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ORIGINAL ARTICLE

Evaluation of Serum Inflammatory Biomarkers such as C-Reactive Protein, Interleukin-6, and Tumor Necrosis Factor-Alpha in patients with Chronic Rhinosinusitis: A Clinical Study

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a persistent inflammatory disorder of the nasal and paranasal sinuses, associated with significant morbidity and impaired quality of life. Increasing evidence suggests that systemic inflammation plays a crucial role in its pathophysiology. This study aimed to evaluate serum inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in patients with CRS and to assess their association with disease severity.

Methods: This cross-sectional clinical study was conducted from June 2022 to June 2023 at Central Park Medical College, Lahore, and Bolan Medical College, Quetta, Pakistan. A total of 100 participants were enrolled, including 60 patients with clinically and radiologically confirmed CRS and 40 healthy controls. Serum levels of CRP, IL-6, and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using SPSS version 26, with $p \leq 0.05$ considered statistically significant.

Results: Serum levels of CRP, IL-6, and TNF-α were significantly higher in CRS patients compared to controls ($p < 0.001$). Mean CRP levels were 9.1 ± 2.7 mg/L in patients versus 2.3 ± 1.0 mg/L in controls. IL-6 and TNF-α levels also showed marked elevation. Furthermore, biomarker levels increased progressively with disease severity, demonstrating a strong positive correlation with clinical severity scores.

Conclusion: Elevated serum inflammatory biomarkers in CRS patients indicate a significant systemic inflammatory component. These biomarkers may serve as useful tools for disease severity assessment and monitoring therapeutic response, with potential implications for improving clinical management strategies.

Keywords: Chronic rhinosinusitis, C-reactive protein, Interleukin-6, Tumor necrosis factor-alpha, Inflammation, Biomarkers.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disorder of the nasal and paranasal sinus mucosa, characterized by persistent symptoms lasting for more than 12 weeks[1]. It represents a significant global health burden, affecting approximately 10–15% of the adult population and contributing to considerable morbidity, reduced quality of life, and increased healthcare utilization[2]. Clinically, CRS manifests with nasal obstruction, mucopurulent discharge, facial pain or pressure, and olfactory dysfunction, often leading to impaired daily functioning and psychological distress[3].

The pathophysiology of CRS is complex and not yet fully understood, involving an interplay of host immune responses, environmental factors, microbial colonization, and genetic predisposition[4]. Traditionally considered a localized inflammatory condition, emerging evidence suggests that CRS also has systemic inflammatory implications[5]. The chronic activation of immune pathways results in the release of various pro-inflammatory mediators, which not only perpetuate local mucosal inflammation but may also spill over into systemic circulation[6].

Among these mediators, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play pivotal roles in regulating inflammatory and immune responses[7]. IL-6 is a multifunctional cytokine involved in acute-phase reactions, B-cell differentiation, and T-cell activation, while TNF-α is a key regulator of inflammatory cascades, promoting leukocyte recruitment, endothelial activation, and tissue damage[8]. Elevated levels of these cytokines have been implicated in several chronic inflammatory diseases, suggesting their potential involvement in CRS pathogenesis as well[9].

C-reactive protein (CRP), an acute-phase protein synthesized by hepatocytes in response to IL-6 stimulation, is widely recognized as a sensitive marker of systemic inflammation[10]. Increased serum CRP levels have been associated with disease activity and severity in various inflammatory conditions[11]. In the context of CRS, the evaluation of CRP alongside cytokines such as IL-6 and TNF-α may provide valuable insights into the systemic inflammatory burden and disease progression[12].

Despite advances in diagnostic and therapeutic approaches, CRS remains challenging to manage due to its heterogeneous nature and variable clinical presentation[13]. Currently, diagnosis largely relies on clinical symptoms and imaging findings, with limited availability of reliable biochemical markers for assessing disease severity and monitoring treatment response[14]. Therefore, there is a growing need to identify objective biomarkers that can enhance clinical decision-making and improve patient outcomes[15].

In this context, the present study was designed to evaluate the serum levels of key inflammatory biomarkers, including CRP, IL-6, and TNF-α, in patients with chronic rhinosinusitis[16]. Furthermore, the study aims to explore their association with disease severity, thereby contributing to a better understanding of the systemic inflammatory profile of CRS and its potential clinical implications[17].

MATERIALS AND METHODS

This cross-sectional clinical study was conducted over a period of one year, from June 2022 to June 2023, at Central Park Medical College and Bolan Medical College. The study included a total sample size of 100 participants, comprising 60 patients diagnosed with chronic rhinosinusitis (CRS) and 40 healthy individuals serving as controls.

