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Original Article

Critical Role of Monocyte Chemotactic Protein -1 and Macrophage Migration Inhibitory Factor in Children who Have Pneumonia

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ABSTRACT

Background: The leading cause of death for children under the age of five years old worldwide is pneumonia. The assessment of illness progression and clinical stage is necessary for the management of healthcare resources and the provision of efficient treatment options. Macrophage migration inhibitory factor (MMIF) is an inflammatory cytokine that, when produced, causes macrophages to release additional cytokines, including as interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-α), interleukin IL--1, IL-6, IL-8, and IL-12, resulting in a significant inflammatory response. Monocyte chemotactic protein-1 (MCP-1) is a crucial chemokine involved in a number of clinical situations, such as endothelial dysfunction, cancer, respiratory infections, and cardiovascular illnesses.
Objectives: The aim of this study was to examine the levels of MMIF and MCP-1 in patients with pneumonia and compare them to those in healthy controls to determine whether there may be a relationship between the severity of the disease and its results.
Results: MMIF and MCP-1 levels were substantially greater in pneumonia patients than in controls, and they were also significantly higher in patients who did not survive as opposed to those who did. The Pediatric Critical Illness Score (PCIS) and the Pediatric Risk of Mortality (PRISM) scores were significantly positively correlated with both indicators. A significant positive connection between MMIF and MCP-1 was observed.
Conclusion: The severity of pneumonia and prognosis for patients are directly correlated with MMIF and MCP-1.

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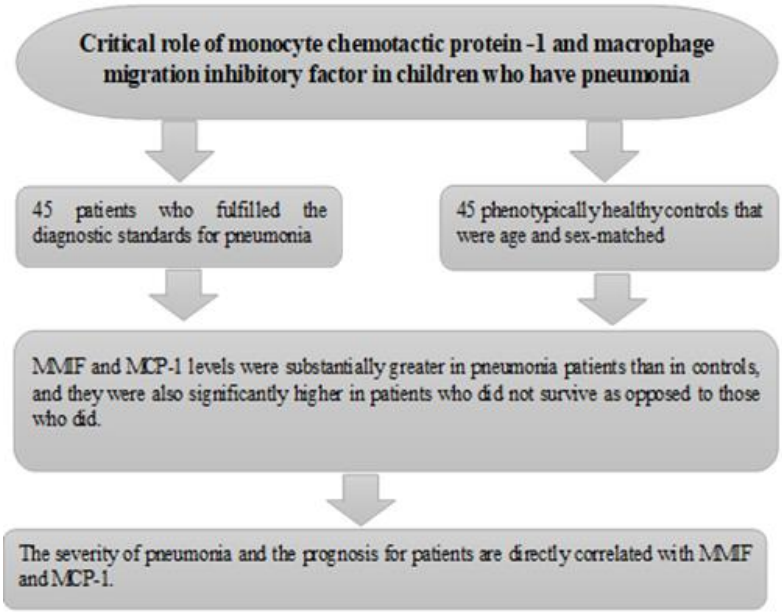
GRAPHICAL ABSTRACT



Introduction

One of the top causes of death in children worldwide is pneumonia, with the bulk of these deaths occurring in environments with low resources [1]. Annually, there are about 156 million new reported cases; 151 million of these instances are in underdeveloped countries, and 7-13% of them are severe enough to require hospitalization [2].

In Egypt, pneumonia causes 19% of under-five mortality [3], where children under the age of 5 make up roughly 13.4% of the total population [4]. According to statistics, Egypt has between 0.11 and 0.20 occurrences of pneumonia per children [5].

In pediatrics, pneumonia may be pathogen- or age-specific. Through the birth canal, newborns run the danger of contracting diseases such group *B streptococci*, *Klebsiella*, *Escherichia coli*, and *Listeria monocytogenes* [6]. While most of pneumonia infections in older infants and toddlers between the ages of 30 days and 2 years are caused by viruses. The same situation holds true for kids between the age range of 2 and 5-year-old. Most commonly affecting this age range are *S. pneumoniae* and *H. influenzae type B* [7].

