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Correlation of CXCL3 levels, Inflammatory Markers, and COVID-19 Infection with Severity of Asthma in Asthmatic Patients

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ABSTRACT

Background: *Asthma is a chronic inflammatory disorder of the airways influenced by a complex network of cytokines and chemokines, among which CXC chemokine ligand 3 (CXCL3) plays an important role and has been linked to airway remodeling and disease severity. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, induces systemic immune dysregulation with elevated inflammatory biomarkers such as C-reactive protein (CRP), ferritin, and D-dimer. The interaction between CXCL3-mediated airway inflammation and systemic inflammatory responses in asthmatic patients during COVID-19 infection remains insufficiently elucidated, with limited data clarifying its contribution to disease severity and outcomes.* ***Objective:*** *To evaluate the correlation of serum CXCL3 and classical inflammatory markers (CRP, ferritin, D-dimer) with asthma severity among patients with and without COVID-19 infection and to determine their relationship with lung function (FEV_1) and predictors of severe asthma.* ***Methods:*** *A cross-sectional study was conducted on 200 asthmatic patients, stratified according to COVID-19 infection status (76 positive, 124 negative). Demographic, clinical, and laboratory parameters were analyzed. Serum levels of CXCL3 and inflammatory markers (CRP, ferritin, and D-dimer) were compared between groups and correlated with asthma severity and FEV_1.* ***Results:*** *COVID-19-positive asthmatics exhibited significantly higher levels of CXCL3 (241.5 ± 83.7 vs. 173.8 ± 76.4 ng/mL, $p<0.001$) and inflammatory markers, along with lower FEV_1 (54.3 ± 17.2 vs. 62.1 ± 18.9; $p=0.003$) compared to COVID-19-negative patients. CXCL3, CRP, and D-dimer levels increased progressively with asthma severity ($p<0.001$), furthermore, significant positive correlations were observed between CXCL3 and asthma severity ($r = 0.62$) as well as between CXCL3 and CRP ($r = 0.41$). Logistic regression revealed FEV_1 <60% as an independent predictor of severe asthma (OR 3.12, 95% CI 1.78–5.47, $p<0.001$), whereas COVID-19 infection showed an inverse association with severe asthma (OR 0.48, 95% CI 0.25–0.91, $p=0.026$).* ***Conclusion:*** *Serum CXCL3 and systemic inflammatory markers are significantly associated with asthma severity and lung function impairment, particularly in the presence of COVID-19 infection. CXCL3 may serve as a potential biomarker for assessing asthma severity and guiding clinical management in patients with concurrent COVID-19.*

Keywords: CXCL3, CRP, Ferritin, D-Dimer, FEV1, COVID-19 Status, Asthma Severity.

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INTRODUCTION

Asthma is a heterogeneous respiratory disease characterized by chronic inflammation, airway hyperresponsiveness, and structural remodeling that often lead to variable varying degrees of airflow limitation and clinical severity [1]. Multiple cytokines and chemokines contribute to asthma pathogenesis, among them, the CXC chemokine ligand 3 (CXCL3), also known as GRO-γ or MIP-2β, as growth-regulated oncogene-γ (GRO-γ) or macrophage inflammatory protein-2β (MIP-2β), has emerged as an important key mediator due to its potent neutrophil-chemotactic activity and capacity to influence airway smooth muscle cell (ASMC) behavior and proliferation through CXCR1 and PI3K pathways, thereby exacerbating airway remodeling and asthma severity [2,3,4].

Asthma exacerbations are frequently triggered or worsened by viral respiratory infections such as rhinoviruses and SARS-CoV-2 through chemokine upregulation and increased CXCL3 concentrations in serum and airway secretions have been associated with higher asthma severity and enhanced recruitment of inflammatory cells to the airways [5,6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, triggers marked immune dysregulation characterized by increased levels of inflammatory markers such as C-reactive protein (CRP), ferritin, and D-dimer, which correlate with disease severity and adverse clinical outcomes [7,8]. In addition to these systemic markers, chemokines including CX3CL1 and CXCL3 have been implicated in the immunopathogenesis of COVID-19 and may influence the clinical course in individuals with underlying asthma [9,10]. This study aimed to evaluate the relationship between serum CXCL3 and classical inflammatory markers (CRP, ferritin, and D-dimer) with asthma severity in patients with and without COVID-19 infection. Additionally, the study aimed to explore the association of these biomarkers with lung function (FEV1) and identify predictors of severe asthma in this clinical context.

