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Pediatric non-COVID community-acquired pneumonia: Correlation of etiology, innate immune responses and the impact of feeding practices

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Abstract: Community-acquired pneumonia (CAP) is a lower respiratory tract infection in a healthy child who has not recently been admitted to the hospital. Being the primary line of defense against bacterial and viral infections, the innate immune system is vital to protecting against CAP. The study aims to inspect the effects of feeding practices on the innate immune response in pediatric NCCAP, with particular attention paid to WBCs, CRP, TLR2, and TLR4.The study was a multi-center, cross-sectional enlisted 190 participants, separated into three groups based on the forms of feeding that the children engaged received: 80 were breastfed, 90 received artificial feeding, and 20 received mixed feeding. The following data were collected from every participant: demographic features, clinical parameters, and laboratory tests of TLR2, TLR4, CRP, WBCs, and identification of the microbial causation of pneumonia. Polymerase chain reaction tests were used to exclude patients with COVID-19 infection. Most of the immune parameters (WBC and the differential count) have means that are comparable between males and females. There are variations in the values of TLR4 with P- 0.028 and TLR2 with P- 0.025, between sexes. Breastfed infants show significantly lower TLR4 and TLR2 levels compared to artificially fed infants, while there were no significant differences are observed in CRP levels among the feeding groups. Feeding practices influence immune parameters, highlighting different profiles in breastfed babies. While presenting valuable insights, the conclusions warrant justification through larger clinical trials.

Keywords: *Artificial feeding, Breastfeeding, Community-acquired-pneumonia, C-reactive protein, Toll-like receptors (TLR2, TLR4).*

1. Introduction

Community-acquired pneumonia (CAP) is a term used to describe lower respiratory tract infection in a healthy child who has not recently been admitted to the hospital. CAP is caused by several microbiological organisms, such as fungi, bacteria, or viruses. Although CAP is less common in children under the age of six months, it can still lead to serious consequences. Young children typically experience more severe cases of CAP and require more hospitalization [1]. Pneumonia is the single major infectious cause of death universally among children. Pneumonia killed 740,180 children younger than 5 years in 2019, accounting for 14% of all childhood deaths below 5 years old and 22% of all deaths in children aged 1–5 years globally [2].

Innate immunity, critical in CAP, involves interleukins [3], myeloperoxidase [4], tumor necrosis factor [5], and Toll-like receptors (TLRs) [6]. TLR2, TLR4, and C-reactive protein (CRP) play key roles in pathogen recognition and immune responses [6]. TLR2, forming heterodimers with TLR1 and TLR6, is pivotal in recognizing gram-positive bacteria like *Streptococcus pneumoniae* [7]. However, TLR2 is not indispensable; TLR4 is more crucial in the lungs. TLR4 is involved in pneumonia caused by *S. pneumoniae* and *Klebsiella pneumoniae*, playing a limited role in *S. pneumoniae* and a more critical one

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in *K. pneumoniae*. TLR4 is vital in the innate immune response to pneumococcal pneumonia in the nasopharynx [8]. Understanding TLR roles aids in developing pneumonia treatments.
C-reactive protein (CRP) recognizes pathogens and altered self-determinants [9,10]. Recent studies show CRP as an active immune participant, activating complement, interacting with Fcγ receptors, and enhancing phagocytosis and reactive oxygen species formation [11]. CRP is an inflammation marker, that rises during bacterial infection. Studies suggest its role as a pattern recognition molecule activating adaptive immune responses [12]. Therefore, it can be concluded that CRP is indeed expressed by innate immunity.

The objective of the research is to inspect the effects of feeding practices on the innate immune response in pediatric NCCAP, with particular attention paid to WBCs, CRP, and TLR2, TLR4.

