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Comparison of blood biomarkers sTREM-1, C-reactive protein (CRP), CHI3L1 and WBC levels in pediatric patients with pneumonia

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Abstract

Introduction: Pneumonia which is a form of acute lower respiratory tract infection, affects the lung parenchyma and destructs alveolar air space. Pneumonia continues to be a leading cause of morbidity and mortality in children. An institutional cross-sectional study was employed.

Aim: The aim of this study specifically focused on dynamically monitoring the levels of specific biomarkers, including C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cell (s-TREM), Chitinase-3-like protein 1 (CHI3L1) and white blood cell (WBC) in the blood (serum) of children with pneumonia.

Material and methods: The study involved 120 children diagnosed with pneumonia in Iraq, classified into different age groups. In total, 53 individuals with pneumonia infection were investigated. Biomarker levels including sTREM-1, CRP, CHI3L1, and WBC were analyzed to assess the severity of the disease. The data was collected from November 2023 to April 2024 and analyzed using SPSS software and Microsoft Excel 2019. Pearson's correlation was used to evaluate the relationship between biomarker levels and pneumonia severity.

Results and discussion: The results indicated that pneumonia was more frequent in children of under 5 years old. Interestingly, sTREM-1 level was consistently higher than other biomarkers, while WBC counts were the lowest among all biomarkers in all ages and pneumonia cases of study children. These differences were statistically significant, meaning they are likely not random findings.

Conclusions: sTREM-1 followed by CHI3L1 may be more useful tools for identifying pneumonia and assessing its severity in young children compared to traditional biomarkers like WBC and CRP.

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1. INTRODUCTION

Pneumonia, which is a highly serious respiratory illness that affects the lungs, is caused by various pathogens such as viruses, fungi, and bacteria.[1–3] In children, the leading bacterial culprit behind the development of pneumonia is *Streptococcus pneumonia* followed by *Haemophilus influenzae* type b (Hib), whereas the principal viral cause is syncytial virus. Additionally, children born with human immunodeficiency virus (HIV) are particularly vulnerable to *Pneumocystis jiroveci*, a major fungal cause of this condition.[4,5]

About 1,8 million fatalities globally occur from pneumonia each year, making it the leading cause of death for children under the age of 5.[6,7] When pediatric pneumonia manifests clinically, it usually causes fever, cough, and other symptoms. In addition, it's critical to recognize that a sizable percentage of impacted kids have different issues, and recurrence is a possibility.[1,2] Recent years have seen a steady increase in the prevalence of pediatric pneumonia, which has a major effect on children's general health with every year that goes by.[2,8] This disease can be seen in the fall and winter periods. It is one of the three major pediatric illnesses identified by the World Health Organization as occurring worldwide, and it is the cause of death for children under the age of 5 years everywhere. Children around the world are affected by pneumonia, although differences still exist between different areas and nations. The majority of this disease's primary burden is seen in low- and middle-income nations.[4,9,10]

Previous researches investigated a number of blood biomarkers to see if they can help with pneumonia diagnosis and prognosis. Procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) are examples of inflammatory cytokines that have clinical value as prognostic or predictive indicators of infection.[11] Triggering receptors expressed on myeloid cells-1 (TREM-1) an essential component of the immunoglobulin superfamily, function as a positive regulator of the immune response after the detection of microbial risk factors.[12] TREM-1 is an innate immune system receptor that is expressed on innate immunity cells. It comes in two forms: a soluble protein (sTREM-1) and a membrane-bound receptor (mTREM-1).[13,14]

The sTREM-1 has been measured in body fluids, including serum, cerebrospinal fluid, and bronchoalveolar lavage fluid from patients with various inflammatory conditions.[15] Poor clinical outcomes in both infectious and non-infectious disorders have been linked to elevated levels of sTREM-1.[16–18]

Chitinase-3-like protein 1 (CHI3L1) are enzymes found in many parts of nature. They break the chain of chitin into low molecular weight chitooligomers. Bacteria, fungi, plants, actinomycetes, arthropods, and vertebrates all manufacture these enzymes. The human genome has multiple genes encoding distinct human chitinases despite lacking any genes for chitin synthases.[19] Furthermore, these genes are active, and several human tissues have proteins that exhibit strong chitinolytic activity. Given that human bodies only contain tiny amounts of chitin; this phenomenon is intriguing. Chitinases most likely function as a defense mechanism against fungi and parasites that carry chitin. Furthermore, it's possible that these enzymes aid in the elimination of strong chitin antigens.[20]

C-Reactive protein (CRP) is a protein produced by the liver that rises in response to inflammation throughout the body. It was first discovered in 1930 in the blood of patients with pneumonia. Since then, CRP has become a crucial tool for evaluating patients suspected of having infections.[21] It was used, along with other clinical observations, to diagnose various bacterial infections. These include serious conditions like sepsis, meningitis, bone infections (osteomyelitis), and skin infections (cellulitis)[22,23], appendicitis[24], and joint infections.[25] CRP is also helpful in identifying other infectious and inflammatory diseases.

