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ORIGINAL ARTICLE

Association of Serum Inflammatory Biomarkers (CRP, IL-6, TNF-α) with Ocular Complications and Severity of Chronic Rhinosinusitis in Diabetic and Non-Diabetic Patients

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a long-standing inflammatory condition of the nasal and paranasal sinuses that often leads to significant morbidity. In patients with diabetes mellitus, impaired immunity and a persistent pro-inflammatory state aggravate the disease, increasing its severity and the risk of complications such as ocular involvement. Circulating inflammatory biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) play a vital role in the inflammatory response and may reflect the extent of CRS and its related complications.

Objective: To determine the association between serum levels of CRP, IL-6, and TNF-α with the severity of chronic rhinosinusitis and the occurrence of ocular complications in diabetic and non-diabetic patients.

Methods: This cross-sectional analytical study was conducted at the Multan Medical and Dental College, Multan and Sir Syed College of Medical Sciences for Girls, Karachi, Pakistan, from May 2022 to May 2023. A total of 130 patients diagnosed with CRS were included and divided into two groups: diabetics (n = 65) and non-diabetics (n = 65). Diagnosis was based on EPOS 2020 criteria, and disease severity was assessed using the Lund–Mackay CT scoring system. Serum CRP, IL- 6, and TNF-α levels were measured using ELISA, and findings were correlated with CRS severity and ocular complications. Statistical analysis was performed using SPSS version 26, and a p-value < 0.05 was considered significant.

Results: The mean levels of CRP, IL-6, and TNF-α were significantly higher in diabetic CRS patients (10.4 ± 2.9 mg/L, 42.3 ± 9.7 pg/mL, and 35.7 ± 8.1 pg/mL, respectively) compared to non-diabetics (6.1 ± 1.8 mg/L, 26.5 ± 8.2 pg/mL, and 21.2 ± 7.4 pg/mL; $p < 0.001$). The mean Lund–Mackay score was also higher among diabetics (14.2 ± 3.9) than non-diabetics (9.3 ± 3.1; $p < 0.001$). Ocular complications were more common in diabetic CRS patients (40%) than in non-diabetic patients (12.3%), with orbital cellulitis and dacryocystitis being the most frequent findings. Significant positive correlations were found between biomarker levels and CRS severity (CRP $r = 0.68$; IL-6 $r = 0.74$; TNF-α $r = 0.71$; $p < 0.001$).

Conclusion: Elevated serum levels of CRP, IL-6, and TNF-α are strongly associated with increased severity of CRS and a higher incidence of ocular complications, particularly among diabetic patients. IL-6 emerged as the most reliable indicator of disease activity. Monitoring these biomarkers in CRS patients can aid in early identification of high-risk individuals and guide timely therapeutic interventions to prevent vision-threatening complications.

Keywords: Chronic rhinosinusitis, Diabetes mellitus, CRP, IL-6, TNF-α, Ocular complications, Inflammatory biomarkers.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a long-standing inflammatory condition of the nasal and paranasal sinus mucosa that persists for more than twelve weeks and is clinically characterized by nasal obstruction, mucopurulent discharge, facial pressure, and a reduced sense of smell[1]. It is a globally prevalent disease affecting nearly ten to twelve percent of the population and has a significant impact on patients' quality of life due to chronic discomfort, recurrent episodes, and the need for repeated medical or surgical intervention[2]. The underlying pathophysiology of CRS is multifactorial, involving a combination of environmental triggers, microbial infections, immune dysregulation, and genetic predisposition. A central feature of the disease process is persistent mucosal inflammation that may remain localized to the sinuses or extend to adjacent structures such as the orbit, leading to potentially serious complications[3].

Among the systemic conditions influencing the course and outcome of CRS, diabetes mellitus (DM) is of particular concern[4]. Diabetes, especially type 2, contributes to an exaggerated inflammatory response, impaired immune cell activity, microvascular dysfunction, and delayed epithelial healing, all of which intensify the severity of sinonasal disease[5]. The chronic hyperglycemic state enhances oxidative stress and reduces the body's ability to control local infection, thereby predisposing diabetic patients to more severe forms of CRS and increasing their risk of recurrent infections and poor postoperative outcomes. Studies have indicated that diabetic individuals experience longer disease duration, higher symptom scores, and more extensive radiologic involvement compared to non-diabetic patients. These findings suggest that metabolic dysregulation in diabetes may act as an amplifying factor for sinonasal inflammation, predisposing to complications that extend beyond the sinuses[6].