2. Material and Methods

2.1. Study Plan and Patients' Characteristics

The study was a multi-center, cross-sectional investigation that was part of a long line of investigations into the non-COVID-19 CAP. The study enlisted 190 participants, separated into three groups based on the forms of feeding that the children engaged received: 80 were BFB, 90 received artificial feeding, and 20 received mixed feeding. All participants were carefully selected with a history of full-term and normal weight at birth. The participants' ages ranged from one to thirty months. From November 2021 to April 2022, cases were chosen from pediatric hospitals in Babylon, in the center of Iraq. The pediatrician's identification of CAPn was made depending on the patient's history, clinical examination, lab blood tests, and plain chest X-rays. Additional information, such as their age, gender, history of feedings, and the length of the disease was obtained from the applicants. As well, blood samples were taken to assess WBCs, immunological factors such as TLR2, TLR4, and CRP levels, as well as to determine pneumonia's microbiological etiology. Those with pneumonia caused by COVID-19 or due to other causes like aspiration pneumonia, tracheoesophageal fistula, foreign body inhalation, tuberculosis pneumonia, pneumonia with septicemia, and immune-compromised children were excluded from this study. Children with inadequately defined feeding histories or whose caregivers were not close relatives were also excluded.

2.2. Hematological Assays

Polymerase chain reaction tests were used to exclude patients with COVID-19 infection. An automated Coulter counter from "Beckman Coulter Analyzer® Life science-USA", was applied to assess the WBCs counts. Levels of serum CRP, TLR2, and TLR4 were analyzed based on corresponding ELISA kits from Calbiotech®, California, USA. To identify the microbial causation of pneumonia, the "indirect immunofluorescent assay, (Vircel® S.L. Biotechnology, Granada, Spain)" was used.

2.3. Statistical Analysis

Microsoft Excel 2021 and SPSS IBM® software for PCs, Version 27, USA, were used to conduct the statistical analysis. Student's t-test and Mann-Whitney U-tests were applied to compare quantitative parameters based on the distribution. A chi-square test was applied to match qualitative traits. Multiple Post Hoc comparisons were used to assess the variations among the variables using an ANOVA technique. The ROC curve analyses were performed to estimate the efficacy of the constructed model as well as to determine the differentiating abilities of quantitative immunological parameters between breast and artificial feeding. Statistically, the 0.05 p-value was regarded as significant.

2.4. Ethical Respects

All participants provided verbal informed consent, and the institutional health directorate and the hospital scientific committee in the public hospitals both accepted the study plan. The College of Pharmacy/University of Babylon's ethical scientific committee also gave its approval to the entire study methodology.

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3. Results

Table 1 effectively communicates a comprehensive set of demographic and clinical information, making it a valuable resource for the characteristics of pediatric subjects with non-COVID community-acquired pneumonia and facilitating a clear understanding of the distribution of cases across different parameters. The majority of cases involve children below 6 months and those between 6 to 12 months old. There is a slight prevalence of females (51.6%) over males (48.4%). The majority of patients are artificially fed (47.4%). The most common etiology appears to be atypical (46.3%) followed by bacterial (32.5%), and viral cases (21.2%). The near-equal split between rural and urban residency indicates that NCCAP affects children across different living environments.

Table 1:
Demographic appearances of pediatric cases with non-COVID community-acquired Pneumonia.

Characteristics	Descriptions	Number	Percent
Age classes	Less than 6 M	80	42.1%
	6 - 12	48	25.3%
	12 - 24	38	20%
	> 24	24	12.6%
Sex	Females	98	51.6%
	Males	92	48.4%
Types of feeding	Artificial	90	47.4%
	Breast	80	42.1%
	Mixed	20	10.5%
Etiology of NCCAP	Viral	40	21.2%
	Bacterial	62	32.5%
	Atypical	88	46.3%
Residency	Rural	97	51.1%
	Urban	93	48.9%

The data presented in Table 2 provides a detailed insight into the clinical parameters and laboratory values of pediatric patients with non-COVID community-acquired pneumonia (NCCAP). The mean age of patients is approximately 9.8 months, with a wide age range from 1 to 30 months. The duration of illness (period) ranges from 2 to 60 days, with a mean of 7.7 days. The white blood cell count (WBC) is within the normal range, with a mean of 7.3 x 10^3. The variability (standard deviation) suggests some dispersion in the data.

