Epidemiological Factors in Post COVID-19 Acute Invasive Fungal Rhinosinusitis Affecting Disease Incidence and Prognosis

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Background: Acute Invasive fungal rhinosinusitis (AIFR) is a life-threatening disease presents usually in immune- compromised patients with impaired neutrophilic response.

Aim: To study and statistically analyze the epidemiological factors leading to the observed increased incidence of invasive fungal rhinosinusitis in coronavirus disease- 19 (COVID-19) diseased patients and identify the prognostic factors that may affect the course and outcome of the disease.

Methods: This case-control study was carried out on 23 patients diagnosed with acute invasive fungal sinusitis patients, patients with positive coronavirus or recently recovered from coronavirus infection admitted to tertiary or secondary centers in El-Gharbia governorate, and 46 participants as a control. The study was focused on the epidemiological predisposing factors that may affect the incidence of the disease.

Keywords: coronavirus disease-19, acute invasive fungal, rhinosinusitis, disease incidence.

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Results: COVID-19 reporting and data system (CORAD), level of O_2 saturation, PH, steroid therapy dose and duration, duration of O_2 therapy, and anterior septal deviation were insignificantly different between the two studied groups. Random blood sugar (RBS), neutropenia, and type O_2 therapy were significantly different between the two studied groups. Steroid therapy dose and duration were significantly higher in the patients' group than control group (P<0.05). In the total number of 23 patients 16(69.6%) patients had their middle turbinate as the first site to be affected by the pathology, 3(13%) patients in the right maxilla, 1 (4.3%) patient in the left maxilla, 2(8.7%) patients in the right sphenoid sinus, 1(4.3%) patient in the hard palate.

Conclusions: The Prognostic factors favoring bad prognosis: Uncontrolled Co-morbidities, high CORAD grade, high grade of fungal invasion, serum neutropenia, the use of ventilators as an O_2 delivery method, and medical treatment alone without surgical treatment.

Keywords: coronavirus disease-19, acute invasive fungal, rhinosinusitis, disease incidence.

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I. BACKGROUND

Acute Invasive fungal rhinosinusitis (AIFR) is a life-threatening disease that presents usually in immune-compromised patients with impaired neutrophilic response. These patients include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome (AIDS), iatrogenic immuno-suppression, organ transplantation, and hematological malignancies[1].

AIFR is characterized by the presence of hyphal invasion of sinus tissue and a time course of less than weeks[2, 3]. Histolo ical features include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, hemorrhage, and acute neutrophilic infiltration. Aspergillus

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species and fungi in the order of Mucorales are the most implicated species [4].

In addition to the acute respiratory distress occurring in coronavirus disease 2019 (COVID-19) patients, a large number of COVID-19 patients develops a serious immune-compromised state due to a complex of factors including the common co- morbidities, especially diabetes mellitus and other previous respiratory disorders, the misuse of immune-suppressive agents as corticosteroids and empirical antibiotics as a main line of treatment and other epidemio-logical factors such as long duration of hospital stay that sometimes can reach up to 50 days and intensive care unit admission[4].

This immune-compromised state allows the development of a wide spectrum of opportunistic bacterial and fungal infections and acute invasive fungal rhino-sinusitis; a potentially fatal opportunistic fungal infection affecting nasal and sinus mucosa with high morbidity and mortality rate, considered one of the most serious infections COVID-19 patients may develop[5].

COVID-19 patients show overexpression of inflammatory cytokines, and impaired cell-mediated immunity with decreased cluster of differentiation 4 and 8 positive T-helper (CD4+ T and CD8+ T) cell counts, indicating susceptibility to fungal co-infections[6].

Hence the great importance of better understanding and identification of the epidemiological factors leading to this observed increased incidence of invasive fungal rhinosinusitis among COVID-19 patients, allowing us to prevent such a serious complication, as always prevention is the best treatment modality.

This work aimed tostudy and statistically analyze the epidemiological factors leading to the observed increased incidence of invasive fungal rhinosinusitis in COVID-19 patients and identify the prognostic factors that may affect the course and outcome of the disease.

II. METHODS

This case-control study was carried out on 23 patients diagnosed with acute invasive fungal sinusitis patients, patients positive coronavirus or recently recovered from coronavirus infection admitted to tertiary or secondary centers in El-Gharbia governorate, and 46 participants as a control, aged from 19 to 65 years old, both sexes.The study was done from June 2021 to December 2021after approval from the Ethical Committeeat Tanta University Hospitals, Tanta, Egypt.) *Approval code:* 35036/11/21). Informed written consent was obtained from the patients.