Most researches on CRP and pneumonia have focused on adults, particularly its ability to distinguish between bacterial and viral causes. However, a 2008 analysis of studies involving over 1,200 children found that high CRP levels weren't a strong indicator of bacterial pneumonia.[26,21] While CRP isn't a definitive indicator of bacterial pneumonia in children, it can be a helpful tool when used alongside other clinical findings and tests like chest X-rays.[21]

2. AIM

The aim of this study specifically focused on dynamically monitoring the levels of specific biomarkers, including CRP, sTREM, CHI3L1 and white blood cell (WBC) in the blood (serum) of children with pneumonia. By measuring these markers over time, they hoped to gain insights into the ongoing inflammatory response and potentially track the effectiveness of treatment. This approach could offer valuable information for diagnosing and managing childhood pneumonia.

3. MATERIAL AND METHODS

3.1. Patients

A total of 120 children were involved in the present study who grouped from less than one year to fourteen, which grouped into four groups; <1 year, 1–4 years, 5–9 years and 10–14 years. These children were diagnosed by a pediatrician in a Babil Teaching Hospital for Maternity and Children and AL-Nour hospital. Children with pneumonia were included in this study. So, among study children, 53 individuals with pneumonia infection were investigated and divided into three groups: sever, moderate and mild according to the severity of disease. The patients were investigated immunologically and biochemically from November 2023 to April 2024.

3.2. Blood sample collection

The blood samples were collected from each patient during morning with amount of 5 mL. Each blood sample was separated into two parts, first part: 2 mL of blood put into

an anticoagulant tube containing ethylene-diamine-tetra acetic acid (EDTA) to measuring (WBC) by using the SystemXP-300, and second part: 3 mL of blood put into gel tube to measuring (sTREM, CHI3L1 by ELISA system and CRP by DIRUI CS-T180).

3.3. Detection of biomarkers

A sandwich enzyme linked immunosorbent assay kit was used to detect serum sample sTREM-1 and CHI3L1 expression levels The concentration of the serum sTREM and CHI3L1 level in patients were determined according to the manufacturer's guidance (ELK Biotechnology, USA). An antibody specific to human sTREM-1 and CHI3L1 were pre-coated on the microtiter plate used to detect and absorbance optical density (OD) was read at a wavelength of 450 nm. The concentration of human sTREM and CHI3L1 in the samples were determined by comparing the OD of the samples to the standard curve. The blood sTREM-1 and CHI3L1 concentrations were compared among the different age groups and compared among the severe, moderate and mild cases the detected blood sTREM-1 concentration values were compared among the three groups.

3.4. Diagnostic criteria

Pneumonia has been diagnosed according to the following criteria: (1) fever or a noticeable rise in body temperature (usually above 38°C or 100.4°F); (2) cough; (3) difficulty breathing and chest pain; (4) chest X-ray revealing any areas of inflammation in the lungs; and (5) blood tests to evaluate the level of infection in the body and identify the type of bacteria causing pneumonia.

3.5. Statistical analysis

All data were analyzed using SPSS software (V.28 Inc., Chicago, USA) and Microsoft Excel 2019. Pearson's correlation was used to determine associations between variables all values are expressed as mean ± standard deviation (SD), *P* value of less than 0.05.

4. RESULTS AND DISCUSSION

4.1. Prevalence of pneumonia among age groups

The clinical diagnoses of pneumonia show a relationship with age groups, as shown in Table 1 and Figure 1. The distribution of pneumonia cases across age groups, starting from less than 1 year to 10–14 years, was as follows: 24 cases in the less than 1-year age group, 22 cases in the 1–4 years age group, 5 cases in the 5–9 years age group, and 2 cases in the 10–14 years age group.

Table 1. Distribution of pneumonia infection according to age groups.