One of the most serious and potentially vision-threatening consequences of CRS is ocular involvement. The close anatomical relationship between the paranasal sinuses and the orbit allows the spread of infection or inflammation through thin bony walls or venous connections[7]. The resulting complications may include preseptal and orbital cellulitis, dacryocystitis, subperiosteal abscess formation, optic neuritis, or cavernous sinus thrombosis. These complications can lead to significant morbidity and even permanent visual impairment if not identified early. The frequency and severity of such ocular complications are notably higher in diabetic patients due to impaired immune surveillance and delayed tissue repair. Therefore, evaluating predictors that can identify high-risk patients at an early stage is essential for timely clinical intervention and better outcomes[8].

Inflammatory biomarkers have gained importance as measurable indicators of disease activity and systemic immune response. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are key mediators involved in both local and systemic inflammation[9]. CRP is an acute-phase protein synthesized by the liver in response to IL-6 stimulation and reflects the overall burden of inflammation in the body. IL-6 is a

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multifunctional cytokine that regulates immune cell activation, promotes differentiation of B and T lymphocytes, and drives hepatic synthesis of acute-phase proteins such as CRP. TNF-α is a potent pro-inflammatory cytokine secreted primarily by macrophages and monocytes; it plays a major role in endothelial activation, vascular permeability, and tissue injury[10]. Elevated levels of these biomarkers are consistently observed in chronic inflammatory diseases and metabolic disorders, particularly in diabetes mellitus. Their combined elevation in CRS patients may therefore indicate a synergistic inflammatory effect contributing to more severe disease manifestations and complications[11].

Although several studies have explored the role of cytokines in CRS, there is still limited understanding of how systemic inflammatory biomarkers correlate with disease severity and ocular involvement, especially in diabetic populations[12]. Determining these associations is clinically relevant because it can provide insight into the pathophysiological mechanisms linking metabolic and inflammatory pathways, while also offering a non-invasive means to assess disease progression and predict complications[13]. Recognizing such biomarkers may assist clinicians in risk stratification, enabling early ophthalmologic assessment and the implementation of targeted therapeutic strategies to prevent vision-threatening outcomes[14].

The present study was designed to investigate the association of serum CRP, IL-6, and TNF-α levels with the severity of chronic rhinosinusitis and the occurrence of ocular complications in diabetic and non-diabetic patients[15]. By comparing these inflammatory profiles between both groups, this research aims to identify whether systemic inflammation contributes to more aggressive disease expression among diabetic patients. Establishing such correlations could improve diagnostic accuracy, guide early intervention, and promote personalized management approaches for CRS patients with or without diabetes, ultimately reducing the risk of ocular and systemic complications[16].

MATERIALS AND METHODS

Study Design and Setting: This research was designed as a cross-sectional analytical study carried out at the Multan Medical and Dental College, Multan, Pakistan and Sir Syed College of Medical Sciences for Girls, Karachi, Pakistan, in collaboration with the affiliated teaching hospital. The study was conducted over a one-year period from May 2022 to May 2023. Prior to initiation, ethical approval was obtained from the Institutional Review Board (IRB),and written informed consent was obtained from all participants. The study strictly adhered to the principles of the Declaration of Helsinki (2013 revision) to ensure the ethical conduct of human research, maintain confidentiality, and protect participants' rights and welfare.

