table 5: Prevalence of hyponatremia in study population**

n=80

Variables	characteristics	Frequency	Percentage
Serum sodium level	Hyponatremia	38	47.5
	Normal Sodium	42	52.5
<b>Hyponatremia (n=38)</b>			
Severity of hyponatremia	Mild (131-135)	25	65.79
	Moderate( 126-130)	10	26.31
	Severe (less than 125)	3	7.89

The above table 6 shows prevalence of hyponatremia in the study population. Among the study population 38 (47.5%) had hyponatremia. Among hyponatremic children 25 (65.79%) had mild hyponatremia followed by moderate 10 (26.31%) and severe hyponatremia (7.89%).

**Table 6: Association of hyponatremia with need of non-rebreathing face mask**

n=80

Sodium	Need non-rebreather			p*
	No	Yes	Total	
Hyponatremia	23	15	38	0.001
Normal Sodium	41	1	42	
Total	64	16	80	

\* Chi square test was used to find association of hyponatremia with need of non-rebreathing face mask

Above table shows association of hyponatremia with need of non-rebreathing facemask. Total sixteen patients required non rebreathing face mask. Among them 15(93.75%) patients with had hyponatremia needed non rebreathing facemask however only 1(6.25%) patients had normal sodium . Association of hyponatremia with need of non rebreathing face mask was statistically significant (p= 0.001)

**Table 7: Association of hyponatremia with need of CPAP**

n=80

Sodium	Need CPAP			p*
	No	Yes	Total	
<b>Hyponatremia</b>	34	4	38	0.702
<b>Normal sodium</b>	39	3	42	
<b>Total</b>	73	7	80	

\* Fisher exact test was used to find association of hyponatremia with need of CPAP

Above table 7 shows association of hyponatremia with need of CPAP. Total seven children needed CPAP. Four cases with hyponatremia needed CPAP however three patients with normal sodium also needed CPAP. Association of hyponatremia with need of CPAP was not statistically significant (p=0.702).

**Table 8: Association of hypoonatremia with need ventilator**

n=80

Sodium	Need ventilator			p*
	No	Yes	Total	
<b>Hyponatremia</b>	32	6	38	0.009
<b>Normal sodium</b>	42	0	42	
<b>Total</b>	74	6	80	

\*Fisher exact was used to find association of hyponatremia with need of ventilator

Above table 8 shows relation of hyponatremia with the need of ventilator. Among eighty children, six patients were ventilated and all of them had hyponatremia. Therefore association of hyponatremia with need of ventilator was highly significant ( $p=0.009$ ).

**Table 9: Association of hyponatremia with outcome**

Serum sodium level	Outcome		Total	p*
	Mortality	Improved		
<b>Hyponatremia</b>	4	34	38	0.047
<b>Normal Sodium</b>	0	42	42	
<b>Total</b>	4	76	80	

\*Fisher exact test test was used to find association of hyponatremia with outcome

The above table 9 shows association between hyponatremia and outcome. Among the study population, 4 patients with hyponatremia had mortality and none of the patient with normal sodium expired. Association of hyponatremia with outcome was statistically significant ( $p=0.047$ ).

**Table 10: Association of hyponatremia with Duration of stay**

n=80

Sodium	Duration of stay			p*
	<7 days	>7days	Total	
<b>Hyponatremia</b>	22	16	38	0.002
<b>Normal sodium</b>	37	5	42	
<b>Total</b>	59	21	80	

\*Chi square test was used to find association of hyponatremia with duration of stay

Above table 10 shows association of hyponatremia with duration of stay. Duration of stay was divided into more than and less than 7 days. Among eighty patient 59(73.75%) patient had duration of stay less than 7 days and 21 (26.25%) had stay more than 7 days. Sixteen patients with hyponatremia had stay more than 7 days and 5 patients with normal sodium had stay more than 7 days. Association of hyponatremia with duration of stay was statistically significant (p value= 0.002).

**Table 11: Association of hyponatremia with oxygen saturation**

Level of Sodium	Saturation			p*
	<90%	>90%	Total	
Hyponatremia	18	20	38	0.13
Normal sodium	13	29	42	
<b>Total</b>	31	49	80	

\*Chi square test was used to find association of hyponatremia with oxygen saturation

The above table shows association of hyponatremia with oxygen saturation level at presentation. Association of hyponatremia with oxygen saturation level was not statistically significant (p=0.13). The mean time required for resolution of hypoxia in children with hyponatremia with severe LRTI (4.5 days) was more compared to mean time required for resolution of hypoxia in children with normal sodium with severe LRTI (2.58 days).