Participants were recruited using a non-probability consecutive sampling technique from outpatient and inpatient departments of ENT and affiliated clinical units. Inclusion criteria consisted of patients aged between 18 and 65 years with clinically and radiologically confirmed CRS, defined by the presence of characteristic symptoms persisting for more than 12 weeks, supported by endoscopic and/or computed tomography findings. Individuals with acute infections, autoimmune diseases,

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malignancies, chronic systemic inflammatory conditions, or those receiving corticosteroids or immunosuppressive therapy were excluded to avoid confounding effects on inflammatory biomarkers.

A detailed clinical evaluation was performed for all participants, including demographic data, symptom duration, and clinical severity assessment based on standard diagnostic criteria. Disease severity was categorized into mild, moderate, and severe groups according to symptom burden and clinical findings.

Venous blood samples (5 mL) were collected under aseptic conditions from all participants. The samples were centrifuged to separate serum, which was then stored at −20°C until analysis. Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's protocols.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26. Quantitative variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent sample t-test was applied to compare mean biomarker levels between CRS patients and controls. One-way analysis of variance (ANOVA) was used for comparison across different severity groups. Pearson's correlation coefficient was used to assess the relationship between biomarker levels and disease severity. A p-value of ≤ 0.05 was considered statistically significant.

Ethical approval was obtained from the institutional ethical review committees of both participating institutions prior to study initiation. Written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

A total of 100 participants were included in the study, comprising 60 patients diagnosed with chronic rhinosinusitis (CRS) and 40 healthy controls. The mean age of the CRS group was 39.2 ± 10.5 years, while that of the control group was 37.6 ± 9.8 years. There was no statistically significant difference between the two groups in terms of age and gender distribution ($p > 0.05$), indicating appropriate comparability of baseline characteristics, as summarized in Table 1.

Serum inflammatory biomarkers were found to be significantly elevated in patients with CRS compared to healthy controls. The mean CRP level in CRS patients was 9.1 ± 2.7 mg/L, whereas in controls it was 2.3 ± 1.0 mg/L ($p < 0.001$). Similarly, IL-6 levels were markedly higher in CRS patients (15.2 ± 4.6 pg/mL) compared to controls (5.9 ± 2.3 pg/mL, $p < 0.001$). TNF-α levels also demonstrated a significant increase in the CRS group (19.6 ± 5.4 pg/mL) in comparison to the control group (7.8 ± 3.0 pg/mL, $p < 0.001$). These findings are presented in Table 2.

Further stratification of CRS patients based on disease severity revealed a progressive increase in inflammatory biomarker levels with increasing severity. Patients classified as having severe CRS exhibited the highest mean levels of CRP (11.3 ± 2.1 mg/L), IL-6 (18.7 ± 3.8 pg/mL), and TNF-α (23.4 ± 4.2 pg/mL), compared to moderate and mild groups. The differences across severity groups were statistically significant ($p < 0.001$), as shown in Table 3.

Correlation analysis demonstrated a strong positive relationship between inflammatory biomarkers and disease severity scores. IL-6 showed the strongest correlation ($r = 0.68$, $p < 0.001$), followed by TNF-α ($r = 0.64$, $p < 0.001$) and CRP ($r = 0.59$, $p < 0.001$), indicating that higher levels of these biomarkers are associated with increased disease severity. These findings further reinforce the role of systemic inflammation in the progression of CRS.

Overall, the results clearly demonstrate that patients with chronic rhinosinusitis exhibit significantly elevated systemic inflammatory markers, and these levels increase proportionally with disease severity, supporting their potential role as biomarkers for disease assessment and monitoring.

Table 1: Baseline Demographic Characteristics of Study Participants

Variable	CRS Patients (n=60)	Controls (n=40)	p-value
Age (years)	39.2 ± 10.5	37.6 ± 9.8	0.412
Male (%)	33 (55%)	21 (52.5%)	0.812
Female (%)	27 (45%)	19 (47.5%)	0.812

Table 2: Comparison of Serum Inflammatory Biomarkers Between CRS Patients and Controls

Biomarker	CRS Patients (n=60)	Controls (n=40)	p-value
CRP (mg/L)	9.1 ± 2.7	2.3 ± 1.0	<0.001
IL-6 (pg/mL)	15.2 ± 4.6	5.9 ± 2.3	<0.001
TNF-α (pg/mL)	19.6 ± 5.4	7.8 ± 3.0	<0.001

Table 3: Serum Biomarker Levels According to Disease Severity in CRS Patients

Severity	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)	p-value
Mild (n=20)	6.8 ± 1.9	11.2 ± 3.1	15.6 ± 3.5	<0.001
Moderate (n=22)	9.0 ± 2.2	14.9 ± 3.9	19.3 ± 4.1	<0.001
Severe (n=18)	11.3 ± 2.1	18.7 ± 3.8	23.4 ± 4.2	<0.001