Macrophage migration inhibitory factor (MMIF), a pro-inflammatory cytokine, was initially identified as a component in the supernatants of activated T lymphocyte cultures in 1966 [8]. Pro-inflammatory cytokine Macrophage Migration Inhibitory Factor (MMIF) has a broad range of biological effects involved in the development of inflammatory and cancerous illnesses. MMIF is released following an acute stress or inflammation and is naturally present in various cell types and non-lymphoid tissues. In response to stressful circumstances, immune and non-immune cells, such as neutrophils eosinophils, monocytes/macrophages, granulocytes, B and T lymphocytes, and endocrine, neuronal, endothelial, and epithelial cells of varied histogenetic origin [9]. Interleukin-1 (IL-1), interleukin-6 (IL-6), interferon (IFN), and Tumor necrosis factor (TNF) are among the extra cytokines that macrophages produce in response to MMIF, which causes a significant inflammatory response [10].

Hopes have been raised that this pro-inflammatory cytokine can be used therapeutically to provide additional treatment options as a result of the discovery that rising levels of MMIF are significantly correlated with the clinical manifestation and progression of sepsis and autoimmune disease [11].

A potent monocyte chemotactic factor called MCP-1 is either created naturally or is brought on by cytokines, growth factors, or oxidative stress [12].

MCP-1 participates in the regulation of immune cell contacts as well as the coordination and recruitment of immune cells to and from tissues [13]. In addition, MCP-1 supports proper immune responses that are protective in lung infection situations [14].

We attempted to examine MMIF and MCP-1 serum concentrations in pneumonia patients and compare them to healthy controls to determine whether there may be a correlation between the severity of disease and survival rates. This was done due to the regulatory importance of MMIF and MCP-1 in inflammatory and immune response.

Materials and Methods

Study subjects and design

This study is a hospital-based cohort prospective includes two groups: patients and controls. At Al-Zahraa University Hospital in Egypt, 45 patients who fulfilled the diagnostic standards for pneumonia in children under the age of five years old were hospitalized. Based on the World Health Organization (WHO) diagnostic standards, pneumonia was identified including cough and/or breathing problems with at least one of the following symptoms: irregular breathing, less than 40 breaths per minute in children between the ages of 12 and 59, or lower chest intrusion [15]. This study contained 45 phenotypically healthy controls that were age and sex-matched. They came from the hospital's outpatient during the period between April 2021 and April 2022.

The Pediatric Critical Illness Score (PCIS) [16] was used to evaluate severity, and the common Pediatric Risk of Mortality score (PRISM III-24) [17] was used to forecast prognosis in the intensive care unit (ICU).

Subjects receiving anticoagulant or immune suppressive therapy, children with chronic or clinically significant infectious or inflammatory conditions, burns, thromboembolism, or inherited immune deficiency, as well as those with any systemic illnesses that could affect MMIF and MCP1 were excluded from this study.

Sample size estimation

Both power and sample sizes were used to determine the sample size. One matched control has been planned for every case in the research of matched sets of cases and controls. To be able to reject the null hypothesis that the odds ratio equals 1 with a probability (power) of 0.8, we looked at 45 patients with one matched control per case. The probability of a type I error in this test of the null hypothesis was 0.05.

Laboratory analysis

Ten milliliters of venous blood were collected, divided into four portions, and then two milliliters were evacuated into a tube containing ethylene diamine tetra acetic acid for CBC. Heparin was given an additional 2 mL to analyze arterial blood gas (ABG). Three milliliters of serum were utilized to measure kidney function tests (urea and creatinine), sodium, potassium, and C-reactive protein from the remaining fraction, which was evacuated in two serum-separator tubes and centrifuged at 3,500 rpm for ten minutes (CRP.). The remaining 3 mL of serum were frozen at 20°C for MMIF and MCP-1 analyses.

A completely automated cell counter was used to calculate the complete blood count (Sysmex KX21N, Kobe, Japan). Cobas C311 (Germany) and Roche kits were used to quantify urea and creatinine (Germany). CRP was quantified using the latex agglutination kit CRP Visilatex. GEM PREMIER 3000 (Instrumentation Laboratory, Lexington, MA) and AVL 9180 were used to perform ABG (Roche Diagnostics, Germany).