Table 2:
Clinical parameters and laboratory values of pediatric patients with non-COVID community-acquired Pneumonia.

Characteristics	Mean	Std. deviation	Minimum	Maximum
Age/Months	9.8	10.2	1.0	30.0
Period/days	7.7	8.0	2.0	60.0
WBC 1x103	7.3	2.8	3.2	18.1
Neutrophil	3.0	1.7	0.5	11.7
Lymphocyte	3.5	1.8	1.0	12.5
Monocyte	0.4	0.3	0.1	1.6
Eosinophil	0.1	0.1	0.0	0.6
Basophil	0.2	0.2	0.0	1.0
TLR4 ng/ml	1.3	0.7	1.0	3.0
TLR2 ng/ml	1.5	0.7	1.0	3.0
CRP mg/ml	9.9	21.2	0.5	159.5

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Table 3 provides insights into the distribution of immune parameters among male and female NCCAP patients. For most immune parameters (WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils), the mean values are comparable between males and females (P-value > 0.05). Notably, there are variations in the mean values of TLR4 (P- 0.028) and TLR2 (P- 0.025) between males and females, suggesting potential gender-related variations in these immune parameters. However, on average, CRP levels are similar in both male and female NCCAP patients (P-value > 0.05).

Table 3:
Distribution of the immune parameters among the studied NCCAP children according to the gender of NCCAP.

Characteristics mean (SE)	Males (N-92)	Females (N-98)	P-value
WBC	7.2 (0.3)	7.3 (0.3)	> 0.05
Neutrophils	2.9 (0.14)	3.1 (0.18)	> 0.05
Lymphocytes	3.5 (0.18)	3.5 (0.16)	> 0.05
Monocytes	0.48 (0.03)	0.42 (0.03)	> 0.05
Eosinophils	0.13 (0.02)	0.1 (0.01)	> 0.05
Basophils	0.17 (0.02)	0.17 (0.01)	> 0.05
TLR4	5.9 (0.6)	4.2 (0.4)	0.028
TLR2	14.8 (1.7)	19.2 (1.8)	0.025
CRP	8.8 (1.7)	11.37 (2.2)	> 0.05

Table 4 provides a detailed overview of the distribution of immune parameters among pediatric patients with non-COVID community-acquired pneumonia (NCCAP), categorized by types of feeding. Breastfed infants show a significantly lower mean WBC (6.9 x 10^3) compared to artificially fed infants (7.4 x 10^3), with mixed feeding falling in between. Post Hoc Tests indicate significant differences between breast and mixed feeding, as well as between breast and artificial feeding. Breastfed infants have a significantly lower mean lymphocyte, monocyte, and eosinophil count compared to feeding types. Post Hoc Tests indicate significant differences between breast and artificial feeding, as well as between breast and mixed feeding. No significant differences are observed in mean neutrophil and basophile counts among the feeding groups.

Breastfed infants show significantly lower mean TLR2 levels compared to artificially fed infants, while there was no significant difference observed in mean CRP levels among the feeding groups.

Table 4:
Distribution of the immune parameters among the studied NCCAP children according to types of feeding.