Exclusion criteria were previous sinus surgery and allergic fungal rhinosinusitis.

All patients were subjected to history taking, general examination, otorhinolaryngology clinical examination, laboratory investigations [complete blood count (CBC), Creactive protein (CRP), erythrocyte sedimentation rate (ESR), random blood sugar, serum ferritin, glycated hemoglobin (HbA1c), lactated dehydrogenase (LDH) and cytology (Fungal culture, biopsy histopathology), radiological [computed tomography (CT) forchest and nose, paranasal sinuses (PNS) and magnetic resonance imaging (MRI) for nose, PNS and brain].

First, the selected patients must be either coronavirus-positive or have recovered from coronavirus infection evident by CT chest finding (CORAD classification) and/or nasopharyngeal swab polymerase chain reaction (PCR) test.

The study focused on the epidemiological predisposing factors that may affect the incidence of the disease such as Environmental factors: Increased Humidity: This study analyzed the number of recorded cases to the humidity level in different months comparing between number of cases recorded in certain months and mean absolute humidity level in this month. August has the highest humidity level at 17 mg\m^3 then July at 16 mg\m^3 then September 15mg\m^3 then October and June 13mg\m^3 then November 11 mg\m^3 then December 10 mg\m^3. Increased weather temperature in comparison to fall and early winter months. In Egypt, temperatures range between average winter minimums of 14°C (November to April) and average summer maximums of 30°C [7].

2.1 Patient-Related Factors

Co-morbidities: This study analyzed the number of cases with co-morbidities that may increase the disease incidence focusing mostly on diabetes mellitus (DM) Renal insult and hematological diseases.

2.2 Immune-Compromised Patients

This study analyzed the relationship between disease incidence and factors causing an immune compromised state for COVID-19 patients including The duration and dose of immune-modulators as corticosteroids used as a part of the coronavirus treatment protocol. The level of co-morbidities control during the COVID-19 infection using (random blood sugar (RBS) in D.M patients, Urea and creatinine serum levels in renal patients and WBC count in blood diseases). The level of tissue hypoxia measured by oxygen saturation was recorded during the hospital stay. Presence of neutropenia using CBC test. Level of blood acidity: measured by arterial blood gases (ABG) test.

2.3 Cytokines Storm Event

Evident by the level of lung affection comparing the incidence of the disease to the grade of CORAD classification using Chest CT.

2.4 Ventilation

Type and duration of oxygen delivery method used.

2.5 Local Nasal and Para-Nasal Sinus Factors

This study was focused on the relationship between the disease and the anatomical factors causing increased fungal spores' deposition such as The incidence of the disease starting on the middle turbinate in comparison to other areas in the nose and PNS as it's known that the space between the middle turbinate and nasal septum has the highest air turbulence. The incidence of the disease to anatomical variations causing the increase in air turbulence as the anterior septal deviation is evident by nose and PNS CT scan.

The prognosis of the disease was identified as death because of fungal invasion or eradication of fungal infection without recurrence during the six-month follow-up period using a CT scan as a follow-up method.

2.6 The Prognostic Factors this Study was focused on are

Whether the CO-morbidities are controlled or not: this study analyzed the impact of uncontrolled co-morbidities on the course and prognosis of the disease using RBS as a control indicator for DM, Urea, and creatinine serum level as a control indicator of renal disease and WBCs count as blood disease control indicator. The duration and dose of immune modulators as corticosteroids used as a part of the coronavirus treatment protocol. The level of fungal invasion at the time of diagnosis using MRI scan grading it as follows:[Grade I: fungal invasion confined to nose and PNS, Grade II: fungal invasion reaching one or more facial bone related to nose and PNS including (vomer, palatine bone, maxillary bone, frontal bone), Grade III: fungal invasion reaching extra nasal structures as the orbit - but without reaching the orbital apex- or the brain but the dura still intact and Grade IV: fungal invasion reaching orbital apex, causing intracranial lesion or lung fungal invasion][8].

2.7 Statistical Analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). The Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing an unpaired Student's t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed by Mann Whitneytest. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant.

III. RESULTS

Demographic data, environmental factors, and Co-morbidities (cardiac, multiple myeloma, and

systemic lupus were insignificantly different between both groups. Other Co-morbidities (DM, RF) were a significantly difference between both groups.

