Lymphocyte to neutrophil ratio and procalcitonin as prognostic factors in children with lower respiratory tract infection

by

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Abstract

Background Illnesses that impact the respiratory system below the throat are known as lower respiratory infections.

Aim: to assess how blood biomarkers (leucocyte, PCT, and CRP levels), clinical symptoms, and their interaction help differentiate pediatric pneumonia from lower respiratory tract infections (LRTIs).

Patients and Methods. This prospective study was performed on 100 cases with LRTI who were admitted to pediatric ICU of Mallawi specialized hospital from May 2023 to Nov 2023. The studied patients were divided into two subgroups: 21 Patients who need admission to PICU and 79 patients who didn't need admission to PICU. The two groups were sub divided into another 2 subgroups which were (pneumonia and other LRTI.) 53% male and 47% female. The other LRTI were bronchitis, bronchiolitis, lung abscess, tuberculosis, bronchial asthma.

Lab. Evaluations including CBC, ABG, CRP, procalcitonin results were recorded. Absolute lymphocyte count divided on absolute neutrophil count to calculate LNR.

In our study we used RISC (respiratory index of severity in children score) which is a six-predictor standardized means for assessment of severity of respiratory illness among children.

Variables in RISC score (hypoxia, chest indrawing, feed refusal, wheeze, malnutrition, age) represent known risk factors for severe outcomes of pneumonia in children with a maximum score of 6 points.

Results: There was significant increase in patients who needed PICU than who didn't need PICU regarding lymphocyte to neutrophil ratio, CRP, and Procalcitonin, while there was significant decrease in patients who needed PICU than who didn't need regarding Lymphocyte, while there was no statistically significant distinction among two groups regarding HB, neutrophil, Platelets, pH, PCO2, and HCO3. **54%** of the patients was diagnosed as pneumonia and 46% was diagnosed as other LRTI (viral bronchitis 25%,10% recurrent wheezy chest,11% complicated asthma). Patients who needed PICU admission were 21 (20 diagnosed as pneumonia and 1 other LRTI), and those who didn't need PICU were 79 (34 diagnosed as pneumonia and 45 other LRTI.

Conclusion Procalcitonin, CRP increase in patient admitted to PICU more than those who didn't need. neutrophil-lymphocyte ratio (NLR) increases in patient who admitted to PICU more than those who didn't need. RISC score was higher in patient who admitted to PICU. Duration of hospital stay increases when patient need PICU admission. Mortality rate increases when patients admitted to PICU. PCT, CRP, NLR higher in pneumonia rather than other LRTI.

Keywords Lower respiratory tract infections, respiratory syncytial virus, procalcitonin, lymphocyte to neutrophil ratio.

Introduction

Illnesses that impact the respiratory system below the throat are known as lower respiratory infections. Lower respiratory tract infections (LRTIs) include bronchitis, lung abscess, bronchiolitis, TB, and pneumonia. Lower respiratory infections are defined as any infection that affects the lower airways and lungs. While many LRTIs are transmissible and viral in nature, some have bacterial roots. **(Dangor, Z et al 2021)**.

LRTIs are the leading cause of death from infections worldwide. They are characterized by symptoms such as fever, weakness, dyspnea or shortness of breath, exhaustion, coughing, and tightness in the chest. In younger children, up to 90% of LRTI infections were caused by viral infections. Acute lower respiratory tract infections (ALRTIs) are more common in children under the age of five, whereas lower respiratory tract infections (LRTIs) accounted for over 11.9 million of the young children hospitalized worldwide and are major causes of mortality in children under the age of two. Twenty percent of pediatrics deaths among the ages of one and twelve months, twelve percent of pediatrics deaths among the ages of one and four years, and six percent of neonatal deaths were related to LRTIs. (**Khan, M. A. 2022)**.

The two most common lower respiratory tract illnesses in children are bronchitis and pneumonia, which both cause coughing fits and rapid breathing. Pneumonia causes the lung's alveoli to swell and fill with fluid or pus. Pneumonia was the leading cause of death for children under five years old worldwide. The swelling or inflammation of the bronchial tubes is known as bronchitis. Influenza that is seasonal affects the upper and lower respiratory systems. It is estimated that respiratory infections account for 20 to 30 percent of all pediatrics mortality under the age of five. (**Don, M et al 2009).**

Acute pneumonia is a lung infection characterized by coughing, dyspnea, and elevated body temperature. It can be detected through chest imaging or unusual auscultatory results. The World Health Organization (WHO) states pneumonia as a condition diagnosed through clinical observations, including respiratory rate timing and visual examination, and is primarily characterized by coughing, dyspnea, and elevated body temperature (**Don, M et al 2009)**.