Characteristics mean (SE)	Types of feeding			P-value	Post Hoc tests
	Breast (N-80)	Artificial (N-90)	Mixed (N-20)		
WBC	6.9 (0.3) *	7.4 (0.3)	8.8 (1.0) *	> 0.05	* 0.02
Neutrophils	2.9 (0.2)	3.0 (0.2)	3.1 (0.3)	> 0.05	-
Lymphocyte	3.3 (0.2) *	3.6 (0.2)	4.7 (0.7) *	0.016	* 0.007, 0.031
Monocytes	0.4 (0.03) *	0.5 (0.02)	0.6 (0.08) *	0.029	* 0.012. 0.042
Eosinophils	0.1 (0.01) *	0.2 (0.01) *	0.02 (0.02) *	0.021	* 0.001, 0001
Basophils	0.2 (0.01)	0.2 (0.01)	0.1 (0.06)	> 0.05	-
CRP	10.1 (2.3)	9.1 (1.7)	19.0 (6.5)	> 0.05	-
TLR4	5.5 (0.7) *	4.1 (0.4)	9 (2.8) *	0.011	* 0.046, 0.005
TLR2	11.2 (1.5) *	21.9 (1.8) *	17.4 (5.8)	0.001	* 0.001

Note: * Indicate significant statistical differences with the other two variables by Post Hoc Tests.

Table 5 presents a comparison of the distribution of immune parameters among pediatric patients with non-COVID community-acquired pneumonia (NCCAP) based on their feeding practices, specifically between those on suboptimal breastfeeding and those on pure artificial feeding. No substantial difference is detected in the mean WBCs and the differential count apart from a considerable difference observed in the eosinophil counts between the suboptimal breastfeeding and pure artificial

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feeding groups (P-0.03). A significant difference is observed in the mean TLR4 and TLR2 levels, meanwhile, no significant difference is detected in the mean CRP levels between the suboptimal breastfeeding and pure artificial feeding groups (P-0.028 and P-0.025), respectively.

Table 5:
Distribution of the immune parameters between those on suboptimal breastfeeding and those on pure artificial feeding NCCAP children.

Characteristics mean (SE)	Suboptimal breast (N-100)	Artificial (N-90)	P-value
WBC	7.2 (0.3)	7.4 (0.3)	> 0.05
Neutrophils	2.9 (0.14)	3.1 (0.18)	> 0.05
Lymphocytes	3.5 (0.17)	3.6 (0.17)	> 0.05
Monocytes	0.44 (0.03)	0.45 (0.03)	> 0.05
Eosinophils	0.08 (0.01)	0.2 (0.01)	0.03
Basophils	0.15 (0.01)	0.19 (0.02)	> 0.05
TLR4	6.0 (0.8)	4.1 (0.4)	0.025
TLR2	12.0 (1.5)	21.9 (1.8)	0.001
CRP	11.3 (2.3)	9.07 (1.8)	> 0.05

Table 6 presents a comparison of the distribution of immune parameters among pediatric patients with non-COVID community-acquired pneumonia (NCCAP) based on their feeding practices, specifically between those on pure breastfeeding and those on mixed feeding. No significant statistical difference is detected in the mean WBC counts the differential count apart from a significant difference observed in the eosinophil counts between the pure breastfeeding and mixed feeding groups (0.03). No significant differences are distinguished in the mean TLR4, and CRP levels between the pure breastfeeding and mixed feeding groups (P-value > 0.05). Meanwhile, TLR2 displayed a significant difference (p=0.001).

Table 6.
Compared distribution of the immune parameters among the studied NCCAP children between those on pure breastfeeding and those on mixed feeding.

Characteristics mean (SE)	Pure breast (N-80)	Mixed feeding (N-110)	P-value
WBC	6.8 (0.2)	7.5 (0.3)	> 0.05
Neutrophils	2.9 (0.15)	3.7 (0.17)	> 0.05
Lymphocytes	3.3 (0.15)	3.6 (0.17)	> 0.05
Monocytes	0.41(0.03)	0.47 (0.03)	> 0.05
Eosinophils	0.09 (0.01)	0.14 (0.01)	0.03
Basophils	0.15 (0.01)	0.18 (0.02)	> 0.05
TLR4	55.5 (0.7)	4.7 (0.5)	> 0.05
TLR2	11.2 (1.5)	21.4 (1.8)	0.001
CRP	10.2 (2.4)	10.2 (1.8)	> 0.05

Table 7 presents Pearson correlations among various study variables in infants with NCCAP. Overall, the correlations provide valuable insights into the interrelationships among immune parameters and age in pediatric NCCAP patients.

