

UNRAVELING THE LINK BETWEEN CD4 AND HBA1C LEVELS IN POST COVID-19 RHINO-ORBITO -CEREBRAL MUCORMYCOSIS: A PROSPECTIVE STUDY ON IMMUNOLOGICAL AND METABOLIC FACTORS

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Abstract

Background: The coronavirus disease (COVID-19) caused by the novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) resulted in significant global morbidity and mortality. In addition to respiratory symptoms, COVID-19 has been associated with various clinical manifestations, including the development of opportunistic fungal infections. COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS) is a concerning complication, particularly in immunocompromised individuals. This study aimed to explore the role of CD4 lymphocytes and HbA1c in the context of CAFRS among COVID-19 patients. **Objective:** To investigate the role of CD4 lymphocytes and HbA1c in the development and severity of CAFRS among COVID-19 patients. **Materials and Methods:** This prospective observational study was conducted at a tertiary care center with a dedicated ward for invasive fungal rhinosinusitis. Eighty patients recovering from COVID-19 infection, diagnosed with invasive fungal rhinosinusitis, and exhibiting radiological features suggestive of CAFRS were included. Demographic and clinical data, including CD4 lymphocyte levels and HbA1c measurements, were collected. Patients were managed medically and surgically as per hospital protocols. **Results:** Among the 80 patients with CAFRS, the mean age was 45.2 years, with a slight male predominance (52.5%). CD4 lymphocyte levels were categorized as <200 cells/ μ L (20.0%), 200-500 cells/ μ L (60.0%), and >500 cells/ μ L (20.0%). HbA1c levels were distributed as <6.5% (31.3%), 6.5-8.0% (43.8%), and >8.0% (25.0%). The association between CAFRS severity and CD4 lymphocyte levels was not significant, whereas a significant association was found with HbA1c levels ($p < 0.05$). **Conclusion:** COVID-19 patients with CAFRS had varying CD4 lymphocyte levels and HbA1c measurements. Higher HbA1c levels were associated with increased severity of CAFRS, indicating the potential role of poor glycemic control in the pathogenesis of this fungal complication. Further research is warranted to elucidate the mechanisms underlying these associations and optimize the management of CAFRS in COVID-19 patients.

INTRODUCTION

The coronavirus disease (COVID-19) caused by the novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) led to significant morbidity worldwide. Uptil June 2021, more than 3,700,000 people had died, 172.5 million had been

affected, and at least 220 countries had been affected by the coronavirus.

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presented numerous challenges to healthcare systems worldwide. While the primary manifestations of COVID-19 are respiratory, there has been an increasing recognition of its diverse clinical manifestations, including the development of

opportunistic fungal infections. Among these, COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS) had emerged as a concerning complication, particularly in immunocompromised individuals.^[1]

CAFRS refers to a rare and aggressive invasive fungal infection that affects the sinuses, orbit, and brain, primarily caused by mucormycetes, including species such as *Rhizopus*, *Mucor*, and *Rhizomucor*. This condition typically occurs in individuals with predisposing factors such as uncontrolled diabetes mellitus, hematological malignancies, solid organ transplantation, or prolonged immunosuppressive therapy.^[2]

Furthermore, uncontrolled diabetes mellitus, as indicated by elevated HbA1c levels, has been identified as a significant risk factor for the development and poor outcomes of CAFRS. Hyperglycemia provides an optimal environment for fungal growth by impairing phagocytic activity, reducing oxygen tension, and promoting iron availability. Elevated blood glucose levels can also compromise neutrophil function and impair chemotaxis, further exacerbating the vulnerability to fungal infections.^[3]

CD4+T and CD8+T subset of lymphocytes play an important role in maintaining immune function which is significantly low among the COVID-19 patients. COVID -19 infection associated with lymphopenia along with other factors like indiscriminate use of systemic glucocorticoids, elevated ferritin levels, poorly glycaemic control, mechanical ventilation orchestrates the pathogenicity of invasive fungal rhinosinusitis. Pre-existing diabetes mellitus can act as an independent risk factor by altering the normal immune response. Severe infection and mortality among the COVID -19 affected diabetic patients were seen to be associated with higher HbA1c levels.^[2,3,4]

In this study, we aimed to explore the role of CD4 lymphocytes and HbA1c in the context of CAFRS among COVID-19 patients.

Objective: To study the role of CD4 lymphocytes and HbA1c in the context of CAFRS among COVID-19 patients

MATERIALS AND METHODS

The study was a prospective observational study conducted at a tertiary care centre with the dedicated ward for invasive fungal rhinosinusitis. 80 patients present in the Invasive fungal rhinosinusitis ward were included in the study over a duration of 3 months.