**Table 12: Association of severity of hyponatremia with need of CPAP of study population**

n=80

Characteristics		Need CPAP			p*
		No	Yes	Total	
Sodium level	Mild hyponatremia	21	4	25	0.534
	Moderate hyponatremia	10	0	10	
	Severe hyponatremia	3	0	3	
	Normal sodium	39	3	42	
<b>Total</b>		73	7	80	

\*Fisher exact test was used to find association of severity of hyponatremia with need of CPAP

Above table 12 depicts association of hyponatremia with need of CPAP. Among 80 patients, 7 patients required CPAP. Among seven patients only 4 i.e. (57.1%) with mild hyponatremia required CPAP however 3 i.e. (42.9%) with normal sodium also required CPAP. Severity of hyponatremia with need of CPAP was not significant ( $p=0.534$ ).

**Table 13: Association of severity of hyponatremia with need of non-rebreathing facemask**

n=80

Characteristics		Need non rebreathing facemask			p*
		No	Yes	Total	
Sodium level	Mild hyponatremia	15	10	25	0.001
	Moderate hyponatremia	8	2	10	
	Severe hyponatremia	0	3	3	
	Normal sodium	41	1	42	
Total		64	16	80	

\*Fisher exact test was used to find association of severity of hyponatremia with need of non-rebreathing facemask

Among the eighty study population sixteen patients required non rebreathing facemask. Among 16 patient 10 (62.5%) had mild hyponatremia followed by 2 (12.5%) moderate and 3(18.75%) severe hyponatremia, all three patients with severe hyponatremia required non rebreathing face mask. Therefore association of severity of hyponatremia with need of non-rebreathing face mask was highly significant ( $p=0.001$ ).

**Table 14: Association of severity of hyponatremia with need ventilator of study population**

n=80

Characteristics		Need ventilator			p*
		No	Yes	Total	
Sodium level	Mild hyponatremia	24	1	25	0.01
	Moderate hyponatremia	7	3	10	
	Severe hyponatremia	1	2	3	
	Normal sodium	42	0	42	
Total		74	6	80	

\*Fisher exact test was used to find association of severity of hyponatremia with need of ventilator

Above table 14 shows association of severity of hyponatremia with need of ventilator, among 80 patient 6 patient required ventilator support. Among the ventilated children 3 (50%) had moderate hyponatremia, 2 (33.3%) had severe hyponatremia and 1 (16.67) % had mild hyponatremia. Association of severity of hyponatremia with need of ventilator was statistically significant (p=0.01).

**Table 15: Association of severity of hyponatremia with outcome**

n=80

Characteristics		Outcome			p*
		Mortality	Improved	Total	
Sodium level	Mild hyponatremia	0	25	25	0.001
	Moderate hyponatremia	3	7	10	
	Severe hyponatremia	1	2	3	
	Normal sodium	0	42	42	
Total		4	76	80	

\*Fisher exact test was used to find association of severity of hyponatremia with outcome

Above table 15 depicts association of severity of hyponatremia with outcome. Among 80 patients four patients expired. Among four expired patient 3 (75%) patient had moderate hyponatremia and 1(25%) had severe hyponatremia. Association of severity of hyponatremia with outcome was statistically significant (p=0.001).

**Table 16: Association of severity of hyponatremia with duration of stay**

n=80

Characteristics		Duration of stay			p*
		<7days	>7 days	Total	
Sodium level	Mild hyponatremia	17	8	25	0.001
	Moderate hyponatremia	5	5	10	
	Severe hyponatremia	0	3	3	
	Normal sodium	37	5	42	
Total		59	21	80	

\*Fisher exact test was used to find association of severity of hyponatremia with duration of stay

Above table 16 depicts association of severity of hyponatremia with duration of hospital stay.

## Discussion

Lower respiratory tract infection is associated with electrolyte abnormalities like hyponatremia, hypernatremia, hypokalemia, hyperkalemia. Among them hyponatremia is the most common electrolyte imbalance(17).