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Table 7:
Pearson correlations among the study variables with each other among patients with NCCAP.

		Age	WBC	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	TLR2	TLR4	CRP
Age	Correlation	1									
	P-value										
WBC	Correlation	0.078	1								
	P-value	0.252									
Neutrophils	Correlation	0.137*	0.732**	1							
	P-value	0.044	0								
Lymphocytes	Correlation	-0.038	0.762**	0.140*	1						
	P-value	0.575	0	0.04							
Monocytes	Correlation	-0.014	0.490**	0.069	0.525**	1					
	P-value	0.841	0	0.312	0						
Eosinophils	Correlation	0.073	-0.131	-0.234**	-0.047	-0.013	1				
	P-value	0.281	0.054	0.001	0.495	0.847					
Basophils	Correlation	0.129	0.186**	0.127	0.024	0.420**	0.044	1			
	P-value	0.058	0.006	0.062	0.721	0	0.519				
TLR2	Correlation	0.062	-0.023	-0.019	-0.021	-0.06	0.217**	0.003	1		
	P-value	0.365	0.736	0.777	0.76	0.378	0.001	0.966			
TLR4	Correlation	0.106	0.209**	0.177**	0.162*	0.027	-0.109	-0.092	0.314**	1	
	P-value	0.121	0.002	0.009	0.017	0.693	0.11	0.177	0		
CRP	Correlation	0.147*	0.154*	0.262**	-0.048	-0.052	-0.143*	-0.012	0.093	0.272**	1
	P-vale	0.03	0.023	0	0.483	0.448	0.035	0.858	0.17	0	

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The ROC curves (Figure 1) were made to further assess the potential differentiating value of all the studied immune parameters in predicting children breastfeeding from children on a bottle or mixed feeding in patients with NCCAP. The accuracy, sensitivity, specificity, significance, and 95%CI were displayed for each parameter.

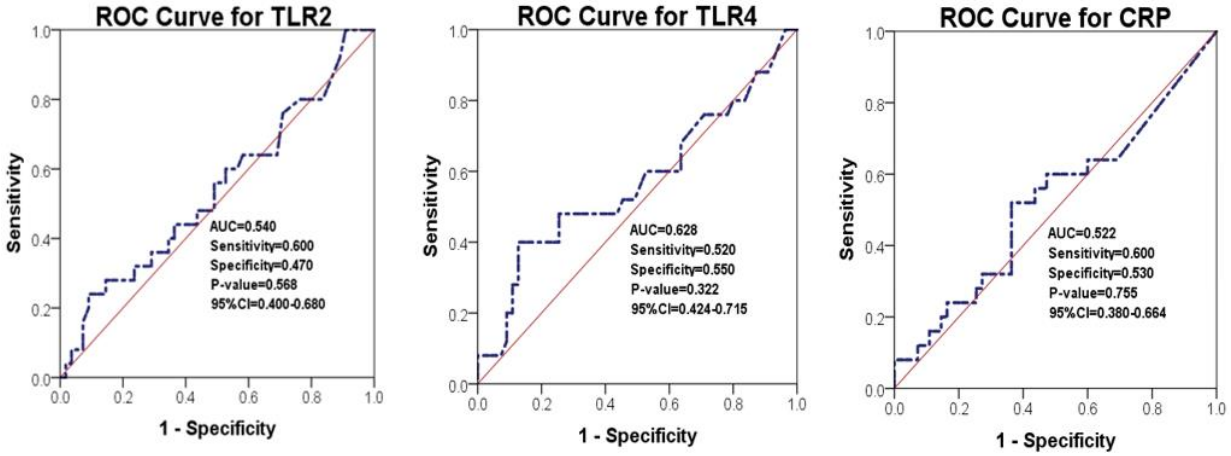

Figure 1:
A visual representation of the discriminatory ability of immunological study factors in distinguishing between infants based on their feeding methods.