The quantitative double-antibody sandwich ELISA kit, provided by Bioassay Technology Laboratory (BT LAB), China, was used to quantify the levels of MMIF and MCP1 in the serum (lot.no. 202203013 and 202106011, respectively). The test range was, respectively, 0.1-40 ng/mL and 5-1,500 ng/mL.

Statistical analysis

The findings were examined, categorized, and entered into the version 23 of the Statistical Package for the Social Science Sciences (IBM Corp., Armonk, NY, USA). When displaying

quantitative data, medians and inter-quartile ranges were used for nonparametric data whereas means, standard deviations, and ranges were used for parametric data. Furthermore, percentages and numbers were used to represent non-quantitative facts. The chi-square test was not used to compare any quantitative data. The Mann-Whitney U-test was used to compare quantitative data with nonparametric patterns, and the independent t-test was used to compare quantitative data with parametric patterns. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. P-values were therefore regarded as significant if they were 0.05. The Pearson and Spearman rank correlation equation was used to analyze the correlation between different variables.

Results and Discussion

In this study, 45 pneumonia cases and 45 control cases were used. The investigated groups' anthropometric measures and demographic information are presented in (Table 1).

According to test results for both groups under study, the patient group's hemoglobin level and absolute lymphocytic count significantly decreased; however, the patient group's platelet count and CRP level significantly increased as compared to the control group (Table 2).

Cases had considerably higher median serum levels of MMIF (18.7 ± 19.03) and MCP-1 (480.6 ± 496.7) than controls (3.18 ± 1.2 and 68.7 ± 36.2, respectively) (Table 3).

In the patient group, the proportion of non-critical cases (66.7%) was substantially greater than the proportion of critical cases (22.2%) and the proportion of highly critical cases (11.1%), with regard to PCIS risk variables and patient outcome.

The percentage of patients who survived (77.8%) in the patient group was significantly greater than the percentage of patients who did not survive (22.2%) (Table 4).

The non-survival group had substantially higher MMIF (51.01± 5.12) and MCP-1 (1341.5 ± 263.7) levels than the survival group (9.52 ± 8.26 and 234.6 ± 144.2, respectively) in terms of the relationship between biomarker levels (MMIF and MCP-1) and patient outcomes (Table 5). The illness severity assessed by the PCIS was positively connected with MMIF (r = 0.923; p = 0.001) and MCP-1 (r = 0.963; p = 0.001), according to Pearson correlation (Figures 1 and 2).

Table 1: Demographic data and anthropometric measurements of the studied groups

Demographic data	Patient group (n=45)	Control group (n=45)	P-value
Sex Male N (%) Female N (%)	 25 (55.6%) 20 (44.4%)	 20 (44.4%) 25 (55.6%)	0.2945
Age (months) Median (Min-Max)	4 (1-36)	8 (1-48)	0.061
Residence Rural Urban	 30 (66.7%) 15 (33.3%)	 20 (44.4%) 25 (55.6%)	0.034
Smoking exposure at home Yes No	 32 (71.1%) 13 (28.9%)	 20 (44.4%) 25 (55.6%)	0.01
Weight (Kg) Mean ± SD	6.35± 2.23	6.93± 1.36	0.141
Height/ Length (m) Mean ± SD	0.656±0.12	0.685±0.08	0.209
BMI Mean ± SD	14.70± 2.56	15.27± 1.72	0.220

Table 2: Comparison between patient group and control group regarding laboratory data

variable	Patient group (n=45)	Control group (n=45)	P value
Hemoglobin (g/dl) Median (Min-max)	10.1 (6.9-14.4)	12.2 (8.8-13.6)	≤0.001*
WBCS (10^9/L) Median (Min-max)	8.7 (2.9-27.7)	6.8 (4.54-13.5)	0.116
Neutrophils (10^9/L) Median (Min-max)	3.6 (0.1-24.2)	2.78 (1.25-7.50)	0.123
Lymphocytes (10^9/L) Median (Min-max)	2.3 (0.9-7.0)	3.49 (1.5-5.6)	0.003*
Platelets (10^9/L) Median (Min-max)	400 (61-869)	254 (160-434)	≤0.001*
Creatinine (umol/L)	100.07±22.68	93.60±8.95	0.079
Blood Urea Nitrogen (BUN) (mmol/L)	7.15±2.19	6.49±0.90	0.067
Na (mmol/L)	136.96±8.13	139.40±5.24	0.094
K (mmol/L)	4.90±0.65	4.88±0.50	0.886
CRP Positive Negative	 28 (62.2%) 17 (37.8%)	 7 (15.6%) 38 (84.4%)	≤0.001*