This study was conducted to find association between hyponatremia and adverse outcome of severe lower respiratory tract infection in children between 2 month to 16 year admitted in Emergency, ward and PICU of Tribhuvan University Teaching Hospital. The study was conducted over 12 months duration from September 1<sup>st</sup> 2017 to September 1<sup>st</sup> 2018. Total 80 cases were enrolled.

In current study, 47.5% of the study population presenting with severe lower respiratory tract infection at admission were found to have hyponatremia. Most of them (65.78%) had mild hyponatremia. Association between hyponatremia and need of non-rebreathing facemask ( $p=0.001$ ), need of ventilator ( $p=0.009$ ) and clinical outcome (mortality or improvement) ( $p=0.047$ ) was statistically significant ( $P<0.05$ ). During the course of hospital stay, the mean time required for resolution of hypoxia was found higher in children with hyponatremia (4.5 days) as compared to the children with normal sodium (2.58 days). Association of hyponatremia with oxygen saturation at presentation was not significant. Children with hyponatremia had prolonged hospital stay compared to children with normal sodium and the association was statistically significant ( $p=0.047$ ).

### Age and gender of study population

In this research mean age of study population was (2.3± 1.4) years and 66.25% of study population were boys.

In a study conducted by Chaitra et al had similar results. The study was conducted in 91 patients suffering from LRTI admitted in PICU of Kempegowda Institute of Medical Sciences, Bangalore in children age 2 months to 16 years. The mean age of study population was 2 years and 59% of the children were boys(1).

In the cross sectional study done to see prevalence of hyponatremia in children admitted at Kenyatta national hospital with pneumonia in 135 children aged between 2 month to 12 years, the mean age was 1.8 + 2.3 years and 54.8% of the study population were boys(35).

### **Prevalence of hyponatremia**

In present study 47.5% of study population had hyponatremia. When evaluated for severity of hyponatremia, 65.79% had mild hyponatremia followed by 26.31% children with moderate and 7.89% with severe hyponatremia.

In a study conducted by Chaitra et.al in Bangalore, India to find frequency of hyponatremia in 91 children from July, 2014 to December, 2014, prevalence of hyponatremia was 46.7%. Among children with hyponatremia, 20 (71%) had mild, 6 (21.4%) had moderate and 2(7%) had severe hyponatremia. These findings are similar to the present study(1).

Hospital based cross sectional study was carried out at Assam Medical College and Hospital, Dibrugarh from April 2012 to March 2013 to find frequency of hyponatremia in pneumonia. They found hyponatremia in 46.7% with bronchopneumonia. In the majority of cases, 71% had mild hyponatremia, 21.4% had moderate and 7% had severe hyponatremia. The results were consistent with current research(37).

The findings of the present study are also consistent with the study conducted by Sakellaropoulou et al in Bielanski hospital in Warsaw, Poland. The study was conducted from January 2009 to December 2010 to find prevalence of hyponatremia in pneumonia. Nineteen children (35.18%) with pneumonia had hyponatremia at admission of whom 18(33.3%) had mild hyponatraemia and 1 (1.9%) had moderate hyponatremia.(36)

In a study done by Shingi S et.al to determine the frequency of electrolyte disturbance in pneumonia in 264 hospitalized children in Chandigarh, India, hyponatremia was present in 27% children with pneumonia. The percentage of moderate and severe hyponatremia was 27% and 4.5% respectively, results are consistent to our research(17).

In the cross sectional study to find prevalence of hyponatremia in children admitted at Kenyatta national hospital with pneumonia in 135 children, 71.9 % ( 97) children had hyponatremia. Among patients identified with hyponatremia, 40.6% had severe, 28.1% had moderate while 31.3% had mild

hyponatremia. The result is higher compared to current finding. This may be because most of the children studied in Kenyatta national hospital presented late in hospital and they were critically ill and most of them also had associated complications(35).

### **Outcome – Need of respiratory support**

During this study, 38.75% patients were hypoxic at presentation. All patients were provided either noninvasive or invasive oxygen support. Noninvasive supports were nasal prongs, simple facemask and non-rebreathing facemask. Invasive respiratory support included bubble continuous positive air pressure (CPAP) and mechanical ventilation. Oxygen was provided via nasal prongs in 87.5% patients and via simple facemask in 76.25% during their hospital stay. Non re-breathing facemask was required 20% patient, CPAP in 8.75% patient. Total 6 (7.5%) patients were mechanically ventilated.