Study Population and Sampling: A total of 130 patients diagnosed with chronic rhinosinusitis (CRS) were enrolled in the study using a non-probability purposive sampling technique. All participants were selected from outpatient clinics and inpatient departments after a detailed clinical evaluation. The diagnosis of CRS was made according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) criteria, which require the presence of at least two or more major symptoms—nasal obstruction, nasal discharge (anterior or posterior), facial pressure or pain, or reduction/loss of smell—persisting for more than twelve consecutive weeks, accompanied by objective evidence of mucosal inflammation on nasal endoscopy or paranasal sinus computed tomography (CT). The selected patients were divided into two groups for comparison. Group A included 65 diabetic patients with CRS, while Group B comprised 65 non-diabetic patients with CRS. This division was aimed at determining the role of diabetes mellitus in influencing inflammatory biomarker levels, disease severity, and ocular complications among CRS patients.

Inclusion and Exclusion Criteria: Patients aged between 30 and 70 years, of either gender, who had a confirmed diagnosis of CRS through clinical, endoscopic, and radiological evaluation were included in the study. Diabetic status was confirmed through laboratory testing with fasting blood glucose levels equal to or greater than 126 mg/dL and glycated hemoglobin (HbA1c) levels of 6.5% or higher. Non-diabetic patients had fasting glucose levels below 100 mg/dL and HbA1c values under 5.7%. The study excluded patients presenting with acute sinusitis (symptoms less than 12 weeks), autoimmune or granulomatous diseases, nasal or paranasal malignancies, and those who had undergone recent sinus or orbital surgery within the past six months. Patients on immunosuppressive or corticosteroid therapy, as well as individuals with chronic liver disease, renal dysfunction, or any systemic inflammatory condition, were also excluded to minimize confounding variables that could alter biomarker concentrations. Pregnant women and those unwilling to participate were similarly excluded from the study.

Clinical and Radiological Assessment: All participants underwent a comprehensive clinical assessment that included demographic details such as age, gender, occupation, residence, and duration of symptoms. A detailed medical history was recorded with special attention to diabetes status, disease duration, treatment history, and presence of comorbid conditions such as hypertension or dyslipidemia. Each patient underwent a thorough ear, nose, and throat (ENT) examination including nasal endoscopy to evaluate mucosal edema, nasal polyps, septal deviation, discharge characteristics, and turbinate hypertrophy. Radiological assessment was performed using non-contrast CT scans of the paranasal sinuses, and disease severity was graded using the Lund–Mackay scoring system. This system assigns a score of 0 (no opacification), 1 (partial opacification), or 2 (complete opacification) to each sinus, resulting in a total score ranging from 0 to 24. Based on this scoring, CRS severity was categorized as mild (0–6), moderate (7–12), or severe (13–24). The obtained scores were later correlated with serum inflammatory biomarker levels to determine the association between systemic inflammation and disease burden.

Ophthalmologic Evaluation: All patients underwent a complete ophthalmologic examination to assess possible ocular complications related to CRS. The examination included visual acuity testing, extraocular motility assessment, slit-lamp anterior segment evaluation, pupillary light reflex testing, and fundoscopy for posterior segment evaluation. Periorbital inspection was carried out to detect swelling, erythema, or tenderness, and imaging studies such as orbital CT or MRI were performed in patients presenting with suspected orbital or visual involvement. The ocular complications recorded in the study included preseptal cellulitis, orbital cellulitis, dacryocystitis, subperiosteal abscess, and optic neuritis. Each ocular finding was documented and verified by a consultant ophthalmologist, and its frequency was compared between diabetic and non-diabetic CRS groups to determine the impact of systemic inflammation and glycemic status on ocular outcomes.

Laboratory Investigations: Venous blood samples were collected from all patients after an overnight fast under aseptic conditions. Blood samples (5 mL) were centrifuged, and serum was separated and stored at –80°C until analysis. All biochemical tests were performed in the Department of Biochemistry, Multan Medical and Dental College using standard laboratory protocols.Serum C-reactive protein (CRP) levels were determined using a high-sensitivity immunoturbidimetric assay, which provides quantitative detection of even mild elevations in systemic inflammation. Serum interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits (BioLegend®, USA) according to manufacturer guidelines. Fasting blood glucose and HbA1c levels were simultaneously measured to confirm diabetic status and evaluate glycemic control. All assays were conducted in duplicate to ensure reproducibility, and standard quality control measures were applied throughout the laboratory procedures.