4. Discussion

Innate immunity, critical in CAP, involves several body immune factors including interleukins, myeloperoxidase, tumor necrosis factor, cathelicidin, C-reactive protein, and Toll-like receptors TLR2, TLR4, that play key roles in pathogen recognition and immune responses [3-13]. The current study draws attention particularly to the role of WBCs, TLR2, TLR4, and CRP as innate immunity elements against admitted cases of NCCAP and evaluates their differences between breastfed and bottle-fed infants.

The data in Table 1 paints a clear picture of the demographic characteristics of pediatric patients with NCCAP in the present study, offering valuable information for healthcare professionals, researchers, and policymakers working in the field of pediatric respiratory health. The majority of cases involve children below 6 months and those between 6 to 12 months old. This indicates a notable vulnerability of infants and young children to NCCAP, which is in line with several other studies [1, 14, 15]. There was a slight preponderance of females (51.6%) over males (48.4%) in the reported cases suggesting a potential gender-related aspect in the incidence of NCCAP, which was concurred by recent studies [15]. However, another recent survey among French Guianese children revealed male predominance (55.9%) [16].

The majority of patients (57.9 %) were either artificially fed or mixed-feeding, while, pure breastfed cases make up a smaller proportion (42.1%). Similar findings were also published earlier exploring the correlation between feeding practices and the occurrence of NCCAP. Exclusive breastfeeding has been revealed to protect infants against CAP, and the protection is maintained even when supplementary foods are introduced [17, 18]. Another study from South Africa, published in Scientific Reports, focused on the occurrence and severity of pediatric pneumonia in the first year of life, comparing breastfed infants with mixed-fed infants and never-breastfed infants. The study found that mixed-feeding infants had a higher incidence of pneumonia compared to never-breastfed infants, while breastfed infants had a lower incidence [19].

Understanding the distribution of causative agents is crucial for effective management and treatment strategies. Most of the worldwide studies of causative pathogens of CAP in children are restricted by difficulty in gaining adequate specimens and in many cohorts the results were controversial [2]. The most common etiology appears to be atypical pathogens' cases (46.3%), followed

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by bacterial (32.5%), and viral cases (21.2%). Similar causative pathogens of NCCAP were also reported by recent academics [16]. According to recent studies, the primary causative agents of CAP in children vary depending on the age of the child. In the initial three months of life, group B pneumococci, gram-negative bacilli, and infrequently Listeria are the primary bacteria responsible for infantile pneumonia [20]. After this period, viruses account for most cases of CAP during the first two years of life, with respiratory syncytial virus being the most common [20]. Bacteria such as Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae become more frequent after this period. S. pneumoniae is the most common cause of bacterial pneumonia in children, accounting for between 17% and 28% of all CAP cases [20]. Further analysis and contextualization of this data could lead to deeper insights into the dynamics of NCCAP in the studied population.

The normal range of WBC with the variability suggests some dispersion in the data. The values for neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts provide insights into the immune response, with a notable range in each category and the distribution of blood cell counts provides information about the nature of the infection, such as potential bacterial involvement. The levels of Toll-like receptors (TLR4 and TLR2) and C-reactive protein (CRP) indicate potential markers of inflammation. The variability in these values, especially the wide range for CRP (0.5 to 159.5 mg/ml), suggests a diverse inflammatory response among pediatric patients.

