

ORIGINAL

## Epidemiological Insights into Invasive Fungal Rhinosinusitis among COVID-19 Inpatients: Unveiling Diverse Pathogens with implications on cancer patients

### Perspectivas epidemiológicas sobre la rinosinusitis fúngica invasiva en pacientes hospitalizados con COVID-19: Revelando diversos patógenos con implicaciones para los pacientes con cáncer

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**Cite as:** Patro PS, Mane A, Rami E, Ojha V, Kaushik V, Swathi V. Epidemiological Insights into Invasive Fungal Rhinosinusitis among COVID-19 Inpatients: Unveiling Diverse Pathogens with implications on cancer patients. Health Leadership and Quality of Life. 2025; 4:591. <https://doi.org/10.56294/hl2025591>


Submitted: 26-05-2024

Revised: 10-12-2024

Accepted: 18-05-2025

Published: 19-05-2025

Editor: PhD. Neela Satheesh 

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#### ABSTRACT

The emergence of invasive fungal rhinosinusitis (IFRS), as well as COVID-19 at the same time, poses a challenge to patients receiving treatment in hospitals. Research have shown various infections caused by fungi that relate to the epidemiology of invasive fungal rhinosinusitis among patients suffering from COVID-19. In this retrospective analysis, examined mycological investigations, subject characteristics, clinical manifestations, antifungal drugs used and length of illness among 68 patients diagnosed with Acute Invasive Fungal Rhinosinusitis (AIFRS). The research results indicated that steroid therapy was applied in 32,81 % of cases and more than half of examines were men. The necessity for early detection is highlighted by the variety of clinical symptoms of headaches (22,40 %). Tissue culture, histological analysis and molecular identification of culture isolates were all part of the mycological research. Amphotericin B (30,21 %) and Nystatin (22,40 %) were the antifungal drugs utilized, indicating a customized approach to therapy. The length of the disease varied by 22,92 % of patients reported symptoms lasting between 16 and 30 days. The age distribution showed that the 50 to 59 age group accounted for a significant amount (13,02 %). The research highlights the vital need for caution while identifying and treating AIFRS in COVID-19 inpatients, with a focus on a variety of infections and specialized treatment modalities.

**Keywords:** Acute Invasive Fungal Rhino-Sinusitis (AIFRS); COVID-19 Inpatients; Epidemiology; Pathogen Diversity; Coexisting Infections.

#### RESUMEN

La aparición simultánea de la rinosinusitis fúngica invasiva (RIFI), así como de la COVID-19, representa un desafío para los pacientes hospitalizados. Diversas investigaciones han demostrado la presencia de diversas infecciones fúngicas relacionadas con la epidemiología de la rinosinusitis fúngica invasiva en pacientes con COVID-19. En este análisis retrospectivo, se examinaron las investigaciones micológicas, las características de los pacientes, las manifestaciones clínicas, los fármacos antifúngicos utilizados y la duración de la enfermedad

en 68 pacientes diagnosticados con rinosinusitis fúngica invasiva aguda (RIFIA). Los resultados de la investigación indicaron que se aplicó terapia con esteroides en el 32,81 % de los casos y que más de la mitad de los pacientes eran hombres. La necesidad de una detección temprana se ve resaltada por la variedad de síntomas clínicos de cefalea (22,40 %). El cultivo de tejidos, el análisis histológico y la identificación molecular de los aislados de cultivo formaron parte de la investigación micológica. Los fármacos antifúngicos utilizados fueron anfotericina B (30,21 %) y nistatina (22,40 %), lo que indica un enfoque terapéutico personalizado. La duración de la enfermedad varió en un 22,92 % de los pacientes, quienes reportaron síntomas con una duración de entre 16 y 30 días. La distribución por edad mostró que el grupo de 50 a 59 años representó una proporción significativa (13,02 %). La investigación destaca la vital necesidad de precaución al identificar y tratar el síndrome de fiebre aftosa aguda (SFA) en pacientes hospitalizados por COVID-19, con especial atención a diversas infecciones y modalidades de tratamiento especializadas.

**Palabras clave:** Rinosinusitis Fúngica Invasiva Aguda (AIFRS); Pacientes Hospitalizados con COVID-19; Epidemiología; Diversidad de Patógenos; Infecciones Coexistentes.