Age groups	Frequent of pneumonia, *n*
<1 years	24
1–4 years	22
5–9 years	5
10–14 years	2
Total	53

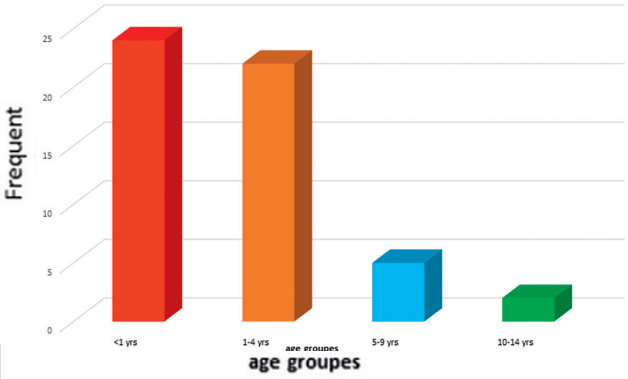

Figure 1. Distribution of pneumonia infection among age groups.

The results of this study found pneumonia was a significant health concern in children of age under 5, the results of our study are consistent with the results of other studies.[27–31]

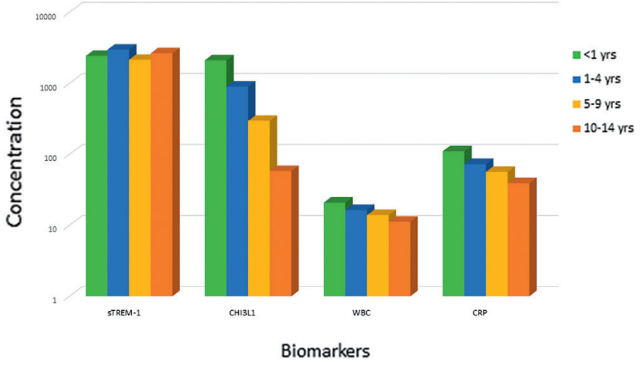

Figure 2. The relationship between the age groups and biomarkers.

Table 2. The relationship between the age groups and biomarkers, mean ± SD.

Age groups	Biomarkers			
	sTREM-1	CHI3L1	WBC	CRP
<1 years	2418.269 ± 2145.870	2094.274 ± 927.587	20.828 ± 3.154	110.040 ± 7.865
1–4 years	2956.508 ± 2994.722	893.412 ± 1062.873	16.321 ± 3.464	72.484 ± 30.776
5–9 years	2132.287 ± 2550.73	294.050 ± 606.037	13.889 ± 2.291	56.346 ± 10.921
10–14 years	2630.721 ± 3499.048	57.775 ± 143.597	11.150 ± 2.694	38.972 ± 4.053
P value	0.001	0.16	0.005	0.02

Table 3. Relationship between the severity of pneumonia and biomarkers in paediatrics, mean ± SD.

Severity	Biomarkers			
	sTREM-1	CHI3L1	WBC	CRP
Mild	2256.952 ± 3309.643	48.553 ± 132.783	11.105 ± 2.507	39.162 ± 3.878
Moderate	2649.117 ± 2514.206	363.429 ± 505.272	14.534 ± 1.403	55.975 ± 9.205
Severe	2841.981 ± 2816.161	2025.397 ± 1016.498	20.637 ± 2.878	110.486 ± 7.065
P value	0.004	0.316	0.031	0.086

4.2. The relationship between the age groups and biomarkers

The age plays a crucial role in influencing biomarkers across various health conditions, the mean ± SD of biomarkers concentrations across age groups as presented in Table 2 and Figure 2.

The average of sTREM-1 concentration in age of less than 1 year were 2418.269 ± 2145.870 ng/mL, 2956.508 ± 2994.722 ng/mL in the second age group of 1–4 years, 2132.287 ± 2550.733 ng/mL, in the third age group of 5–9 years and 2630.721 ± 3499.048 ng/mL in the age of 10–14 years. There were significant differences among the four age groups (P = 0.001). In contrast, CHI3L1 concentration exhibited no statistically significant differences (P = 0.16) among age groups. The average values were: 2094.274 ± 927.587 ng/mL (less than 1 year), 893.412 ± 1062.873 ng/mL (1–4 years), 294.050 ± 606.037 ng/mL (5–9 years), and 57.775 ± 143.597 ng/mL (10–14 years).