Association of hyponatremia with the need of non-rebreathing facemask ( $p=0.001$ ) and mechanical ventilation ( $p=0.009$ ) was significant. However it was not statistically significant with the need of CPAP ( $p=0.702$ ). The reason behind it may be, use of conventional bubble CPAP was not feasible in older children.

Multi centered prospective cohort study was conducted by Hasegawa et al in United States to find association between hyponatremia in children with bronchiolitis and use of respiratory support admitted in pediatric intensive care unit. The study was conducted from winter of 2007 to 2010. In that study, children with hyponatremia had more risk of mechanical ventilation compared to children with normal sodium (58% vs 40%,  $p=0.04$ ). In our study also all mechanically ventilated patient had hyponatremia (40).

In our study, 31 children were hypoxic at presentation. Among them 58% children had hyponatremia and 42% had normal serum sodium level. Association of hyponatremia with oxygen saturation level at admission was not statistically significant ( $p=0.13$ ). The mean time required for resolution of hypoxia in children with hyponatremia with severe LRTI (4.5 days) was more compared to children with normal sodium (2.58 days).

In a study conducted by Basnet et al at Kanti children hospital, Nepal on 610 Nepalese children, aged 2 – 35 months from February 2006 to June 2008, hypoxia was a significant predictor for time till recovery in children with severe pneumonia(50). In our study also hypoxic children with LRTI required more time for recovery than children with normal oxygen saturation.

### **Outcome- Duration of stay**

In the study conducted by Patil et.al. in 300 children in Assam Medical College and Hospital, Dibrugarh, India from April 2012 to March 2013 with objective to compare duration of stay in hyponatremic and normonatremic patient with pneumonia. The mean duration of hospital stay of patient with hyponatremia in pneumonia was around  $9.54 \pm 2.63$  days however in patient without hyponatremia was

6.43±1.16 days. Association of hyponatremia with duration of stay was significant (p value <0.01). The result is consistent with our findings(37).

In a retrospective study was done in 312 children with pneumonia from January 2009 to December 2010 in Bielanski Hospital, Warsaw, Poland, the duration of hospital stay was longer (9 days vs. 8 days, p=0.01) in the hyponatremic children compared with the children without hyponatremia. These findings are similar to results derived from present study (38).

A retrospective cross sectional study done by Lavagno et.al in Cheil General Hospital and Women's Health Care Center, Seoul South Korea in 3938 children with respiratory infections between March, 2011, and February, 2014 is also consistent with present study. In this study, the duration of hospital stay in children with hyponatremia was 4.5±1.5 days and 4.3±1.5 days in children with normal sodium (p=0.020)(39).

Another study was done by Kaneko et.al in Department of Pediatrics, Juntendo University Urayasu Hospital, Chiba, Japan. Medical record of 138 children was reviewed retrospectively in the year 2004. Objective of the study was to find the relation of hyponatremia and duration of hospital stay. Duration of hospital stay was 7.00± 3.38 days (mean ± standard deviation) for the hyponatremic patient and 6.04± 3.82 for normonatremic patient and comparison was statistically not significant (P>0.05).(40)

### **Outcome- Mortality**

In this study, 4 patients with hyponatremia had mortality, none of the patient with normal sodium expired. Association of hyponatremia with outcome was statistically significant (P=0.047). Among 4 expired patient, 3 (75%) patient had moderate hyponatremia and 1 (25%) had severe hyponatremia. Association of severity of hyponatremia with outcome was statistically significant (p=0.001).

The finding is consistent with the single-center retrospective cohort study done in Children's Hospital Colorado, USA done by Luu et.al. One hundred and two children were studied from January 1, 2011 to July 1, 2011 to characterize the relationship between hyponatremia and clinical outcomes in children ages 1 month to 2 years admitted to the pediatric intensive care unit (PICU) with bronchiolitis. Thirteen percent of patient with hyponatremia expired, however none of children with normal sodium expired. The association was significant (p=0.001)(18)

### **Conclusion**

Hyponatremia was found in 47.5% of children with severe lower respiratory tract infection. Among hyponatremic children, 65.79% had mild hyponatremia 26.31% had moderate and 7.89% had severe hyponatremia. Hyponatremia in severe lower respiratory tract infection is significantly associated with need of non-rebreathing facemask, need of ventilator and mortality. Children with hyponatremia in severe lower respiratory tract infection had prolonged hospital stay.