## INTRODUCTION

A serious perhaps lethal disease known as Invasive Fungal Rhinosinusitis (IFRS) is caused by fungus invading the paranasal sinuses and surrounding tissues. Because of its immediate course and potential for complications, this illness presents a substantial therapeutic challenge. Therefore, epidemiological insights are essential to comprehend the incidence, associated risks, and worldwide health effect.<sup>(1)</sup> Although IFRS cannot be highly prevalent, its occurrence has been increasing, especially in individuals with immuno-compromised conditions which could be related to environmental variables though IFRS can affect everyone at any age, it is mostly seen in adults, particularly in those with underlying medical illnesses that weaken their immune systems.<sup>(2)</sup> Determining the people individuals could be more exposed to IFRS requires an understanding of the risk variables related to the disease. The risk of IFRS is raised in immuno-compromised situations, such as carried on by solid organ transplantation, blood cancers, or long-term steroid treatment.<sup>(3)</sup> The most prevalent *Aspergillus* species that cause IFRS are *Aspergillus fumigatus*. Nonetheless, invasive fungal infections in the sinonasal area are also being caused by other fungi, such as *Mucorales* and dematiaceous molds.<sup>(4)</sup> IFRS has a greater effect on public health because of its severity and propensity for consequences, even though it is not common as other respiratory illnesses. A significant financial burden on healthcare systems results from the conditions frequently need for expensive medicinal and surgical procedures.<sup>(5)</sup> Early-stage symptoms of IFRS include headache, face discomfort and congestion in the nasal passages. The need for early identification and treatment is highlighted by the symptoms of rapid development. Early identification of IFRS is crucial to improve patient outcomes and reduce morbidity and mortality from their condition.<sup>(6)</sup> Researchers and practitioners in medicine are focused on the relationship between infectious illnesses and the vulnerability to opportunistic fungal infections. IFRS is increasing in COVID-19 patients. The current health crisis has presented hitherto of unseen difficulties in the treatment of SARS-CoV-2-related viral respiratory disease.<sup>(7)</sup> Medical practitioners and academics are focused on the relationship between opportunistic fungal infections and infectious disease susceptibilities. In addition to present hitherto unheard-of difficulties in treating the SARS-CoV-2 virus-induced respiratory disease, the current worldwide pandemic has highlighted the complex interactions between infectious viruses and subsequent fungal consequences.<sup>(8)</sup> COVID-19 patients are more susceptible to secondary infections, especially those caused by fungi, due to the complex immunological disruptions that the virus induces. Prolonged hospitalization and intensive care are required for severe COVID-19 cases, exposing patients to a variety of nosocomial risks, such as opportunistic fungi.<sup>(9)</sup> Invasive fungal problems are possible because the immuno-compromised condition caused by severe COVID-19 that becomes worse by the use of steroids and other immune-modulating medications to treat the viral infection.<sup>(10)</sup> There are several difficulties in the clinical setting of IFRS for COVID-19 hospital patients. Healthcare professionals have diagnostic challenges while treating patients with IFRS since its symptoms, which include headaches, facial discomfort and congestion in the nose, can mimic those of severe COVID-19 or other respiratory illnesses.<sup>(11)</sup> The potential for severe issues treatment becomes more difficult because to the rapid progression of IFRS and such visual and brain involvement. Since delayed cares are worsen the severity of disorders, understanding the unique characteristics of IFRS in the context of COVID-19 is essential for prompt diagnosis and action.<sup>(12)</sup> The delicate balance of the microbiota is disturbed by the use of immune suppressive treatments and broad-spectrum antibiotics in the treatment of COVID-19, which puts patients at risk for fungal overgrowth. Determining the precise preventative measures and treatment approaches to lessen the effects of IFRS in the context of COVID-19 requires an understanding of these complex relationships.<sup>(13)</sup> Despite the complexities of clinical care, the public health consequences of IFRS among COVID-19 in patients are significant. Extended hospital admissions, the possibility of higher death,

morbidity rates, the need for costly medical and surgical procedures add the overall strain that the pandemic's demands have placed on healthcare systems.<sup>(14)</sup> The research provides guidance for clinical efforts aimed at improving patient care in spite of these interdependent competitors as the medical community continues to manage the difficulties restored by the coexistence of COVID-19 and opportunistic fungal infections.