Pneumonia is a common respiratory infection induced by bacteria, fungi, inhaled compounds, or solid substances. It often arises as an adverse effect of upper respiratory infections like the common cold or influenza. Bronchiolitis, an inflammation or enlargement of the bronchioles, primarily affects children below two years old and infants aged three to six months. The main cause is respiratory syncytial virus (RSV). RSV can be prevented through vaccination or medication, with palivizumab, a vaccine administered to high-risk children and premature infants, being administered monthly throughout the RSV season (**Brady, M. T et al 2014)**.

Aim of the study: This study aim to determine the usefulness of blood biomarkers (leucocyte, PCT, and CRP levels), clinical symptoms, and their interaction in aiding the differentiation of pneumonia from lower respiratory tract infection (LRTI) in pediatrics cases.

Patients and methods:

This prospective study was performed on 100 cases with LRTI that admitted to pediatric ICU of Mallawi specialized hospital from May 2023 to Nov 2023. The 100 patients were divided into two groups: 21 Patients who need admission to PICU and 79 patients who didn't need admission to PICU. The two groups were sub divided into another 2 groups which are (pneumonia and other LRTI.). The patient CBC, ABG, CRP, X-ray finding, procalcitonin results were recorded. Absolute lymphocyte count divided on absolute neutrophil count to calculate LNR.

Sample size

To get the sample size for this study the following formula by (Yamane (1967:886)) will be used:

$$n = \frac{N}{1 + N(e)^2}$$

N is the population size

e is the level of precision

Therefore,

$$n = \frac{120}{1+120(0.05*0.05)} = 92.3 \approx 92$$

Adding a 10 % non-response rate gave the required minimum sample size 100 of participants.

Ethical consideration:

*****Voluntary participation**:** all research subjects were free to choose to participate without any pressure. *****Informed consent**:** Parent informed consent was obtained from every individual. The approval included application of research tools and completing case data sheet. An informed written consent was obtained from all patient's parents to participate in the study, after explaining the research aim and procedures to them.

*Confidentiality

*Potential for harm

*No conflict of interest regarding the study or publication.

*No fund regarding the study or publication

Inclusion criteria: Children age between (1month to 11y) years old presented with signs of lower respiratory tract infections which are: Tachypnea <40 breath/minute (12-59 months) and >30 breath/minute (>60 months), refusal of feeding, any sign of distress like tachypnea, working ala nasi subcostal retraction, grunting, cyanosis. (Abnormal x-ray findings accompanying drawling findings (consolidation or perihilar infiltration) with or without wheezing.

Exclusion criteria: Those having underlying chronic diseases. Immunosuppressed status. Patients with congenital heart diseases. Patient on mechanical ventilation.

Study procedure:

All patients enrolled in this study were subjected to the following at time of admission:

Full History: Name. Age. Sex. Residence, complaint, present history, History of contact with patients with LRTI. Past history of previous admission in hospital or previous attack or surgeries were done. History of chronic illness or medications have been taken, history suggestive LRTI (cough, wheezy chest, fever, difficulty of breathing, refusal of feeding). Family history and consanguinity.

General physical examination: anthropometric measurements**:** Weight in kilogram. Height in cm. BMI, length, head circumference. Vital signs: heart rate, respiratory rate, blood pressure, temperature. Systemic physical examination. Chest examination: inspection (subcostal retraction and increase RR) palpation and auscultation (diminished air entry, audible wheezes, Ronchi, crepitation). Neurological examination. Cardiac examination. pelvic & Abdominal examination.

Degree of distress:1 tachypnea, 2 working ala nasi and subcostal retraction, 3 grunting, 4 cyanosis. Oxygen saturation and RISC score (hypoxia, chest indrawing, feed refusal, wheeze, malnutrition, age) represent known risk factors for severe outcomes of pneumonia in children with a maximum score of 6 points.

Investigations including:
CBC by: sysmex, model: XNL-330 ABG by: ABL-800 flex.
C.R.P by: Beckman, model: AU480
Procalcitonin: Cobas e 411

Radiological: chest x-ray

Results

Table 1: Demographic data of all patients.

		Descriptive statistics (n=100)
Age	Median IQR	11.5 (4.3-42)
Gender	Male Female	53(53%) 47(47%)
Mother education	Median IQR	10 (6-15)
Residence	Median IQR	10 (6-15)

According to table 1, there were 53 cases (53%) were men, and 47 cases (47%) were women, median age was 11.5 and mother education was 10.