The role of TLR2 and TLR4 expression and their specific differences between males and females in the context of their impact on the susceptibility to CAP in children has been not well-established. Notably, there are differences in the mean values of TLR4 (P- 0.028) and TLR2 (P- 0.025) between males and females, suggesting potential gender-related variations in these immune parameters. One study found that despite the greater expression of TLR4 among females, the extent of the inflammatory response is possibly compensated by immunomodulatory factors [22]. Another study concluded that TLR4 is involved in innate immunity during pneumonia caused by either Streptococcus pneumoniae or Klebsiella pneumoniae, with a more significant role in Klebsiella pneumonia [23]. However, these studies do not specifically address the differences in TLR2 and TLR4 expression between males and females in the context of CAP in children. The differences in TLR4 and TLR2 mean values may have clinical implications, warranting further investigation into the potential gender-specific variations in the immune response to NCCAP.

In this study, on average, CRP levels were similar in both male and female NCCAP patients, which was not far from the available evidence [9]. Nonetheless, one study found that women had higher median CRP levels compared to men, even after accounting for body mass index (BMI) and other confounding variables [24]. Another study found that male gender was linked with elevated high-sensitivity CRP, particularly in the oldest age group [25].

The significant differences in immune parameters among feeding groups suggest potential associations between feeding practices and the immune response to NCCAP in pediatric patients. The Post Hoc Tests indicate specific pairs of feeding types that exhibit significant differences in immune parameter means. These tests provide additional context beyond the overall P-values. Table 5 provides insights into the differences in immune parameters among pediatric NCCAP patients based on suboptimal breastfeeding and pure artificial feeding. The significant differences in eosinophil counts and Toll-like receptor levels suggest that feeding practices may influence certain aspects of the immune response. Table 6 provides insights into the differences in immune parameters among pediatric NCCAP patients based on pure breastfeeding and mixed feeding. The significant difference in eosinophil counts and TLR2 suggests a potential impact of feeding practices on this specific aspect of the immune response, while other parameters do not demonstrate significant changes between the two feeding types.

The available search results do not provide specific information on the types of feeding associated with CAP in children. However, it is well-established that breastfeeding plays a protective role against pneumonia in infants, reducing the incidence and severity of the disease [26]. Mixed feeding, on the other hand, has been correlated with a higher incidence of pneumonia compared to exclusive breastfeeding [17, 27]. The available literature suggests that the protective effect of breastfeeding against pneumonia is mediated by various factors, including the transfer of maternal antibodies, the presence of immune cells in mother milk, and the modulation of the infant's gut microbiota [28].

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Exclusive mother feeding until the age of 4-6 months and moderately thereafter was linked with a significant decrease in respiratory and gastrointestinal morbidity in infants [26, 29].

In the current study, although there were several indicators of the role of factors constituting the innate immunity in pure breastfed infants compared to the mixed feeding or artificial fed infants, yet, the evidence does not strongly confirm such correlation and a recent survey revealed a contradictory outcome [30]. This inconsistency with several published reports might be explained by a history of a preterm birth among breastfeeding infants among the included infant population [26]. Secondly, a lack of uniform definition for measuring exclusive breastfeeding in many studies [29]. Thirdly, variations among the demographic features of CAP between countries and territories [31]. Lastly, being breastfed when mothers carry a respiratory infection may increase the risk of transmission, acting as a proxy for closer contact [32].

The relationships observed among the existing study parameters suggest an intricate and dynamic immune body response, with different types of machinery manipulating each other. These outcomes can guide additional studies to realize the clinical implications of these associations and their significance in managing NCCAP cases in pediatric patients.

5. Conclusion

This study shows nuanced immune body responses in pediatric NCCAP. TLR2, TLR4, CRP, and WBCs display potential sex-specific differences. Feeding practices influence immune parameters, highlighting different profiles in breastfed babies. While presenting valuable insights, the conclusions warrant justification through larger clinical trials. This study contributes to recognizing innate immune responses in NCCAP, guiding probable targeted therapeutics.

Clinical Implication:

The results carry vital clinical implications for treating pediatric NCCAP. Identifying sex-specific differences in TLR expression delivers insights into personalized therapeutic protocols. The influence of feeding practices on the body's immune factors highlights the protective role of breastfeeding. Pediatricians should consider these parameters when evaluating illness severity and tailoring management.

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