Examining immunocompromised populations and specific risk variables, the research examined the incidence of AIFRS in COVID-19 patients. The three main pathogens were *Absidiomucor*, *Aspergillus fumigatus*, and *Rhizopusoryzae*.<sup>(15)</sup> Immuno-compromised people were vulnerable to Acute Invasive Fungal Rhinosinusitis (AIFRS). Due to its well-known effects on immunological dysregulation and respiratory health, COVID-19 raises concerns for secondary fungal infections. It was becoming increasingly apparent that COVID-19 individuals have fungal respiratory super infections.<sup>(16)</sup> However, there was a dearth of research on acute invasive fungal sinusitis in the particular context. The purpose of the research was to close the knowledge gap by highlighting the need of early intervention to improve outcomes and increase survival rates. The comorbidities, clinical traits, course of the illness, and prognosis of rhino-orbito-cerebral invasive fungal disease that was unrelated to COVID-19 were compared in research.<sup>(17)</sup> Non-COVID individuals had higher HbA1c and blood sugar levels, but COVID cases showed longer hospital stays and higher steroid usage. Diabetes surfaced as a major risk factor and survival rates varied. Better results were associated with surgical therapy, highlighting the need of combining medicinal and surgical strategies. Using a retrospective analysis, the research looked at invasive fungal sinusitis associated with COVID-19 in 124 people.<sup>(18)</sup> The research underscores the important roles that steroid usage, glycemic management and serum ferritin play in the development of illness and identifies important risk variables, such as comorbidities and drugs. The investigation was prompted by the lack of understanding of COVID-19 patients' mixed invasive fungal infections (MIFIs), which was highlighted in the research that comprised 10 cases of COVID-associated mucormycosis-aspergillosis. The results emphasized how crucial early diagnosis has to put into practice successful treatment techniques in the face of the pandemic's changing fungal epidemic.<sup>(19)</sup> 206 cases of COVID-19-associated aggressive fungal sinusitis were documented, and 68,0 % of those cases were found to have occurred in India, according to research.<sup>(20)</sup> The most common variables were steroid usage (65,0 %) and diabetes (73,3 %). Diabetes and steroid usage were prevalent in the center's case series and the prevalence of IFS did not decrease after the pandemic. In those with COVID-19 rhinosinusitis, the research looked at the different fungus species, clinical signs, and associated comorbidities.

<sup>(21)</sup> Acute fulminant fungal rhinosinusitis, due to *mucor* was notably associated with a considerable risk of diabetes, highlighting the crucial need of prompt diagnosis and treatment. Eleven incidences of co-infection between rhino-orbital mucormycosis (ROM) and severe COVID-19 individuals were found, according to the research, which involved a prospective observational analysis of 32,814 patients. Together with the association of severe COVID-19, the research emphasized the impact of steroid use, immunological dysregulation and higher mortality rates.<sup>(22)</sup> The evidence supports enhancing physician knowledge and using a multidisciplinary approach to lower ROM-associated mortality. In particular, magnetic resonance imaging (MRI) and computed tomography (CT) scans are essential for the diagnosis of fungal rhinosinusitis, according to a research.<sup>(23)</sup> It highlighted the dangers of depending on radiological modalities and promotes thorough diagnosis strategy that incorporates microbiological methods such as KOH microscopy and culture together with clinical correlation. The research which included 57 suspected cases highlighted the shortcomings of a single diagnostic approach and recommended a combination approach that includes both radiological and microbiological evaluations for patients that were clinically ambiguous. It focused on the ongoing debate on the factors that increase the risk of invasive fungal sickness in COVID-19 patients.<sup>(24)</sup> It highlighted the need of steroid consumption, especially in diabetics, by doing a retrospective investigation of instances of mucormycosis related with COVID-19. Larger, longer-term researches were necessary to uncover common predisposing variables, according to the results. As fungal co-infections in respiratory virus patients were increasingly identified to have a mortality effect, the research concentrated on the issue.<sup>(25)</sup> The research highlighted the lack of complete information on invasive fungal illness related with COVID-19, which has led to a nationwide, multicenter, prospective assessment to ascertain incidence, risk factors and outcomes. The results confirmed the significance of antifungal medication by showing a significant incidence (26,7 %) and increased death rates in individuals with fungal illness. In addition to suggesting antifungal prophylaxis for COVID-19 patients, the research emphasized the efficacy of a strategic diagnostic approach in improving overall care.

## METHOD

### Dataset

It uses in-house MRI data from 68 patients who were diagnosed with AIFRS to do a retrospective analysis. Insights into diagnosis and therapy within a Comprehensive Antifungal Management program are provided by the dataset, which contains factors including patient demographics, clinical symptoms, comorbidities, imaging results, therapies received, and outcomes.