MATERIALS AND METHODS

This cross- section study was conducted at Al-Sadr Medical City, Al-Najaf Al-Ashraf Province during the period from November 2024 to June 2025. This study comprised (200) patients with asthma disease (100 females and 100 males), with age ranged from (18-66) years. All patients were admitted to the outpatient clinic of allergy in Al-Sadr hospital. Asthma patients were clinically diagnosed by Clinician and the severity of asthma were classified based on clinical symptoms, lung function (FEV1), and medication use according to Global Initiative for Asthma (GINA) guidelines (mild: FEV1 ≥ 80%, symptoms less than twice a week, moderate: FEV1 60-80%, daily symptoms and severe: FEV1 < 60%, continuous symptoms [11].

Consent to participate regarding the purpose of the study was obtained from all patients included in this research. However, demographic and clinical data of patients were collected.

The excluded criteria of this study were involved these subjects (all condition of acute and chronic respiratory infection, breastfeeding mothers and pregnant women, immunocompromised patients and other autoimmune cases).

The study was approved by the ethical committee in the Faculty of Medicine, University of Kufa.

Blood Sample collection

Five ml of venous blood were collected from patients with Asthma. Blood samples were allowed to clot, then serum was separated by using centrifugation and was stored in a deep freeze until used.

COVID-19 infection was diagnosed by detecting SARS-CoV-2-specific IgG antibodies using a rapid dipstick immunoassay (Biozek Medical, Netherlands). The assay was performed on serum samples according to the manufacturer's instructions, and the appearance of a test line together with the control line was interpreted as a positive result, indicating previous infection with SARS-CoV-2.

Serum levels of C-reactive protein (CRP) (mg/L), ferritin (ng/mL), and D-dimer (µg/mL) were determined as part of the complete biochemistry profile (CBP) using an automated biochemical analyzer (Cobas c 311, Roche Dianostics, Switzerland). Standard laboratory procedures were followed according to the manufacturer's instructions. Serum levels of CXL3 were measured using an enzyme-linked immunosorbent assay (ELISA) kit (SUNLONG BIOTECH, China; Cat. No. SL3246Hu), following the manufacturer's instructions.

STATISTICAL ANALYSIS

Data were analyzed using SPSS software (version 26). The results of continuous variables were expressed as mean ± standard deviation (SD) but, categorical variables were presented as frequencies and percentages. Independent samples t-test was applied to compare means of continuous variables between two groups. One-way ANOVA was used for comparisons across more than two groups. Chi-square test was employed to evaluate associations between categorical variables. Spearman's rank correlation was conducted to assess correlations between asthma severity and study parameters. Multivariable logistic regression analysis was performed to identify independent predictors of severe asthma, and results were presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

RESULTS

- **Demographic and Clinical Characteristics**

Among 200 asthmatic patients, 76 were COVID-19 positive and 124 were negative. There were no significant differences between groups regarding age (43.1 ± 11.8 vs. 42.1 ± 12.7 years, p=0.572), sex distribution, or residency (urban vs. rural). However, COVID-19-positive patients showed significantly lower FEV_1 values (54.3 ± 17.2 vs. 62.1 ± 18.9, p=0.003) and higher asthma severity scores (2.28 ± 0.65 vs. 1.93 ± 0.61, p=0.004). They also exhibited significantly elevated CRP (22.3 vs. 16.2 mg/L, p=0.031), ferritin (604 vs. 488 ng/mL, p=0.015), and D-dimer levels (1.56 vs. 1.09 µg/mL, p=0.009). The characteristics of demographic and clinical were summarized in (**Table.1**)

Table1: Demographic and clinical characteristic of the study group according to the infection with COVID-19 (N=200).