Table 3: Comparison between patient group and control group regarding MMIF and MCP -1 serum level:

Biomarker	Patient group (n=45)		Control group (n=45)		P-value
	Mean	SD	Mean	SD	
MMIF (ng/mL)	18.7	19.03	3.18	1.2	0.001*
MCP-1 (ng/mL)	480.6	496.8	68.7	36.2	0.001*

Table 4: Pediatric critical illness score (PCIS) risk factors and outcome in the patient group

PCIS risk factors and outcome	Patient group (n=45)
PCIS Risk factors	
Non-critical	30 (66.7%)
Critical	10 (22.2%)
Extremely critical	5 (11.1%)
Chi square	23.333
P.value	< 0.001*
Outcome	
Survived	35 (77.8%)
Non-survived	10 (22.2%)
Chi square	13.889
P.value	0.002*

Table 5: Relation between biomarkers levels (MMIF and MCP-1) and the patient outcomes

Biomarker	Survival (n = 35)		Non-survival (n = 10)		P-value
	Mean	SD	Mean	SD	
MMIF	9.52	8.26	51.01	5.12	0.001*
MCP-1	234.6	144.2	1341.5	263.7	0.002*

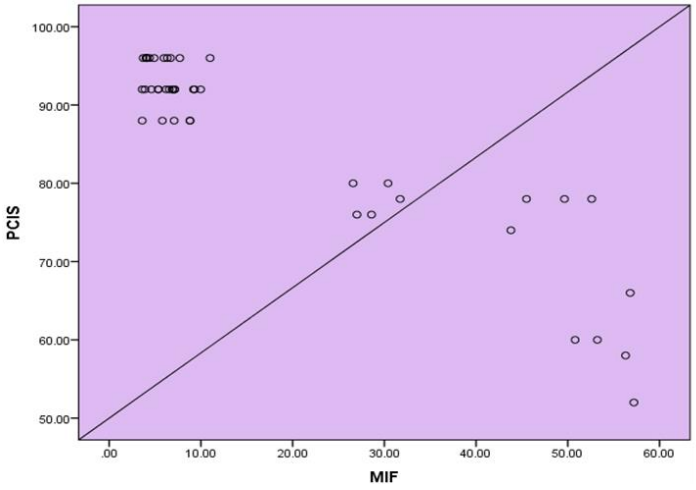


Figure 1: Correlation between MMIF and PCIS

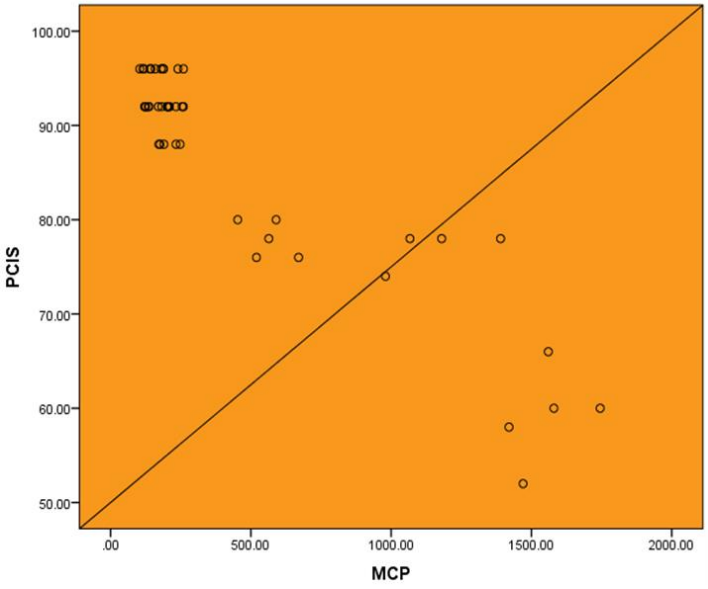


Figure 2: Correlation between MCP-1 and PCIS

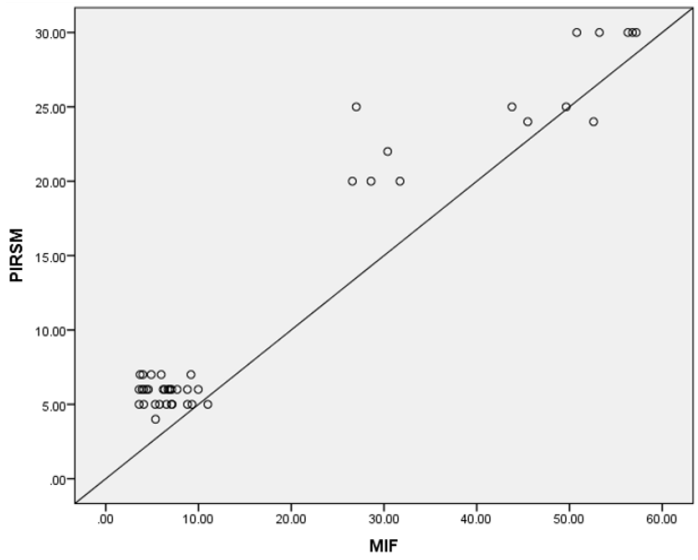


Figure 3: Correlation between MMIF and PRISM

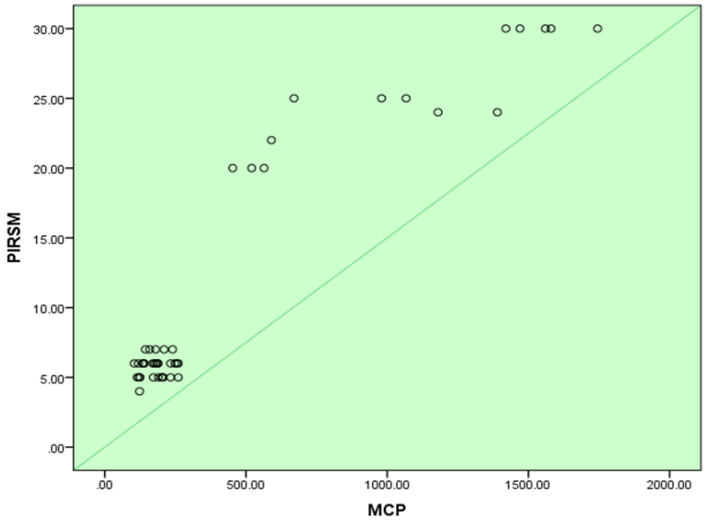


Figure 4: Correlation between MCP-1 and PRISM

Table 6: Correlation between biomarkers (MMIF and MCP-1) and the clinical scores of the patient group

Biomarker	PCIS score		PRISM score	
	R	P-value	R	P-value
MMIF	0.923	0.001*	0.973	0.001*
MCP-1	0.963	0.001*	0.942	0.001*