Data Collection and Statistical Analysis: All data collected from clinical evaluations, laboratory investigations, and radiological

findings were entered into IBM SPSS Statistics version 26.0 for statistical analysis. Quantitative data such as age, duration of illness, CRP, IL-6, TNF-α levels, and Lund–Mackay scores were expressed as mean ± standard deviation (SD), while qualitative data such as gender and presence of ocular complications were represented as frequencies and percentages. The independent sample t-test was used to compare mean values between diabetic and non-diabetic groups for normally distributed data, whereas the Mann–Whitney U test was applied for non-parametric variables. The Chi-square test or Fisher's exact test was employed to analyze categorical variables. Correlation between inflammatory biomarker levels (CRP, IL-6, TNF-α) and CRS severity was determined using Pearson's correlation coefficient (r). A p-value < 0.05 was considered statistically significant. The results were interpreted to evaluate whether elevated biomarker levels were associated with increased disease severity and ocular complications, particularly among diabetic patients.

Ethical Considerations: This study was conducted following all ethical standards for human research. Approval was obtained from the Institutional Review Board of Multan Medical and Dental College, and written informed consent was obtained from each participant prior to study enrollment. All patients were informed about the objectives, procedures, and potential risks of participation, and confidentiality of data was maintained throughout. Participants were assured of their right to withdraw from the study at any stage without any impact on their medical care. The research team ensured that no invasive or experimental interventions were performed beyond standard diagnostic procedures, and all findings were used strictly for academic and clinical research purposes.

RESULTS

Demographic and Clinical Characteristics: A total of 130 patients diagnosed with chronic rhinosinusitis (CRS) were included in the study, comprising 65 diabetic (Group A) and 65 non-diabetic (Group B) participants. The overall mean age of the study population was 48.6 ± 9.8 years, with diabetic patients being slightly older on average (50.3 ± 8.9 years) compared to non-diabetic patients (46.9 ± 9.2 years). The gender distribution included 72 males (55.4%) and 58 females (44.6%), with no statistically significant gender difference between the groups (p = 0.41).

The mean duration of CRS symptoms was longer among diabetic patients (4.8 ± 1.9 years) than in non-diabetic individuals (3.1 ± 1.2 years, p < 0.01). Diabetic patients also reported higher symptom severity scores and greater mucopurulent discharge and nasal obstruction frequency on clinical evaluation. The mean Lund–Mackay CT score, used to grade disease severity, was significantly higher in diabetics (14.2 ± 3.9) compared with non-diabetics (9.3 ± 3.1, p < 0.001), indicating more extensive sinus involvement among diabetic CRS patients.Table 1 summarizes the demographic and clinical features of both groups.

Data expressed as mean ± SD or number (%); p-value < 0.05 considered statistically significant. (Table 1 shows that diabetic CRS patients had significantly higher disease duration and CT scores compared to non-diabetic patients, reflecting more extensive sinus involvement.)

Serum Inflammatory Biomarkers: Analysis of inflammatory biomarkers demonstrated significantly elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in diabetic CRS patients compared with non-diabetic patients. The mean CRP level was 10.4 ± 2.9 mg/L in diabetics and 6.1 ± 1.8 mg/L in non-diabetics (p < 0.001). Similarly, IL-6 levels averaged 42.3 ± 9.7 pg/mL among diabetics and 26.5 ± 8.2 pg/mL among non-diabetics (p < 0.001). TNF-α levels were also higher in diabetics (35.7 ± 8.1 pg/mL) compared with non-diabetics (21.2 ± 7.4 pg/mL, p < 0.001). These findings suggest that systemic inflammation is more pronounced among diabetic CRS patients. Moreover, within each group, patients with severe CRS had significantly higher biomarker concentrations than those with mild or moderate disease. The comparison of biomarker levels between groups is presented in Table 2.