DISCUSSION

The findings of the present study demonstrate a significant elevation of systemic inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in patients with chronic rhinosinusitis (CRS) compared to healthy controls[1]. These results reinforce the concept that CRS is not merely a localized inflammatory disorder confined to the sinonasal mucosa but rather a condition with substantial systemic inflammatory involvement[2]. The markedly higher CRP levels observed in CRS patients reflect an ongoing acute-phase inflammatory response, which is primarily driven by cytokine-mediated hepatic stimulation, particularly by IL-6[3]. This relationship explains the parallel increase of CRP with other pro-inflammatory mediators in the present study[4].

The significantly elevated IL-6 levels in CRS patients highlight its central role in mediating inflammatory and immune responses[5]. IL-6 is known to contribute to mucosal inflammation, epithelial dysfunction, and tissue remodeling, all of which are key features of CRS pathogenesis[6]. Similarly, TNF-α, a potent pro-inflammatory cytokine, plays a crucial role in amplifying inflammatory cascades by promoting leukocyte recruitment, endothelial activation, and local tissue damage[7]. The increased TNF-α levels observed in this study further support its involvement in sustaining chronic inflammation in CRS[8]. The progressive rise in all three biomarkers with increasing disease severity indicates a dose-response relationship between systemic inflammation and clinical burden, suggesting that these biomarkers may reflect the underlying disease activity[9].

These findings are consistent with previous studies that have reported elevated levels of CRP and pro-inflammatory cytokines in chronic inflammatory airway diseases[10]. Studies have shown that IL-6 and TNF-α are significantly increased in patients with CRS and are associated with disease severity, mucosal edema, and polyp formation[11]. Similarly, elevated CRP levels have been correlated with symptom severity and poor clinical outcomes in inflammatory disorders, further supporting its role as a non-specific but sensitive biomarker of inflammation[12]. The strong positive correlations identified in this study, particularly for IL-6, indicate that cytokine-mediated pathways may play a dominant role in the systemic inflammatory profile of CRS patients[13].

The clinical implications of these findings are substantial[14]. The use of serum biomarkers such as CRP, IL-6, and TNF-α may provide an objective and quantifiable method for assessing disease severity, which is otherwise largely dependent on subjective symptom scoring and imaging findings[15]. Incorporating these biomarkers into routine clinical practice could improve diagnostic precision, enable early identification of severe disease, and assist in monitoring response to medical or surgical treatment[16]. Furthermore, targeting these inflammatory pathways may open new avenues for therapeutic interventions, particularly in patients with refractory or severe CRS[17].

However, the present study has certain limitations that must be acknowledged[18]. The relatively modest sample size and cross-sectional design limit the generalizability of the findings and preclude the establishment of causal relationships[19]. Additionally, the study did not evaluate changes in biomarker levels following treatment, which could have provided further insight into their role in monitoring disease progression and therapeutic response[20]. The exclusion of other inflammatory mediators and lack of subgroup analysis based on CRS phenotypes (with or without nasal polyps) are additional limitations[12].

Future research should focus on larger, multicenter longitudinal studies to validate these findings and explore the dynamic changes in inflammatory biomarkers over time[6]. Investigating a broader panel of cytokines and integrating molecular and genetic profiling may further enhance the understanding of CRS pathophysiology[14]. Additionally, exploring the potential of these biomarkers as therapeutic targets could contribute to the development of personalized treatment strategies in CRS management[9].

CONCLUSION

In conclusion, the present study demonstrates that patients with chronic rhinosinusitis exhibit significantly elevated levels of systemic inflammatory biomarkers, including CRP, IL-6, and TNF-α, compared to healthy individuals. These biomarkers not only reflect the presence of an underlying inflammatory state but also show a strong association with disease severity. Their progressive increase with worsening clinical condition highlights their potential utility as objective indicators for disease assessment. The findings suggest that incorporation of these biomarkers into clinical practice may enhance diagnostic accuracy, facilitate risk stratification, and improve monitoring of therapeutic outcomes. Further large-scale and longitudinal studies are warranted to establish their definitive role in the routine management of chronic rhinosinusitis.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contributions

A.A.: Conceptualization, study design, data collection, manuscript drafting
I.A.: Supervision, critical revision, methodological guidance
H.A.: Clinical evaluation, patient recruitment, data acquisition
Q.: Laboratory work, ELISA assays, data entry
N.I.R.: Statistical analysis, data interpretation, results validation
R.M.: Final review, manuscript editing, overall supervision
All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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