Table 7: Correlation between MMIF and MCP-1 serum levels

Biomarkers	R	P-value
MMIF and MCP	0.963	0.001

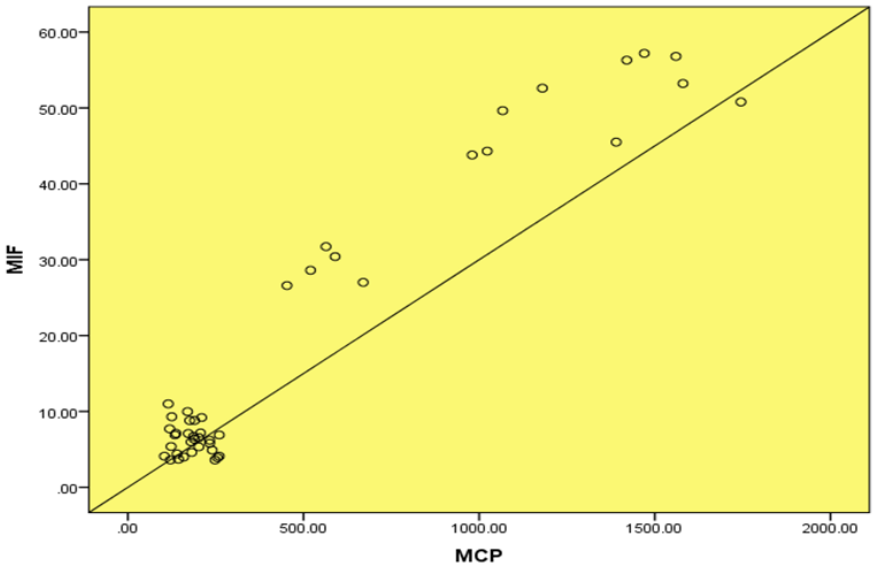


Figure 5: Correlation between MMIF and MCP-1

Figure 3 depicts a substantial link between the MMIF and PRISM score (r = 0.973; p = 0.001), and Figure 4 indicates a significant association between the MCP-1 and PRISM scores (r = 0.942; p = 0.001) (Table 6).

The serum levels of MMIF and MCP-1 were shown to be positively correlated (r= 0.963; p = 0.001) (Table 7) (Figure 5).

The pro-inflammatory cytokine macrophage migration inhibitory factor (MMIF), which is an important immunological regulator and plays a

significant role in the host control of the lung's inflammatory response, is well documented [18].

Based on the information gathered for this investigation, it was shown that cases had significantly higher serum MMIF levels (18.7 ± 19.03) than controls (3.18 ± 1.2) (P ≤ 0.001).

These results support those of Tang *et al.*, who found that the serum levels of MMIF were noticeably greater in children with cases than in healthy children (P < 0.01) [19]. In addition, Aksakal *et al.*'s noted that MMIF levels were noticeably greater in the cases compared to the control group (p = 0.001) in adult COVID-19 patients [11].

Despite these studies, Kofoed *et al.* questioned the usefulness of MMIF as a measure of sepsis or a systemic infection. When compared to CRP or procalcitonin (PCT), which had better ability to identify infection, MMIF's usefulness as an infectious marker in their investigation was equivalent but not superior (positive predictive values: MMIF, 0.73 versus CRP, 0.79 versus PCT, 0.80) [10].

The PICS revealed that 66.7% of the patients in the case group were non-critical; a proportion significantly higher than that of critical cases (22.2%) and extremely critical cases (11.1%) (P ≤ 0.05), allowing us to analyze the relationship between the degree of condition and MMIF concentrations in patients with pneumonia. This study showed a statistically significant connection (r = 0.923; p = 0.001) between the MMIF level and illness severity assessed by the PICS.

This result supports the observation made by Aksakal *et al.* that the MMIF level was statistically significantly greater in severe patients than in moderate adult COVID-19 patients [11]. Additionally, Dheir *et al.* found that there was a statistically significant difference in MMIF levels between the patients in the ICU and those on the ward (p < 0.05) [18].

These findings conflict with those of Yende *et al.*, who claimed that an increase in MMIF levels was unrelated to demographic factors, concomitant conditions, or the illness severity [20]. This discrepancy in the results may be caused by the use of several scores to gauge the severity of a child's illness while they are hospitalized.

The non-survival group had considerably higher MMIF levels (51.01 ± 5.12) than the survival group (9.52 ± 8.26) when MMIF levels were compared between the survival and non-survival groups (P ≤ 0.001).

According to Bozza *et al.*, elevated plasma levels of MMIF (> 1100 pg/mL) exhibited 100% sensitivity and 64% specificity in identifying patients who would experience fatal consequences [21]. High concentrations of MMIF were positively connected with non-survival, while low concentrations of MMIF were related to survival, according to Brenner *et al.* and Pohl *et al.*, supporting these findings [22, 23].