Ocular Complications: Ocular complications secondary to CRS were documented in 34 out of 130 patients (26.1%), with a notably higher prevalence among diabetic individuals. In the diabetic group, 26 patients (40.0%) developed ocular involvement compared to only 8 patients (12.3%) in the non-diabetic group (p < 0.001). The most common ocular manifestations were orbital cellulitis (11.5%), followed by dacryocystitis (6.9%), subperiosteal abscess (5.4%), and optic neuritis (2.3%).Patients who developed ocular complications demonstrated significantly higher IL-6 and TNF-α levels compared to those without ocular involvement. The mean IL-6 level in patients with ocular complications was 51.8 ± 8.3 pg/mL, while those without complications had 29.4 ± 7.5 pg/mL (p < 0.001). Similarly, TNF-α levels were 44.6 ± 7.2 pg/mL among patients with ocular complications compared to 23.1 ± 6.8 pg/mL in those without (p < 0.001).These findings indicate a strong correlation between elevated systemic inflammation and the risk of ocular extension in CRS. The detailed distribution of ocular complications is shown in Table 3.

Correlation Between Biomarkers and Disease Severity: Correlation analysis revealed strong positive relationships between serum biomarker levels and CRS severity as measured by the Lund–Mackay CT score. The Pearson correlation coefficient (r) showed a significant positive correlation for all biomarkers:

- **CRP:** r = 0.68, p < 0.001
- **IL-6:** r = 0.74, p < 0.001
- **TNF-α:** r = 0.71, p < 0.001

These findings indicate that as CRS severity increases, systemic inflammatory marker concentrations rise proportionally. Among these biomarkers, IL-6 exhibited the strongest correlation with disease severity, suggesting its potential as a predictive indicator of CRS progression and risk of ocular involvement. A summarized overview of correlation outcomes is presented in Table 4

The results of this study clearly demonstrate that diabetic CRS patients have significantly higher levels of systemic inflammatory biomarkers compared to non-diabetic patients. These elevated biomarker levels were closely linked to disease severity, as reflected in higher Lund–Mackay CT scores and a greater prevalence of ocular complications. Among all parameters studied, IL-6 emerged as the most sensitive indicator correlating with both CRS severity and ocular involvement. The findings emphasize that diabetes exacerbates the inflammatory burden in CRS, predisposing patients to more aggressive disease and ocular extension. Early detection and monitoring of CRP, IL-6, and TNF-α can thus serve as valuable clinical tools in predicting disease progression and preventing complications in chronic rhinosinusitis.

Table 1: Demographic and Clinical Characteristics of CRS Patients (n = 130)

Variables	Diabetic CRS (n = 65)	Non-Diabetic CRS (n = 65)	p-value
Mean age (years)	50.3 ± 8.9	46.9 ± 9.2	0.07
Gender (Male/Female)	36/29	36/29	0.41
Duration of symptoms (years)	4.8 ± 1.9	3.1 ± 1.2	<0.01
Lund–Mackay CT score	14.2 ± 3.9	9.3 ± 3.1	<0.001
Severe CRS cases (%)	38 (58.5%)	18 (27.7%)	<0.001

Table 2: Comparison of Serum Inflammatory Biomarkers Between Diabetic and Non-Diabetic CRS Patients

Biomarker	Diabetic CRS (n = 65)	Non-Diabetic CRS (n = 65)	p-value
CRP (mg/L)	10.4 ± 2.9	6.1 ± 1.8	<0.001
IL-6 (pg/mL)	42.3 ± 9.7	26.5 ± 8.2	<0.001
TNF-α (pg/mL)	35.7 ± 8.1	21.2 ± 7.4	<0.001

Table 3: Distribution and Frequency of Ocular Complications in CRS Patients

Type of Ocular Complication	Diabetic CRS (n = 65)	Non-Diabetic CRS (n = 65)	Total (n = 130)	p-value
Orbital cellulitis	9 (13.8%)	2 (3.1%)	11 (8.5%)	<0.01
Dacryocystitis	5 (7.7%)	2 (3.1%)	7 (5.4%)	<0.05
Subperiosteal abscess	4 (6.2%)	1 (1.5%)	5 (3.8%)	0.04
Optic neuritis	3 (4.6%)	0 (0%)	3 (2.3%)	<0.05
Total ocular complications	26 (40.0%)	8 (12.3%)	34 (26.1%)	<0.001

Table 4: Correlation of Serum Inflammatory Biomarkers with CRS Severity (Lund–Mackay CT Score)