Table 2: Comparison between patients who didn't need PICU and those who needed PICU as regard to their diagnosis, complications and RISC.

		Not need PICU	**Need PICU**	**P value**
		N=79	**N=21**	
Diagnosis	LRTI other than pneumonia Pneumonia	45(57%) 34(43%)	1(4.8%) 20(95.2%)	<0.001*
LRTI	Viral bronchitis Recurrent Wheezy chest Complicated asthma Pneumonia	24(30.4%) 10(12.7%) 11(13.9%) 34(43%)	1(4.8%) 0(0%) 0(0%) 20(95.2%)	0.001

Complication	None Pneumonia ARDS CNS infection Respiratory failure Lung abscess Pleural effusion Sepsis	72(91.1%) 6(7.6%) 1(1.3%) 0(0%) 0(0%) 0(0%) 0(0%) 0(0%)	5(23.8%) 10(47.6%) 0(0%) 1(4.8%) 2(9.5%) 1(4.8%) 1(4.8%) 1(4.8%)	<0.001*
RISC	Median IQR	1 (1-2)	2 (2-3)	<0.001*

According to table 2, there was greatly statistically significant distinction among who didn't need PICU group and who needed PICU regarding pneumonia, complication, and RISC.

Table 3: Comparison between patients who needed PICU admission and those who didn't need PICU admission as regard lab results.

		Not need PICU	**Need PICU**	**P value**
		N=79	**N=21**	
HB	Range Mean ± SD	(7.5-15) 11.9±1.3	(10-14) 12±1.1	0.927
Lymphocyte (n x 103)	Median IQR	5 (3.1-7.5)	2.1 (1.7-3.1)	<0.001*
neutrophil (n x 103)	Median IQR	5.9 (3.2-10.2)	6.9 (3.4-8.6)	0.912
Neutrophil to lymphocyte ratio	Median IQR	1 (0.6-2)	2.5 (2-3.6)	<0.001*
Platelets	Median IQR	220 (190-250)	220 (170-250)	0.783
pH	Range Mean ± SD	(3-7.5) 7.3±0.5	(7-7.4) 7.3±0.1	0.538
PCO2	Range Mean ± SD	(35-55) 42.8±6.2	(35-56) 42.2±7.1	0.694
HCO3	Range Mean ± SD	(18-30) 23.8±3.2	(18-30) 23.2±3.9	0.472
CRP	Median IQR	8 (4-30)	22 (17.5-61)	<0.001*
Procalcitonin	Median IQR	1.3 (0.5-4)	20 (14.5-30.4)	<0.001*

According to table 3, there was significant increase in who needed PICU than who didn't need PICU regarding Neutrophil to lymphocyte ratio, CRP, and Procalcitonin, while there was significant decrease in who needed PICU than who didn't need regarding Lymphocyte, while there was no statistically significant distinction among 2 groups regarding HB, neutrophil, Platelets, pH, PCO2, and HCO3.

Table 4**:** Comparison between pneumonia and other LRTI as regard to lab findings.

		Other LRTI	**Pneumonia**	**P value**
		N=46	**N=54**	
HB	Range Mean ± SD	(7.5-15) 11.9±1.4	(8-14) 11.9±1.2	0.949
Lymphocyte (n x 103)	Median IQR	5.1 (3.1-8)	3.1 (2.1-5.1)	0.001*
neutrophil (n x 103)	Median IQR	4.1 (2.3-10.2)	7.4 (3.9-10.3)	0.122
Neutrophil to lymphocyte ratio	Median IQR	0.8 (0.6-1.3)	2.1 (1.6-2.8)	<0.001*
Platelets	Median IQR	235 (197-252.5)	205 (180-238.5)	0.041*
Ph	Range Mean ± SD	(3-7.5) 7.2±0.6	(7-7.5) 7.3±0.1	0.523
PCO2	Range Mean ± SD	(35-52) 42±5.6	(35-56) 43.3±7	0.297
HCO3	Range Mean ± SD	(18-30) 23.5±3.2	(18-30) 23.8±3.5	0.749
CRP	Median IQR	5 (4-8.3)	25 (16.8-48)	<0.001*
Procalcitonin	Median IQR	0.9 (0.3-1.7)	5.4 (2.8-17.2)	<0.001*

According to table 4, there was significant increase in pneumonia than other LRTI regarding Neutrophil to lymphocyte ratio, CRP, and Procalcitonin, while there was significant decrease in pneumonia than other LRTI regarding Lymphocyte, and platelets, while there was no statistically significant distinction among 2 groups regarding HB, neutrophil, pH, PCO2, and HCO3.