Although numerous studies have shown that non-surviving individuals had MMIF levels that were noticeably greater than those of survived cases, there is no information in the literature regarding the relationship between MMIF levels and PRISM score. According to this study, the MMIF and PRISM scores have a strong correlation (r = 0.973; p = 0.001).

Nitric oxide, tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon (IFN) are all produced more readily as a result of MMIF's pro-inflammatory cytokine activity [9].

According to Dheir *et al.*, MMIF may trigger pulmonary inflammatory cytokines, which in turn may contribute to inflammatory reactions [18].

In addition, de Souza *et al.* demonstrated that during respiratory syncytial virus infection, MMIF expression regulates the expression of IL-10, MCP-1, and TNF-α. They discovered that an immediate drop in the production of IL-10, MCP-1, and TNF-α following MMIF inhibition leads us to believe that MIF functions in an autocrine manner to regulate the release of these cytokines [24].

Because MMIF and MCP-1 have a strong relationship (r = 0.963; P ≤ 0.001), our study found concordant results.

MCP-1 is an essential chemokine that is involved in many diseases, including cancer, endothelial dysfunction, respiratory infections, brain

pathologies, bone and joint abnormalities, and cardiovascular diseases [25].

In this investigation, we found that patients (480.6 ± 496.8) had significantly higher serum MCP-1 levels than controls (68.7 ± 36.2) (P ≤ 0.001). Li *et al.* showed that MCP-1 plasma concentrations were noticeably higher in the acute stage in patients with ventilator associated pneumonia compared to those in control group (p ≤ 0.001) in accordance with this finding [26]. Furthermore, Xi *et al.* found that both severe and moderate cases of coronavirus 2019 (COVID-19) patients exhibit greater levels of chemokines. Particularly, both severe and mild COVID-19 cases display increased amounts of monocyte chemotactic protein 1 (MCP-1) [27]. Hassuna *et al.* observation's that MCP-1 plasma levels considerably increased in the cases group as compared to those in the control group (p ≤ 0.001) lends support to these findings [28].

MCP-1 level and illness severity as assessed by the PICS were shown to be statistically significantly correlated in this study (r = 0.963; p ≤ 0.001). Li *et al.* reported a positive connection between MCP-1 levels and disease severity assessed by the lung injury score (p = 0.02) and the oxygenation index (p = 0.02) in contrast to this conclusion [26]. Likewise, Wang *et al.* found that early plasma MCP-1 concentrations can be utilized to gauge the severity of the disease [29]. According to Chen *et al.* and Huang *et al.*, serum MCP-1 levels were substantially correlated with the severity of the illness, supporting these findings [30, 31].

These outcomes were in line with those of xi *et al.* who showed that practically all COVID-19 patients, regardless of severity, had MCP-1 overexpression [27].

The inconsistency of the results may be caused by the use of several scores to gauge the severity of a child's illness while they are hospitalized.

The non-survival group had considerably higher MCP-1 levels (1341.5 ± 263.7) than the survival group (234.6 ± 144.2) (P ≤ 0.001) when comparing the MCP-1 levels in the survival and non-survival groups.

Mera *et al.* and Zhu *et al.* found significant variations in serum chemokine levels between the survival and non-survival groups, with the non-survival group having greater levels of MCP-1 [32, 33]. According to Hassuna *et al.*, MCP-1 and PRISM had a positive correlation (r = 0.306; p = 0.019), which supports this finding [28]. In addition, MCP-1 levels and PRISM scores had a favorable association based on the study conducted by Vermont *et al.* (r = 0.62; p < 0.001) [34].

Contrary to their findings, Chen *et al.* discovered no discernible difference between death and survival [30]. This discrepancy may be due to the severe or critical illness of the chosen patients, which led to an excessively high mortality rate without a difference between survival and death.

Conclusion

It was concluded that these cytokines are elevated in patients with pneumonia compared to healthy individuals in this prospective observational study examining MMIF and MCP-1 levels in children with pneumonia. The levels of MMIF and MCP-1 were associated to the illness severity. The levels of MMIF and MCP-1 were significantly increased in non-survivors. The increased levels of both biomarkers may serve as an early warning sign of poor outcomes in pneumonia cases.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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