WBC concentration showed significant differences (P = 0.005) across age groups. The average concentration in the following age groups were: less than 1 year – 20.828 ± 3.154 ng/mL, 1–4 years – 16.321 ± 3.464 ng/mL, 5–9 years – 13.889 ± 2.291 ng/mL, and 10–14 years – 11.150 ± 2.694 ng/mL. Examination of CRP concentration revealed significant differences across age groups (P = 0.02). Mean concentrations were: 110.040 ± 7.865 ng/mL (less than 1 year), 72.484 ± 30.776 ng/mL (1–4 years), 56.346 ± 10.921 ng/mL (5–9 years), and 38.972 ± 4.053 ng/mL (10–14 years).

Analysis of Figure 2 reveals that among all the biomarkers, sTREM-1 concentration was the highest in all age group, the sTREM-1 highest mean concentration (2956.508 ng/mL) was observed in patients within 1–4 years age group. Conversely, WBC concentration was the lowest among all the biomarkers. The lowest mean concentration (11.150 ng/mL) was observed in patients of 10–14 years. This result was because that elevated WBC can suggest the presence of an infection, but it's not specific to pneumonia, it needs to be interpreted in conjunction with other clinical findings and tests like chest X-rays and CRP levels for a more accurate diagnosis. So, this result agreed with some researchers works.[32,33] While sTREM-1, a soluble form of TREM-1, has emerged as a promising diagnostic tool for pneumonia across different patient populations, and this result corresponded with study of Wang et al.[34]

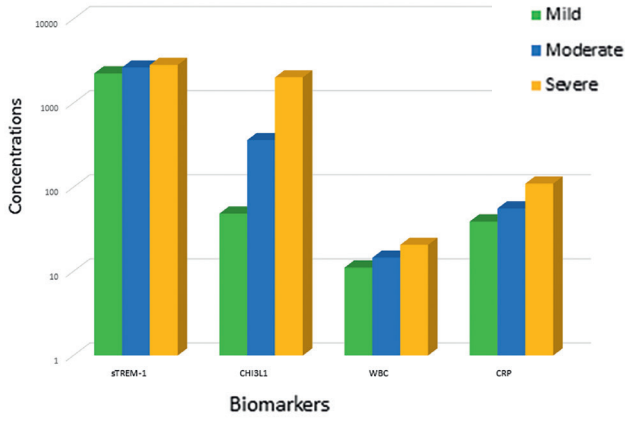

Figure 3. The relationship the severity of pneumonia and biomarkers.

4.3. The relationship between the severity of pneumonia and biomarkers

The severity of pneumonia is closely linked to specific biomarkers that can indicate disease progression and outcome. Table 3 and Figure 3 present the analysis of mean and standard deviation for biomarker concentrations across the spectrum of respiratory tract diseases severity.

The mean sTREM-1 concentrations in mild cases were 2256.952 ± 3309.643 ng/mL, 2649.117 ± 2514.206 ng/mL in the moderate cases and 2841.981 ± 2816.161 ng/mL in the severe cases, indicating significant variations among the cases (P = 0.004). Regarding CHI3L1 concentration, there were no statistically significant differences (P = 0.316) among cases. The mean concentrations were 48.553 ± 132.783 ng/mL (mild cases), 363.429 ± 505.272 ng/mL (moderate cases) and 2025.397 ± 1016.498 ng/mL (severe cases).

Analysis of WBC concentration unveiled significant variations (P = 0.031) across cases with mean concentrations of 11.105 ± 2.507 ng/mL (mild cases), 14.534 ± 1.403 ng/mL (moderate cases) and 20.637 ± 2.878 ng/mL (severe cases). The examination of CRP concentrations indicated no significant distinctions among all cases (P = 0.086) with mean concentrations of 110.040 ± 7.865 ng/mL (severe cases), 72.484 ± 30.776 ng/mL (moderate cases) and 38.972 ± 4.053 ng/mL (mild cases).

Figure 3 shows that all biomarkers level increased with severe cases and decreased with mild cases. sTREM-1 level was the highest among all biomarkers, the highest mean concentration of sTREM-1 (2841.981 ng/mL) was in severe cases. However, WBC has the lowest level among biomarkers, in the mild cases, the concentration of WBC (11.105 ng/mL) was the lowest. These results were corresponded with some works.[32,35]

4.4. Correlation between biomarkers and severity of pneumonia

Statically found a significant correlation in some biomarkers among the severe pneumonia infections, as presented in Table 4. As a result, there is a negative correlation between human CH13L1 and sTREM-1, and negative correlation among WBC with human CH13L1 and sTREM-1, and among CRP with sTREM-1 and human CH13L1, at *P* value of less than 0.05. As a result, there is a positive correlation between WBC and CRP, at the *P* value of less than 0.05.