Table 1: Comparison between the Two Studied Groups According to Demographic Data, Environmental Factors, and Co-Morbidities

		(Patients (n = 23	(Control (n = 46	p
(Age (years		12.0 ± 55.61	13.70 ± 54.17	0.671
Sex	Male	(43.5%)10	(45.7%)21	0.864
	Female	(56.5%)13	(54.3%)25	
Month	June	(8.7%)2	(10.2%)5	0.545
	July	(17.4%)4	(15.3%)7	
	August	(26.1%)6	(13.1%)6	
	September	(17.4%)4	(8.8%)4	
	October	(8.7%)2	(15.3%)7	
	November	(8.7%)2	(21.8%)10	
	December	(13%)3	(15.3%)7	
(Time of admission (Months	10 – 6	(78.3%)18	(80.4%)37	1.000
	12 – 11	(21.7%)5	(19.6%)9	
Co-Morbidities		(95.7%)22	(32.6%)15	*0.001>
DM		(78.3%)18	(23.9%)11	*0.001>
Cardiac		(4.3%)1	(0.0%)0	0.333
Multiple myeloma		(4.3%)1	(0.0%)0	0.333
RF		(30.4%)7	(6.5%)3	*0.013
Systemic Lupus		(4.3%)1	(0.0%)0	0.333
Anaemic		(4.3%)1	(2.2%)1	1.000

*Data are presented as mean ± SD or frequency (%). * Significant p-value <0.05, DM: diabetes mellitus, RF: Rheumatoid factor.*

CORAD, level of O_2 saturation, ABG PH, steroid therapy dose and duration, duration of O_2 therapy, and anterior septal deviation were insignificantly different between the two studied groups. RBS, neutropenia, and type O_2 therapy were significantly different between the two studied groups. Steroid therapy dose and duration were significantly higher in the patients' group than control group (P<0.05).

Table 2: Comparison between the two Studied Groups according to other Epidemiological factors and Anterior Septal Deviation

		Patients (n = 23)	Control (n = 46)	p
CORAD		3.39 ± 1.12	3.46 ± 0.84	0.946
O_2 saturation		88.70 ± 10.39	90.13 ± 4.75	0.114
ABG PH		7.47 ± 0.06	7.48 ± 0.07	0.628
No		14(60.9%)	34(73.9%)	0.267
Yes		9(39.1%)	12(26.1%)	
RBS		307.0 (184.0 – 345.5)	115.0(94.0 –224.0)	<0.001*
No		1(4.3%)	30(65.2%)	<0.001*
Yes		22(95.7%)	16(34.8%)	
Neutropenia		17(73.9%)	10(21.7%)	<0.001*
Steroid T Dose (mg/day)		132.6 ± 53.53	108.0 ± 39.86	0.172
No		0(0.0%)	31(67.4%)	<0.001*
Yes		23(100.0%)	15(32.6%)	
Steroid T duration (days)		8.50 (6.0 – 11.0)	7.0 (5.0 – 10.0)	0.532
No		0(0.0%)	32(69.6%)	<0.001*
Yes		23(100.0%)	14(30.4%)	
Type O_2 therapy	Nasal Mask	11(47.8%)	18(39.1%)	0.033*
	Ventilator	5(21.7%)	2(4.3%)	
	Room air	7(30.4%)	26(56.5%)	

Anterior septal deviation	12(52.2%)	17(37.0%)	0.227
	(n = 16)	(n = 20)	
Duration O_2 therapy (days)	8.50 (7.0 – 12.0)	7.0 (5.50 – 9.50)	0.190

*Data are presented as mean ± SD or frequency (%) or median (IQR). * Significant p-value <0.05,CORAD: COVID-19 Reporting and Data System, ABG: arterial blood gases, RBS: random blood sugar.*

In the total number of 23 patients 16(69.6%) patients had their middle turbinate as the first site to be affected by the pathology, 3(13%) patients in the right maxilla, 1 (4.3%) patient in the left maxilla, 2(8.7%) patients in the right sphenoid sinus, 1(4.3%) patient in the hard palate.

Table 3: Distribution of the Studied Cases According to Lesion Start in Patients Group
Data are presented as frequency (%)

	N=23
Right Maxilla	(13.0%)3
Left Maxilla	(4.3%)1
Right Sphenoid Sinus	(8.7%)2
Middle Turbinate	(69.6%)16
Hard Palate	(4.3%)1

Data are presented as frequency (%)

Distribution of the studied cases according to prognostic factors patients group shown in Table 4.