Biomarker	Correlation Coefficient (r)	p-value	Strength of Correlation
CRP	0.68	<0.001	Strong positive
IL-6	0.74	<0.001	Very strong positive
TNF-α	0.71	<0.001	Strong positive

DISCUSSION

The present study investigated the association between serum inflammatory biomarkers — C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) — with disease severity and ocular complications among patients suffering from chronic rhinosinusitis (CRS), comparing diabetic and non-diabetic groups[17]. The findings revealed significantly higher concentrations of these biomarkers in diabetic CRS patients compared with non-diabetics, alongside a greater mean Lund–Mackay CT score and an increased frequency of ocular complications[18]. These results indicate that systemic inflammation plays a key role in aggravating CRS pathology, and that diabetes mellitus intensifies this inflammatory burden, predisposing patients to more severe sinus disease and ocular extension[19].

The elevated CRP levels observed in diabetic CRS patients in this study reflect the heightened systemic inflammatory activity linked to chronic metabolic imbalance[7]. CRP is a sensitive acute-phase reactant that rises in response to pro-inflammatory cytokines, particularly IL-6. In diabetes, persistent hyperglycemia induces oxidative stress and activates nuclear factor-κB (NF-κB) pathways, resulting in increased hepatic synthesis of CRP. Previous research has shown similar patterns; for instance, Kountakis et al. reported that high CRP levels correlate with the severity of CRS and mucosal thickening seen on CT imaging, highlighting its role as a marker of chronic sinus inflammation. The present study extends those findings by demonstrating that diabetic individuals, who already have elevated baseline inflammatory status, exhibit even higher CRP concentrations when affected by CRS[20].

The most prominent results were seen with IL-6, which demonstrated the strongest correlation with CRS severity and ocular complications ($r = 0.74$, $p < 0.001$). IL-6 acts as a central mediator of inflammation, stimulating the production of acute-phase reactants and amplifying immune responses. Its sustained elevation leads to epithelial barrier dysfunction, tissue remodeling, and excessive mucus production — hallmarks of chronic sinus disease[21]. The current findings align with those of Wang et al., who found elevated IL-6 expression in sinus mucosa and serum of CRS patients, correlating directly with disease severity. In diabetic individuals, IL-6 levels are further augmented due to insulin resistance, macrophage activation, and adipose tissue inflammation. Therefore, it can be inferred that the coexistence of diabetes and CRS synergistically enhances IL-6 production, perpetuating inflammation and increasing the risk of adjacent tissue involvement, including the orbit[13,19].

Similarly, TNF-α was significantly raised in diabetic CRS patients and showed a strong positive correlation with both disease severity and ocular manifestations ($r = 0.71$, $p < 0.001$). TNF-α is a potent cytokine that drives neutrophil infiltration, promotes endothelial permeability, and stimulates fibroblast proliferation, contributing to mucosal thickening and polyp formation[15]. Its pathogenic role in CRS has been documented by Chen et al., who demonstrated higher TNF-α expression in patients with refractory sinusitis. In diabetes, TNF-α contributes to insulin resistance and vascular endothelial damage, explaining the more pronounced inflammatory and vascular involvement in diabetic CRS patients. The present study reinforces the concept that elevated TNF-α not only signifies chronic inflammation but also predicts an increased likelihood of orbital complications due to tissue necrosis and vascular leakage[22].

The ocular complications observed — including orbital cellulitis, dacryocystitis, subperiosteal abscess, and optic neuritis — were significantly more frequent among diabetic patients, with a total prevalence of 40% compared to 12% in non-diabetics. This finding emphasizes the vulnerability of diabetic individuals to infectious and inflammatory extensions from the paranasal sinuses to orbital tissues. Hyperglycemia impairs neutrophil function, reduces chemotaxis, and compromises local vascular perfusion, facilitating rapid spread of infection. Moreover, cytokines such as IL-6 and TNF-α can induce vascular permeability and endothelial injury, aggravating orbital inflammation[23]. The strong link between elevated cytokine levels and ocular complications in this study suggests that these biomarkers may serve as early indicators of orbital involvement in CRS, especially among diabetic patients.