Statically found a significant correlation in some biomarkers among the moderate pneumonia infections, as depicted in Table 5. As a result, there is a significant positive correlation between CRP and WBC, at the *P* value of less than 0.01. While, there is a positive correlation among CRP with human sTREM-1 and human CH13L1, and among WBC with human sTREM-1 and human CH13L1, at the *P* value of less than 0.05. Consequently, there is a negative correlation between Human sTREM-1 and Human CH13L1, at the *P* value of less than 0.05.

Statically found a significant correlation in some biomarkers among the mild pneumonia infections, as shown in Table 6. As a result, there is a significant positive correlation between human CH13L1 and human sTREM-1, at the *P* value of less than 0.05. While, there is a positive correlation between among CRP with Human sTREM-1 and Human CH13L1, at the *P* value of less than 0.05. Accordingly, there is a negative correlation among WBC with Human sTREM-1 and Human CH13L1, at the *P* value of less than 0.05, also, there is a negative correlation between WBC and Human CRP, at the *P* value of less than 0.05.

Table 4. Correlation coefficient among biomarkers for severe pneumonia.

Pearson correlation coefficient	Human CH13L1	Human sTREM-1	WBC	CRP
Human CH13L1	1	—	—	—
Human sTREM-1	-0.100*	1	—	—
WBC	-0.040	-0.186	1	—
CRP	-0.069	-0.004	0.234	1

Comments: * Correlation is significant at the 0.05 level (1-tailed); ** Correlation is significant at the 0.01 level (2-tailed); Positive correlation; Negative correlation.

Table 5. Correlation coefficient among biomarkers for moderate pneumonia.

Pearson correlation coefficient	Human CH13L1	Human sTREM-1	WBC	CRP
Human CH13L1	1			
Human sTREM-1	-0.062	1		
WBC	0.262	0.216	1	
CRP	0.214	0.222	0.436**	1

Comments: * Correlation is significant at the 0.05 level (1-tailed); ** Correlation is significant at the 0.01 level (2-tailed); Positive correlation; Negative correlation.

Table 6. Correlation coefficient among biomarkers for mild pneumonia.

Pearson correlation coefficient	Human CH13L1	Human sTREM-1	WBC	CRP
Human CH13L1	1			
Human sTREM-1	0.269*	1		
WBC	-0.139	-0.187	1	
CRP	0.163	0.211	-0.185	1

Comments: * Correlation is significant at the 0.05 level (1-tailed); ** Correlation is significant at the 0.01 level (2-tailed); Positive correlation; Negative correlation.

5. CONCLUSIONS

The results of this study found pneumonia was a significant health concern in children of age under 5. The results of the present study establish that:

(1) The concentration of all biomarkers increased with increased in the severity of pneumonia.
(2) The blood sTREM-1 levels were significantly higher in patients when compared with other biomarkers, while, WBC levels were lower.
(3) The highest concentrations of sTREM-1 were 2841.981 ng/mL and 2956.508 ng/mL in severe cases and 1–4 year age group, respectively. Similarly, concentrations of CHI3L1 also showed a correlation with severity, with the highest levels (around 2025.397 ng/mL and 2094.274 ng/mL) observed in severe cases and children under 1-year old, respectively.
(4) The maximum concentrations of WBC, around 20.637 and 20.828 ng/mL, respectively, were in severe cases and children under 1-year old.
(5) The maximum concentrations of CRP revealed in the age of less than 1 year and severe cases with concentration of 110.040 ng/mL. However, they were lower compared to sTREM-1.
(6) The results of the current study further exhibited significant difference between the blood sample biomarkers value and all age groups ($P < 0.05$), except CHI3L1 level, which didn't significantly associate with age group ($P > 0.05$).
(7) There were significant differences among WBC and sTREM-1 with severity of pneumonia ($P < 0.05$), while there were no significant differences among CRP and CHI3L1 with severity of pneumonia infection ($P > 0.05$).
(8) This research proposes that sTREM-1 followed by CHI3L1 may be more useful tools for identifying pneumonia and assessing its severity in young children compared to traditional biomarkers like WBC and CRP.

Conflict of interest

Authors declare no competing interest.

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