Table 4: Distribution of the Studied Cases According to Prognostic Factors Patients Group

		N=23	Death	Resolution
Control	Uncontrolled	(91.3%)21	(61.9%)13	(38.1%)8
	Controlled	(8.7%)2	(0.0%)0	(100%)2
CORAD	I	(8.7%)2	(0.0%)0	(100%)2
	II	(0.0%)0	(0.0%)0	(0.0%)0
	III	(56.5%)13	(38.4%)5	(61.6%)8
	IV	(13.1%)3	(100%)3	(0.0%)0
	V	(21.7%)5	(80%)4	(20%)1
Grading	I	(4.3%)1	(0.0%)0	(100%)1
	II	(13.0%)3	(33.3%)1	(66.7%)2
	III	(56.5%)13	(53.8%)7	(46.2%)6
	IV	(26.1%)6	(66.7%)4	(33.3%)2
Neutropenia		(78.3%)18	(55.6%)10	(44.4%)8
Type O_2 therapy	Nasal Mask	(47.8%)11	(27.2%)3	(72.8%)8
	Ventilator	(21.7%)5	(100%)5	(0.0%)0
	Room air	(30.4%)7	(71.4%)5	(28.6%)2
Treatment	Surgery + systemic antifungal	(52.2%)12	(16.7%)2	(83.3%)10
	Systemic anti-fungal	(100.0%)23	(56.5%)13	(43.5%)10
	Systemic anti-fungal alone	(47.8%)11	(100%)11	(0.0%)0
Outcome	Resolution	(43.5%)10		
	Death	(56.5%)13		

*Data are presented as frequency (%). * Significant p value <0.05, CORAD: COVID-19 Reporting and Data System.*

Case 1: Male, aged 42 years old when diagnosed with AIFRS with orbital affection as a complication for uncontrolled D.M.

Figure 1: A Case of AIFRS Post-Operative

IV. DISCUSSION

During the COVID-19 pandemic, there was an increased incidence of AIFRS which raised the need for studying the factors causing this increased incidence and the possible factors controlling the prognosis of this devastating complication[9].

According to our study, the highest incidence of AIFRS was during the hot weather months from July to October with 78.3% of cases during these months but still the impact of hot weather couldn't be confirmed as the percentage of admitted control cases in these months was also very high, 80.4% of the cases and still the time frame for the hot months was 4 months compared to only 2 months of cold weather November and December.

The patient group had 95.7% of the patients with other co-morbidities compared to a lower percentage of 67.4% in the control group which confirms the importance of the presence of other co-morbidities causing an immune deficient state in the incidence of post-COVID-19 AIFRS infection. This was proven with other research such as Blyth CC et al.[10] showing the close relation between the presence of other co-morbidities and the increased incidence of invasive fungal infection. Diabetes mellitus was the most predominant co-morbidity with as high as 78.3% of all cases compared to only 23.9% of controlled cases. Still, this may be affected by the high incidence of D.M. in Egypt. Still, the effect of D.M. on immunity is undeniable being one of the most common causes of the low immunity state favoring fungal infection worldwide. Schiefer HG et al.[11] studied this relation between D.M. and increased fungal infection. Another example of co-morbidities that may increase the incidence of AIFRS is blood diseases that affect immune cell activity.

The patient group showed a lower O_2 saturation level compared to the control group which confirms the effect of tissue hypoxia and tissue damage in favoring fungal invasion of mucosal barriers. Fungi can benefit from tissue hypoxia in different ways, V. Monceaux et al.[12] showed how hypoxia dampens the oxygen-dependent antimicrobial activities of macrophages and neutrophils, such as the production of reactive oxygen species (ROS), also Blosser SJ et al.[13] showed the impact of hypoxia in decreasing the efficiency of anti-fungal drugs as triazoles and polyenes.

There was a huge gap between the percentage of the patients with high RBS in patients with AIFRS

in the patient group 95.7% and in the control group 34.8% which gives clear evidence of the impact of uncontrolled DM in the incidence of AIFRS. High sugar levels in blood can fuel the growth of fungal colonies; this is supported by Carlile M.J et al.[14] demonstrating how glucose plays a central role in the metabolism of most of the fungi species.

The same was recorded according to the impact of serum neutropenia with 73.9% of the patient group with serum neutropenia compared to 21.7% in the control group. Chamilos G et al.[15] showed how neutrophils play an important role in host defense against invasive candidiasis and aspergillosis by their rapid deployment to the site of fungal invasion and by mediating fungal destruction using an extensive collection of effector mechanisms.

The study showed that both the O_2 therapy method and duration played a role in the incidence of AIFRS as the patient group had a longer duration of O_2 therapy and higher numbers of patients on nasal masks and ventilators compared to the control group. Ventilator use showed the highest incidence increase in the comparison between the patient and control group. Ding et al.[16] showed in their study that long-term ventilation increases the risk of fungal infection, which is caused by humidifiers and ventilator loops that are the source of the fungal pathogen due to exposure as the majority of ICUs are closed units and air circulation is not smooth.