Table 5**:** Correlation between procalcitonin and lab findings.

N=100	Procalcitonin	
	Pearson Correlation	Sig. (2-tailed)
Lymphocyte (n x 103)	-0.317	0.001*
neutrophil/lymphocyte ratio	0.539	<0.001*
CRP	0.473	<0.001*
neutrophil (n x 103)	0.072	0.479
HB	0.078	0.443
Platelet	0.050	0.621
PH	0.025	0.808
PCO2	0.143	0.158
HCO3	0.072	0.479

According to table 5, there was significant positive association between procalcitonin and neutrophil/lymphocyte ratio, and CRP, while there was significant negative association between procalcitonin and Lymphocyte.

Table 6**:** Showing the data of ROC curve.

	Procalcitonin	Lymphocytes	Neutrophil/lymphocyte ratio	CRP
Optimal cutoff point	>2	≤ 3.1	>1.56	>15
AUC	0.858	0.695	0.832	0.879
95% CI	0.775-0.920	0.595-0.783	0.744-0.9	0.799-0.936
P value	<0.001*	<0.001*	<0.001*	<0.001*
Sensitivity	77.78	61.11	75.93	77.78
Specificity	89.13	73.91	91.3	93.48
PPV	89	73.3	91.1	93.3
NPV	77.4	61.8	76.4	78.2
Accuracy	83	67	83	85

At cutoff value >2 procalcitonin had sensitivity of 77.78% and specificity of 89.13% with significance. At cutoff value ≤3.1 lymphocytes had sensitivity of 61.11% and specificity of 73.91% with significance. At cutoff value >1.56 Neutrophil/lymphocyte ratio had sensitivity of 77.78%and specificity of 93.48% with significance (**Table** 6).

Table 7: Prognosis of patients.

		Descriptive statistics (n=100)
Duration of stay in hospital	Median IQR	6 (4-8.8)
Prognosis	Improved PICU	79(79%) 21(21%)
Mortality	Survived Died	92(92%) 8(8%)

According to table 7, median duration of stay in hospital was 6, 79 patients (79%) had improved prognosis, and 21 patients (21%) had PICU, 92 patients (92%) were survived, and 8 patients (8%) were died.

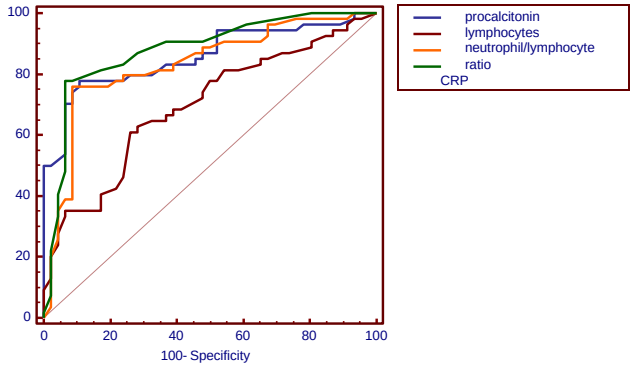

Figure 1: ROC curve.

Discussion

Globally, community-acquired pneumonia (CAP) continues to be the primary cause of morbidity and mortality in children. An estimated 120 million cases of pneumonia in children under five are reported each year; of those, 14 million are severe enough to require hospitalization, and 1.3 million result in death. **(Black, R. E et al 2010).**

In this study, there were fifty-three cases (53%) males, and forty seven cases 47%) females, median age was 11.5.

In 2011, the first randomized controlled trial involving hospitalized children (less than fourteen years of age & greater than one month) with pneumonia was published. Diagnosis of pneumonia was made based on clinical findings (fever or cough, tachypnea, dyspnea or respiratory distress, and breathing with grunting or wheezing with rales) & confirmed by chest radiography (infiltration or consolidation). cases with empyema, pleural effusions, lung necrosis & pneumatocele, underlying chronic disease, malnutrition, and patients under antibiotic treatment were excluded and this comes with agreement with our study. **(Esposito et al. 2011).**

Median period of stay in hospital was 6, 79 days (79%) improved, and 21 cases (21%) were in PICU, while 92 cases (92%) were survived, and 8 patients (8%) were died.