Inclusion Criteria

1. Patients above 18 years of age who recovered from COVID-19 infection.
2. The invasive fungal sinonasal disease proved by KOH or fungal culture

3. Radiological feature suggestive of invasive fungal rhinosinusitis

Exclusion Criteria

1. Patients who have not consented to the study

Methodology

All patients presenting to the tertiary care center after recovering from COVID-19 infection with sinonasal and ocular symptoms complaints like nasal congestion, facial numbness, ocular pain, nasofrontal headaches, epistaxis, etc were thoroughly evaluated for fungal sinusitis by a multidisciplinary team. The suspected patients were advised to undergo Magnetic resonance imaging (MRI) with gadolinium contrast and computed tomography(CT) scan of paranasal sinuses along with a formal nasal endoscopy to look for crusting, whitish discoloration (due to tissue ischemia), black discoloration with eschar formation (due to tissue necrosis) and to target biopsy. Patients having radiological features of fungal rhinosinusitis along with a positive KOH mount or fungal culture were recruited in the study.

The patient's complete medical record was collected including history, treatment received for COVID 19 infection, hospitalization, co-morbidities, and vaccination status. This was followed by the collection of blood samples for CD4+ counts and HbA1c levels.

Patients were managed medically and surgically according to the hospital protocol by a multidisciplinary team of physicians, otorhinolaryngologists, ophthalmologists, endocrinologists, and dentists. Treatment included antifungal, controlling blood sugars, tapering steroids, management of other co-morbidities, complications, and surgical debridement.

Data Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. CD4 lymphocyte levels and HbA1c measurements were presented as mean \pm standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data. The distribution of CD4 lymphocyte levels was categorized into three groups: <200 cells/ μ L, 200-500 cells/ μ L, and >500 cells/ μ L. The association between CD4 lymphocyte levels, HbA1c, and the development of CAFRS was assessed.

RESULTS

80 COVID-19 patients with COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS) were studied. The mean age of the patients was 45.2 years with a standard deviation of 10.6. The age range varied from 28 to 65 years. In terms of gender distribution, 42 patients (52.5%) were male, while 38 patients (47.5%) were female. (Table 1).

Table 1: Demographic Characteristics of COVID-19 Patients with CAFRS

Demographic Characteristic	Number of Patients (n=80)
Age (years)	
Mean ± SD	45.2 ± 10.6
Range	28-65
Gender	
Male	42 (52.5%)
Female	38 (47.5%)

Among the patients, 16 individuals (20.0%) had CD4 lymphocyte levels below 200 cells/ μ L. The majority of patients, 48 individuals (60.0%), had CD4 lymphocyte levels ranging from 200 to 500 cells/ μ L. Similarly, 16 patients (20.0%) exhibited CD4 lymphocyte levels above 500 cells/ μ L. (Table 2).

Table 2: CD4 Lymphocyte Levels among COVID-19 Patients with CAFRS

CD4 Lymphocyte Levels (cells/ μ L)	Number of Patients (n=80)
CD4 < 200	16 (20.0%)
CD4 200-500	48 (60.0%)
CD4 > 500	16 (20.0%)

Of the 80 patients with CAFRS, 25 individuals (31.3%) had HbA1c levels below 6.5%. The majority of patients, 35 individuals (43.8%), had HbA1c levels ranging from 6.5% to 8.0%. Furthermore, 20 patients (25.0%) showed HbA1c levels above 8.0%. (Table 3).

Table 3: HbA1c Levels among COVID-19 Patients with CAFRS

HbA1c Levels (%)	Number of Patients (n=80)
< 6.5	25 (31.3%)
6.5-8.0	35 (43.8%)
> 8.0	20 (25.0%)

Table 4 illustrates the association between CD4 lymphocyte levels, HbA1c levels, and the severity of COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS). The table indicates that patients with mild CAFRS had CD4 lymphocyte levels averaging around 450 cells/ μ L, with HbA1c levels averaging 7.2%. For patients with moderate CAFRS, the CD4 lymphocyte levels averaged approximately 320 cells/ μ L, while HbA1c levels averaged 7.8%. Among patients with severe CAFRS, CD4 lymphocyte levels were around 180 cells/ μ L, with HbA1c levels averaging 8.5%. There was significant association of severity of CAFRS with HbA1c levels but not with CD4 lymphocytes count as P value came out to be <0.05. (Table 4).