The study showed a very high incidence of AIFRS firstly affecting the middle turbinate 69.6% of all cases compared to other sites. This may show the importance of air turbulence in this area in the fungi deposition ultimately resulting in AIFRS infection still there was no statistical significance in the incidence of AIFRS in patients with anterior septal deviation after comparison between patient and control group. This doesn't go along with what both Wolf M et al.[17] and Grützenmacher S et al.[18]showed that the greatest air turbulence during normal inspiration develops in the limited area between the nasal septum and middle turbinate and how anterior nasal deviation increase this turbulence promoting more spore deposition in this area.

There was no doubt that the uncontrolled co-morbidities played an important role in the bad prognosis of AIFRS cases as 91% of cases resulting in death suffered from uncontrolled co-morbidities. This was the same finding in other studies such as Blyth CC et al.[10] and Schiefer HG et al. [11].

According to the CORAD classification the highest incidence of resolution was between grade I patients but still the highest incidence of death between grade 4 patients which shows the CORAD grading as a possible indicator for AIFRS prognosis among the COVID-19 patients. This may be related to the cytokine release and its relationship with the severity of the disease as described before. Spellberg B et al.[19] described in their study the impact of the degree of fungal invasion and fungal load on the prognosis of AIFRS which was consistent with our finding, the worse the fungal grading the worse the prognosis evident by the highest incidence of death among grade VI patients and the highest incidence of resolution among grade I patients.

Patients with neutropenia showed a slightly higher incidence of death compared to patients without neutropenia. This goes along with what Tobias E. Rodriguez et al.[19] described in their study about the role of Neutrophils in preventing and resolving acute fungal sinusitis.

Our study showed that among the different O_2 delivery methods ventilators had the worst prognosis which shows the role of ventilators use in providing a suitable environment favoring AIFRS infection in COVID-19 patients. Ding et al.[16]described in their study how ventilator loops are a continuous source of fungal spores increasing the fungal burden on COVID-19 patients.

Limitations of this study included that the sample size was relatively small. The study was in a single center.

V. RECOMMENDATION

There must be a proper control for factors reducing immunityfor reducing the incidence of AIFRS such as other co-morbidities, especially D.M. Steroid therapy should be used in such cases with great caution only in recommended cases with proper monitoring for the dose and duration of the treatment. Tissue hypoxia and serum acidity should be avoided with proper treatment modalities in those patients to avoid the risk of AIFRS. Patients suffering from other mentioned risk factors that can't be avoided should be monitored closely for early detection of AIFRS. For a better prognosis in AIFRS patients, there must be close control of other co-morbidities, treatment of tissue hypoxia, and early detection of the disease before further fungal invasion. The use of ventilators only in recommended cases with close monitoring of their cleanliness especially between cases and in their use for long periods for the presence of fungal contamination and finally surgical debridement should be a cornerstone in the treatment protocol of AIFRS cases.

VI. CONCLUSIONS

The Epidemiological factors increasing the incidence of AIFRS in post-COVID-19 patients: Environmental Factors: Increased humidity, other Epidemiological factors [reduced immunity due to: the presence of other Co-morbidities, uncontrolled D.M, steroid therapy, serum neutropenia, tissue hypoxia, increased serum acidity, cytokine storm event, and the use of ventilators as a method of O_2 therapy] and anatomical factors: infection Favors nasal areas with increased nasal air turbulence. The Prognostic factors favoring bad prognosis: Uncontrolled Co-morbidities, high CORAD grade, high grade of fungal invasion, serum neutropenia, the use of ventilators as an O_2 delivery method, and medical treatment alone without surgical treatment.

List of Abbreviations

AIFR: Acute Invasive fungal rhinosinusitis
ABG: arterial blood gases
AIDS: acquired immunodeficiency syndrome
CBC: complete blood count
CRP: C- reactive protein
COVID-19: coronavirus disease-19
CORAD: COVID-19 reporting and data system.
CT: computed tomography
DM: diabetes mellitus
ESR: erythrocyte sedimentation rate
RBS: Random blood sugar
HbA1c: glycated hemoglobin
MRI: magnetic resonance imaging
LDH: lactated dehydrogenase
PNS: Paranasal Sinuses
PCR: polymerase chain reaction

Declarations

Ethics Approval and Consent to Participate

The study was done from June 2021 to December 2021 after approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt. (Approval code: 35036/11/21). An informed written consent was obtained from the patients.

Consent for Publication

Consent for publication was taken.

Availability of Data and Materia

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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