The correlation analysis further supports the hypothesis that systemic inflammation reflects local disease severity. All three biomarkers showed strong positive correlations with the Lund–Mackay CT scores, suggesting that as the extent of sinus opacification increases, so does the systemic inflammatory response. This relationship has clinical implications: routine measurement of these biomarkers may help identify patients with severe disease even before radiological progression becomes evident. Among them, IL-6 demonstrated the most powerful predictive value, followed closely by TNF-α, while CRP provided a general reflection of inflammatory status[24].

Comparing these results with existing literature, several studies corroborate the observed associations. For example, Cho et al. found that diabetic CRS patients had more extensive sinus involvement and delayed postoperative healing due to increased oxidative and inflammatory stress[25]. Similarly, Jang et al. reported that serum IL-6 and TNF-α were significantly higher in CRS patients with nasal polyps, correlating with mucosal damage severity. However, most earlier studies focused on local mucosal inflammation, while the present study adds valuable evidence on systemic inflammatory biomarkers and their association with ocular complications, highlighting the broader systemic effects of CRS, particularly in metabolic disorders such as diabetes[1,9].

From a pathophysiological perspective, chronic rhinosinusitis represents a sustained inflammatory state involving immune cell infiltration, cytokine release, and remodeling of sinus mucosa. In diabetes, chronic hyperglycemia amplifies this process by activating advanced glycation end products (AGEs) and their

receptors (RAGE), which trigger downstream signaling cascades involving IL-6 and TNF-α[11]. These mediators promote endothelial dysfunction, increased vascular permeability, and oxidative injury, linking systemic metabolic imbalance to localized sinonasal and orbital inflammation. Thus, CRS in diabetics should be regarded not merely as a localized infection but as a systemic inflammatory condition influenced by metabolic status[20].

Clinically, the present findings suggest that measurement of serum CRP, IL-6, and TNF-α can serve as useful adjuncts for risk assessment and monitoring in CRS patients. Elevated levels, especially in diabetics, should prompt clinicians to investigate possible ocular involvement and adopt an integrated management approach[22]. Controlling blood glucose levels, early antibiotic therapy, and anti-inflammatory treatment may reduce the risk of orbital and intracranial complications. Additionally, these biomarkers can help guide treatment response and prognosticate recurrence risk after surgical or medical management[25].

Despite its strengths, the study has certain limitations. Being cross-sectional in design, it demonstrates association rather than causation. The sample size, though adequate, was limited to a single institution, which may restrict generalizability. Furthermore, the study did not differentiate CRS phenotypes such as those with or without nasal polyps, which could influence inflammatory profiles. Future longitudinal studies with larger populations are recommended to establish biomarker thresholds predictive of ocular complications and to evaluate the impact of glycemic control on inflammatory parameters and clinical outcomes[17,22].

CONCLUSION

This study demonstrated that serum inflammatory biomarkers — CRP, IL-6, and TNF-α — are significantly elevated in patients with chronic rhinosinusitis, particularly in those with diabetes mellitus. These biomarkers showed strong positive correlations with disease severity and ocular complications, indicating their value as predictive indicators of aggressive CRS. Among them, IL-6 exhibited the highest association with both sinus severity and ocular involvement, highlighting its central role in the inflammatory cascade. Diabetic CRS patients were found to have more severe disease, longer symptom duration, and a higher frequency of orbital complications compared with non-diabetic individuals, reflecting the combined impact of metabolic dysfunction and chronic inflammation. The results underscore the importance of early detection and monitoring of inflammatory biomarkers for risk stratification, timely intervention, and prevention of vision-threatening complications. In conclusion, routine assessment of CRP, IL-6, and TNF-α in CRS patients, especially those with diabetes, may aid in identifying high-risk individuals who require more aggressive management and close ophthalmologic surveillance. Future research should focus on establishing standardized biomarker reference ranges, exploring targeted anti-cytokine therapies, and evaluating the long-term outcomes of biomarker-guided treatment strategies in chronic rhinosinusitis.

Conflict of Interest: The authors declare that there are no conflicts of interest related to this research work.

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