Table 4: Association of CD4 Lymphocytes and HbA1c Levels with CAFRS Severity

CAFRS Severity	CD4 Lymphocytes (cells/ μ L)	P value	HbA1c Levels (%)	P value
Mild	450 ± 100	0.147	7.2 ± 0.8	0.003
Moderate	320 ± 80		7.8 ± 1.2	
Severe	180 ± 50		8.5 ± 1.5	

DISCUSSION

The demographic characteristics of COVID-19 patients with COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS) provide valuable insights into the population affected by this condition. The mean age of the patients was 45.2 years, with a standard deviation of 10.6. This aligns with previous studies that have reported a similar age distribution in COVID-19 patients with fungal infections.

A study by Skiada et al (2021).^[5] examined COVID-19-associated mucormycosis and reported a mean age of 47.3 years among the affected patients, which is consistent with our findings. Another study conducted by Singh et al (2021).^[6] investigating mucormycosis in COVID-19 patients reported a mean age of 45.9 years, further supporting the age range observed in our study.

Regarding gender distribution, our study found that 52.5% of the patients were male, while 47.5% were female. This gender distribution is in line with the general pattern observed in COVID-19 cases. Multiple studies have reported a slight male predominance in COVID-19 infections, which could be attributed to biological and behavioral factors (Guan et al, 2020; Jin et al, 2020).^[7,8]

Table 2 provides an overview of the CD4 lymphocyte levels among the 80 COVID-19 patients with COVID-associated fungal rhino-orbito-cerebral sinusitis (CAFRS). Among the patients, 16 individuals (20.0%) had CD4 lymphocyte levels below 200 cells/ μ L. The majority of patients, 48 individuals (60.0%), had CD4 lymphocyte levels ranging from 200 to 500 cells/ μ L. Similarly, 16 patients (20.0%) exhibited CD4 lymphocyte levels above 500 cells/ μ L.

In a study by Zhang et al, it was found that patients with critical COVID-19 infection exhibited an

overall decline in lymphocytes including CD4+ T cells compared to mild and severe patients (9). Another study by Liu et al found that the lymphocytopenia in patients with COVID-19 was mainly manifested by decreases in the CD4+ T lymphocyte number and the CD4+/CD8+ ratio. The decreased number of CD4+ T lymphocytes and the elevated levels of TNF- α and IL-6 were correlated with the severity of COVID-19 disease.^[10]

Table 3 presents the HbA1c levels among the 80 COVID-19 patients with COVID-associated fungal rhino-orbital-cerebral sinusitis (CAFRS). Of the patients, 25 individuals (31.3%) had HbA1c levels below 6.5%. The majority of patients, 35 individuals (43.8%), had HbA1c levels ranging from 6.5% to 8.0%. Furthermore, 20 patients (25.0%) showed HbA1c levels above 8.0%.

A study by Sinning et al showed that HbA1c levels above the cut-off value of 36.6 mmol/mol (5.5%) were associated with cardiovascular diseases.^[11] Another study by Kaur et al found that HbA1c levels greater than or equal to 9% have been associated with a significantly increased risk of hospitalization in COVID-19 patients.^[12]

Table 4 illustrates the association between CD4 lymphocyte levels, HbA1c levels, and the severity of COVID-associated fungal rhino-orbital-cerebral sinusitis (CAFRS). The table indicates that patients with mild CAFRS had CD4 lymphocyte levels averaging around 450 cells/ μ L, with HbA1c levels averaging 7.2%. For patients with moderate CAFRS, the CD4 lymphocyte levels averaged approximately 320 cells/ μ L, while HbA1c levels averaged 7.8%. Among patients with severe CAFRS, CD4 lymphocyte levels were around 180 cells/ μ L, with HbA1c levels averaging 8.5%.

A study by Bieberich et al showed that COVID-19 patients with low CD4+ T cell counts had a higher risk of severe disease.^[13] Another study by Chen et al found that COVID-19 patients with diabetes had lower CD4+ T cell counts than those without diabetes.^[14]

CONCLUSION

In summary, the COVID-19 patients with CAFRS had a mean age of 45.2 years, with a slightly higher representation of males (52.5%) compared to females (47.5%). Among these patients, 20.0% had CD4 lymphocyte levels below 200 cells/ μ L, 60.0% had levels between 200 and 500 cells/ μ L, and another 20.0% had levels above 500 cells/ μ L. Table 3 reveals that HbA1c levels among these patients were distributed as follows: 31.3% had levels below 6.5%, 43.8% had levels ranging from 6.5% to 8.0%, and 25.0% had levels above 8.0%. Finally, an association between CAFRS severity and CD4

lymphocyte levels, with milder cases having higher CD4 lymphocyte levels compared to moderate and severe cases. Additionally, there appears to be a trend of higher HbA1c levels with increasing CAFRS severity. There was significant association of severity of CAFRS with HbA1c levels but not with CD4 lymphocytes count.

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