In other published reports by **(Koh, et al 2017)**, the case mortality rate of severe Community-acquired pneumonia ranges between 8.2 percent & 13.5 percent which is in line with our study (8%).

There was statistically significant difference among who didn't need PICU group and who needed PICU regarding pneumonia, diagnosis and complications. Median RISC score was significantly higher in patients who needed PICU admission compared to who didn't need with P<0.001. There was a significant direct association among RISC score and each of respiratory distress grade, CRP, PICU admission, & mortality. The RISC evaluated within 24h of admission. It's come with agreement with (**Abdallah Abd El Megied et al 2023)**.

Our research found early prognostic indicators such as bacteremia, and co-morbidities as independent risk factors for poor outcome. According to this study, the majority of these risk variables are parts of widely used pneumonia severity scores (such as the Respiratory Index of Severity in Children [RISC] Score). **(Araya, et al 2016).**

There was significant increase in patients who needed PICU than those who didn't need PICU regarding Neutrophil to lymphocyte ratio, CRP, and Procalcitonin, while there was significant decrease in who needed PICU than who didn't need regarding Lymphocyte, while there was no statistically significant distinction among two groups regarding HB, neutrophil, Platelets, pH, PCO2, and HCO3.

An increase in neutrophils was observed in children with serious illnesses due to inflammationinduced factors such as delayed apoptosis, demargination of neutrophils, & growth factor stimulation of stem cells. Additionally, it induces a modification in the

differential leucocyte count, specifically lymphopenia & neutrophilia. Analyses have been conducted on hemogram-derived parameters such as the neutrophil lymphocyte ratio (NLR) in relation to critical illness & inflammatory conditions.

Additionally, these parameters have been applied to the investigation of mortality associated with sepsis in kids. High & low NLR were both correlated with mortality, according to a retrospective study (**Pasaribu *et al*. 2021)** which is consistent with our findings. At cutoff value >2 procalcitonin had sensitivity of 77.78% and specificity of 89.13% with significance. At cutoff value ≤3.1 lymphocytes had sensitivity of 61.11% and specificity of 73.91% with significance. At cutoff value >1.56 Neutrophil/lymphocyte ratio had sensitivity of 77.78%and specificity of 93.48% with significance

(Qi et al. 2021) found similar results, including a high NLR in the reduced group with an area under the curve of 0.798, sensitivity of 56.25 percent, & specificity of 89.83 percent. NLR had the highest predictive ability for mortality between adult cases in an ICU, according to a study that compared various inflammatory markers (AUC: 0.609, p-value < 0.001). It was observed that mortality rates were greater in the case of extremely low and high NLRs in comparison to medium NLR (**Wu, J 2021)**.

There was significant positive correlation between procalcitonin and neutrophil/lymphocyte ratio, and CRP, while there was significant negative correlation between procalcitonin and Lymphocyte. According to the findings of (**Self et al. 2016)**. patients who were diagnosed with CAP and who had high PCT values (greater than two ng per milliliter) at the time of admission to the emergency department had a correlation with raised ICU need & mortality.

Furthermore, a comparable investigation was performed by (**Meng et al. 2009)** wherein an elevated PCT concentration (>10 ng/mL) at the time of ICU admission was significantly correlated with heightened mortality rates among the cases getting intensive care. cases with higher CRP values had a significantly higher probability of death in one study; PCT more than ten milligrams per deciliter increased mortality by 2.364 times. However, no correlation among leukocytosis & mortality was established (AUC: 0.424).

Conclusion

*Procalcitonin, CRP increase in patient admitted to PICU more than those who didn't need. *Lymphocyte neutrophil ratio increases in patient who admitted to PICU more than those who didn't need.

* Pneumonia is the most common cause of PICU admission in our study. RISC score was higher in patient who admitted to PICU.
* Duration of hospital stay increases when patient need PICU admission. Mortality rate increases when patients admitted to PICU.
* PCT, CRP, LNR higher in pneumonia rather than other LRTI.
* RISC score increases in pneumonia more than other LRTI.

*Period of hospital stay increases in patients with pneumonia. Mortality rate higher in patients with pneumonia than other LRTI.

Recommendations:

*Lower respiratory tract infection patients should be a priority in scientific research.

*We recommend including immunocompromised patients in other papers.

*Nutrition must be kept in mind in patients with LRTI.

*Further research and studies are recommended in this field for early detection of infection and good prognosis.

*Further investigations on larger spectrum for detection of accurate relation between PCT, NLR and prognosis of patients with LRTI.

*Measuring PCT and NLR as early as possible to guide us to antibiotic use

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