# Abbreviations

ADH: Anti Diuretic Hormone, ARI: Acute Respiratory Infections, AVP: Arginine Vasopressin, CPAP: Continuous Positive Airway Pressure, DOHS: Department of Health Services, ICU: Intensive Care Unit, IV: Intravenous, LRT: Lower Respiratory Tract Infection, NDHS: Nepal Demographic Health Survey, PICU: Pediatric Intensive Care Unit PRESS: Pediatric Respiratory Severity Score, SIADH: Syndrome Of Inappropriate Antidiuretic Hormone, SD: Standard Deviation, SPSS: Statistical Package for Social Sciences, URTI: Upper Respiratory Tract Infection, WHO :World Health Organization

# Declarations

**Acknowledgement:** The authors extends their sincere appreciations to the department of pediatrics, IOM, Maharajgunj Medical Campus and to all the participants of study for their cooperation during study.

**Authors Contribution:** Guide of research paper: Prof. Dr. Laxman Shrestha, Co-guide: Dr. Luna Bajracharya, and Co-author: Ms. Archana Bagale (assisted during whole study and prepared the whole manuscript)

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**Availability of data:** data sheet was prepared by researcher by entering the respondents informations including outcomes of treatment obtained during data collection on excel for analysis of results. It is attached in section of additional file.

## Ethical approval and consent to participants

The ethical clearance was taken from the Institutional Review Board of Institute of Medicine, Maharajgunj Medical Campus. Initial stabilization of patient was done immediately after presentation. The parents/guardians of children fulfilling the inclusion criteria explained about this study and approached for consent. After informed consent was obtained, the child was enrolled in the study. Participation was voluntarily taken. Informed (verbal and written) consent was taken from each participant's parents/guardians. Confidentiality and anonymity was maintained by writing code number instead of name of participants.

**Competing interests:** The authors declare that they have no competing interests.

**Consent for publication:** Not applicable

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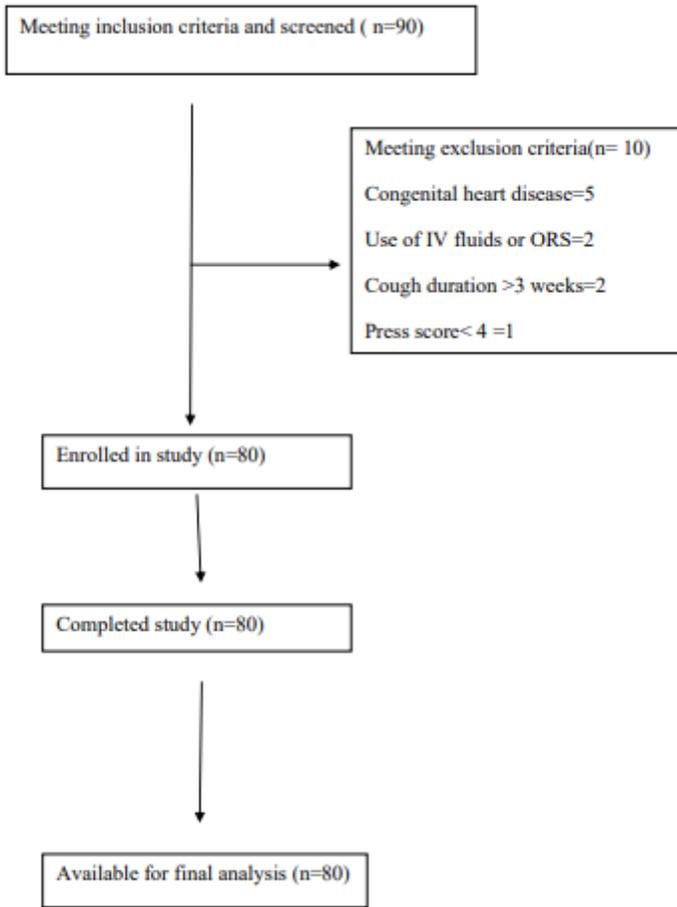
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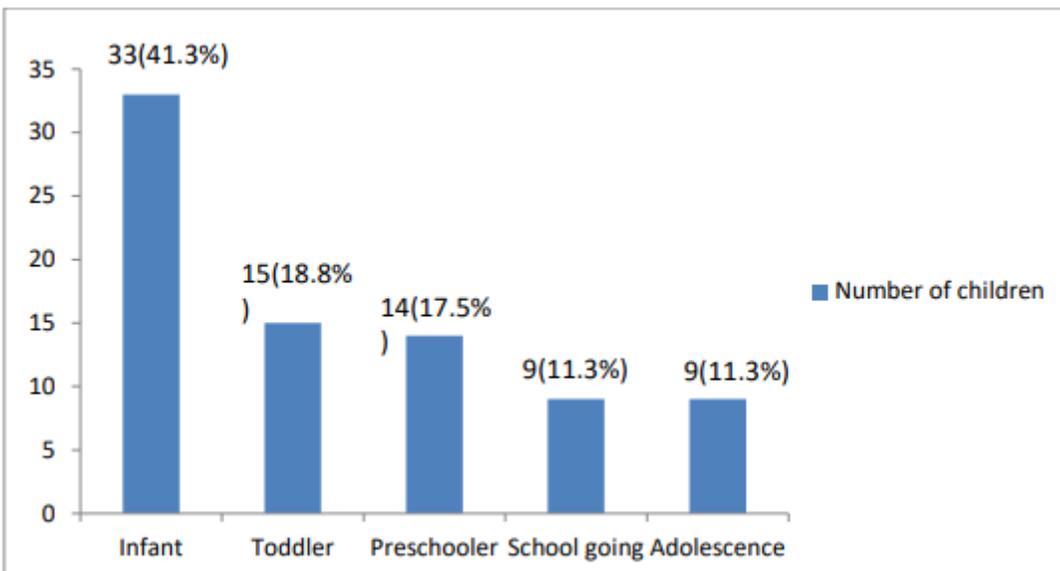
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## Figures