Characterstics	COVID-19(+) (n=76)	COVID-19 (-) (n=124)	P-value
Age (years)	43.1 ± 11.8	42.1 ± 12.7	0.572
Sex **Male** **Female**	 42(55.3%) 34 (44.7%)	 58 (46.8%) 66 (53.2%)	0.271
Residency **Urban** **Rural**	 48 (63.2%) 28 (36.8%)	 82 (66.1%) 42 (33.9%)	0.684
FEV1	54.3 ± 17.2	62.1 ± 18.9	0.003*
Asthma Severity Score	2.28 ± 0.65	1.93 ± 0.61	0.004*
CRP (mg/L)	22.3 ± 15.8	16.2 ± 13.1	0.031*
Ferritin (ng/mL)	604 ± 219	488 ± 194	0.015*
D-Dimer (µg/mL)	1.56 ± 0.72	1.09 ± 0.68	0.009*

n: number, *: significant value .

- **Immunological marker**

Serum CXCL3 levels were markedly higher in COVID-19-positive asthmatics patients when compared to COVID=19 negatives asthmatic patients (241.5 ± 83.7 vs. 173.8 ± 76.4 ng/mL, p<0.001), indicating a significant association between infection by COVID-19 and heightened chemokine response (**Table. 2**)

Table 2: Comparison of immunological marker level between asthmatic patients with and without COVID-19.

Immunological markers	COVID-19 Infection	Number	Mean	P-value
CX3CL1 ng/ml	No	124	173.8 ± 76.4	0.001*
	Yes	76	241.5 ± 83.7	

: significant value

-Asthma Severity and COVID-19 Infection

Table. 3 showed the relation of severity of Asthma with COVID-19 infection. There was no significant difference in the distribution of asthma severity distribution (mild, moderate, severe) with COVID-19-positive and negative groups for mild and moderate cases (p=0.241 and 0.519), respectively. However, severe asthma was significantly less common among COVID-19-positive patients (21.1% vs. 33.9%, p=0.048).

Table3: Association between asthma severity and Covid-19 infection status in study group

Severity		COVID-19 infection		P-value
		No N=124 %	Yes N=76%	
Mild	Count (64)	36 (29 %)	28 (36.8%)	0.241
Moderate	Count (78)	46 (37.1 %)	32 (42.1%)	0.519
Sever	Count (58)	42 (33.9%)	16 (21.1%)	0.048*

: significant value

- **Serum Level of CXCL3 in severity of asthma**

The mean serum CXCL3 concentration increased progressively with asthma severity. Patients with mild asthma had the lowest CXCL3 levels (132.7 ± 58.4 ng/mL), followed by those with moderate asthma (196.3 ± 76.2 ng/mL), while the highest levels were observed in severe asthma (283.5 ± 89.8 ng/mL). The difference across severity groups was statistically significant ($p < 0.001$), indicating a strong positive association between CXCL3 concentration and asthma severity. (**Table.4**).

Table 4: Distribution serum level of CXCL3 among group based on Asthma Severity (N = 200)

Asthma Severity (n)	CXCL3 Mean ± SD (ng/mL)	P-value
Mild (64)	132.7 ± 58.4	< 0.001*
Moderate (78)	196.3 ± 76.2	
Severe (58)	283.5 ± 89.8	

- **Inflammatory Markers in COVID-19-Positive Patients by Asthma Severity**

In COVID-19-positive patients, CRP, ferritin, and D-dimer levels increased significantly across mild, moderate, and severe asthma (all p<0.001). Severe cases had CRP 48.6 mg/L, ferritin 612 ng/mL, and D-dimer 2.75 µg/mL, indicating progressive systemic inflammation with severity as showed in the **table.5**

Table 5: Comparison of inflammatory markers among COVID-19 positive patients according to asthma severity.

Parameters	Mild (28)	Moderate (32)	Sever (16)	P-value
CRP (mg/L)	14.2 ± 5.1	32.8 ± 11.4	48.6 ± 16.3	<0.001*
Ferritin (ng/mL)	195 ± 71	355 ± 108	612 ± 158	<0.001*
D-Dimer (µg/mL)	0.52 ± 0.15	1.35 ± 0.42	2.75 ± 0.91	<0.001*

- **Logistic Regression for Severe Asthma**

Multivariable analysis showed in (**table .6**) revealed $FEV_1 < 60\%$ as an independent predictor of severe asthma (OR 3.12; 95% CI 1.78–5.47; p<0.001). COVID-19 positivity was inversely associated with severe asthma (OR 0.48; 95% CI 0.25–0.91; p=0.026). Age >50 years showed no significant association (OR 1.45; p=0.201).

Table 6: Multivariable logistic regression for asthma severity

Parameters	Adjusted OR	95% CI	P-value
COVID-19 positive	0.48	0.25-0.91	0.026*
Age >50 years	1.45	0.82-2.56	0.201
FEV1 <60%	3.12	1.78-5.47	<0.001*

- **Correlation Analysis**

Asthma severity correlated strongly with CXCL3 (r = 0.62, p<0.001), CRP (r = 0.48, p<0.001), and D-dimer (r = 0.36, p=0.002). CXCL3 also correlated positively with CRP (r = 0.41), (P < 0.001) and D-dimer (r = 0.33), (P < 0.004), suggesting interlinked pathways of inflammation. (**Table.7**).

Table 7: Spearman Correlation Matrix for study parameters.

	Asthma severity	CXCL3	CRP	D-Dimer
Asthma severity	-	+0.62 (P < 0.001)	+0.48 (P < 0.001)	+0.36 (P < 0.002)
CXCL3	+0.62 (P < 0.001)	-	+0.41 (P < 0.001)	+0.33 (P < 0.004)
CRP	+0.48 (P < 0.001)	+0.41 (P < 0.001)	-	+0.29 (P < 0.011)
D-Dimer	+0.36 (P < 0.002)	+0.33 (P < 0.004)	+0.29 (P < 0.011)	-

DISCUSSION

This study demonstrates that CXCL3 and systemic inflammatory markers (CRP, ferritin, D-dimer) are significantly elevated in asthmatic patients with COVID-19 and correlate strongly with disease severity and lung function impairment. The findings of this research indicate that elevated CXCL3 aligns with prior studies demonstrating the role of this type of chemokines in airway smooth muscle migration and neutrophil recruitment in severe asthma [2,7]. CXCL3 concentration strongly correlates with CRP and D-dimer suggests a possible interaction between airway and systemic inflammation. This finding was consistent with Ford et al. who highlighted chemokines as key drivers of airway remodeling [12]. Also Ye Q. et al. mention in a study polished in 2020 that the cytokine storm in COVID-19 results in marked increase of chemokines and cytokines, which is associated with elevated CRP, D-dimer, and fibrinogen [13]. About COVID-19-positive patients exhibited significantly higher CRP, ferritin, and D-dimer levels, reflecting the well-known hyperinflammatory state described in severe COVID-19 [7,14]. Elevated D-dimer in particular supports previous findings linking coagulopathy and adverse outcomes in SARS-CoV-2 infection [15]. Importantly, the concentrations of these markers rose in parallel with increasing asthma severity, highlighting their potential value as indicators for tracking disease progression [16].

An unexpected finding was the inverse relationship between COVID-19 positivity and severe asthma in multivariable analysis. This may reflect behavioral factors (greater shielding among severe asthma patients) or immune modulation due to long-term corticosteroid/biologic therapy, which could attenuate cytokine storms in COVID-19 [12]. Others cause may have related to that severe asthma was less common among patients with COVID-19 or that patients with severe asthma were less likely to contract COVID-19[17, 18]. Study was appeared strong predictive value of $FEV_1 < 60\%$ for severe asthma that supports its established role as a key functional marker of disease burden [19]. Combining spirometry with biomarker profiles such as CXCL3 could refine phenotyping and management strategies.

Strengths and Limitations

Strengths include comprehensive biomarker analysis and correlation with clinical severity. Limitations include the cross-sectional design, reliance on IgG dipstick for COVID-19 diagnosis (which indicates prior rather than active infection), and lack of treatment stratification.

Implications

CXCL3 may represent a promising biomarker for assessing asthma severity, particularly in patients with concurrent or prior COVID-19. Future longitudinal studies should validate its predictive value and explore therapeutic targeting of chemokine pathways.

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