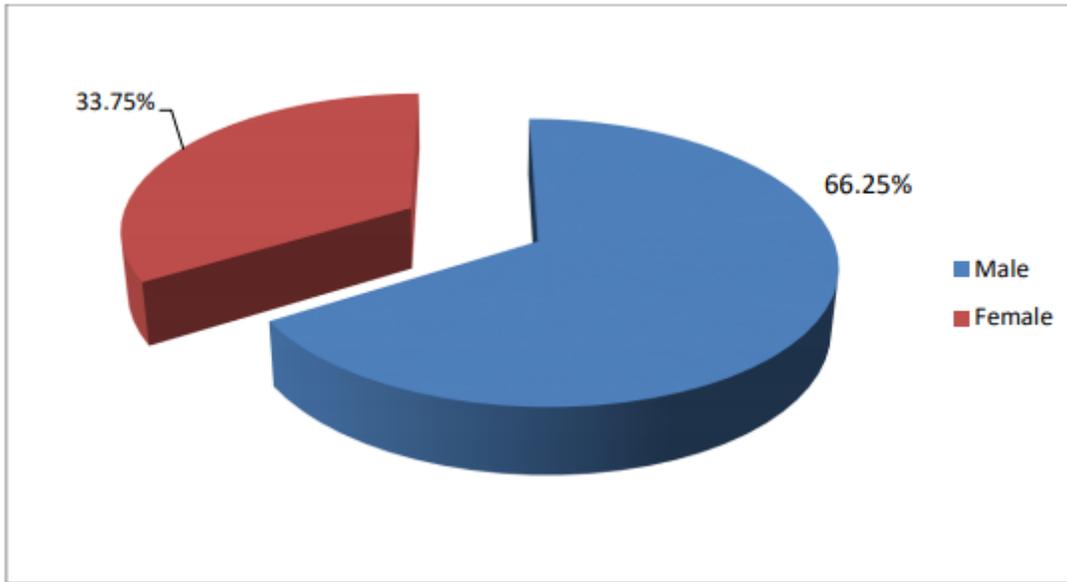
**Figure 1**

Flow chart of screened and enrolled cases in the study



**Figure 2**

## Age of study population



**Figure 3**

## Sex of study population