### **Mycological research**

Fungal components often necessitate a detailed examination for mycological investigations to establish the aetiological agent in AIFRS patients. Taking tissue samples from nose or sinuses to isolate and characterize the specific type of fungus causing the disease. Certain unique features of the attacking fungus as well as extent of mycosis can be seen under microscope when looking at every slice of tissue collection. Blood tests also exist that intend to find specific antifungal antibodies or antigens which are unique to fungal infections. Fungal Deoxyribonucleic acid (DNA) is found and identified using molecular techniques like polymerase chain reaction (PCR) which guarantees an accurate and timely diagnosis. To identify the fungus responsible for the disease, blood tests are important in detecting certain antigens or antibodies linked to fungal infections. The effectiveness of any antifungal therapy should be determined by whether or not the isolated fungus is sensitive to existing antifungal drugs. This allows for an easier identification of the organism that causes the disease. During and after antifungal treatment, common imaging techniques including follow-up MRI scans help monitor the progress or regression of these fungal lesions. This mycological research offers guidance in the identification of precise fungal infections, the guiding of treatment options and evaluation of patients' responses to medication in AIFRS instances. This avails significant information on the effectiveness of such treatments. Therefore, effective mycological research is demanded by certain important aspects in AIFRS cases including identification of specific fungal infection, direction of treatment options, and assessment of patients' responses to drugs.

### **The culture isolates of molecular identity**

Microorganisms, which have been identified and grown from the biological materials, are being identified very accurately with the use of a complex method known as Molecular Identification of Culture Isolates in microbiology. Molecular identification instead focuses on genetic composition of such isolates unlike traditional approaches that emphasize on the assessment of their physical and chemical properties thereby leading to more accurate results. The introduction molecule biology instruments, such as DNA sequencing and polymerase chain reaction (PCR), forms a basis for this method. The only target segments of the microbial genome can be focused on, so that the nucleotide sequence of the respective organisms from which appear can be specified, isolated and analyzed. For example, fungi have their internal transcribed spacers while bacteria have their 16S Ribosomal ribonucleic acid (RNA) genes as focused areas. A major advantage of molecular identification is its high degree of specificity and sensitivity than that exhibited by traditional methods. It capable to tell the difference between strains in a species and can even tell them apart from similar species by examining the genetic code. Such level of detail is useful particularly in health care settings where accurate pathogen identification is important for effective management of diseases. Additionally, using molecular methods identification of microorganisms is with speed. This is extremely important in clinical settings because one can need to identify various microorganisms that are hard or take a long time to grow accurately and rapidly.

### **Data analysis**

In the data analysis, descriptive statistics were employed, and the distribution of the variables was displayed using percentages and proportions. This technique gave a concise summary of the dataset's contents. The T-test was used to look into associations between measured variables. Because it can be used to assess the significance of observed fluctuations, the T-test is useful for continuous data. This dual method allows the analysis to combine a broad grasp of the structure of the dataset with a concentrated evaluation of particular variable interactions, which helps to provide a nuanced interpretation of the results.

## **RESULTS**

The outcome provides important patient characteristics such as age groups, sex distribution, clinical signs and duration of disease, predisposing variables and antifungal treatment. There are substantial links with clinical symptoms, the majority of findings are male and steroid use is prevalent. Understanding patient characteristics and treatment patterns is made possible by these insights.

The data considering indicates predisposing variables that are common underlying illnesses among patients. Steroid treatment was the most prevalent factor, impacting 32,81 % of the population, suggesting possible immune system regulation. Significant contributions from diabetes mellitus and hypertension, which affected 21,88 % and 13,02 % of the population, respectively, highlight the importance of cardiovascular and metabolic health. Heart diseases, hyperlipidemia and deviated nasal septum were the conditions that were noteworthy and provided insight into nasal anatomical and cardiovascular issues.

Figure 1 and table 1 illustrates the patients' varied medical histories including examples of kidney disease/failure, asthma, hypothyroidism and cancer. Allergies and a transplant history point to possible immunological complications. Furthermore, a distinct category of 0,52 % had no discernible predisposing variables. This awareness of predispositions is essential for treating patients with AIFRS in a variety of medical scenarios and

customizing treatment plans.

Table 1. Factors Predisposing Acute Fungal Patients	
Predisposing factors	Patients
transplantation	1(0,52 %)
No Predisposing Factor	1 (0,52 %))
Treatments with steroids	63 (32,81 %)
Diabetes Mellitus	42(21,88 %)
Hypertension	25(13,02 %)
Heart Diseases	15(7,29 %)
Hyperlipidemia	14(7,29 %)
Deviated nasal septum	10(5,21 %)
Kidney disorder / failure	7(3,65 %)
Asthma	5(2,60 %)
Hypothyroidism	4(2,08 %)
Malignancy	3(1,56 %)
Allergy	2(1,04 %)

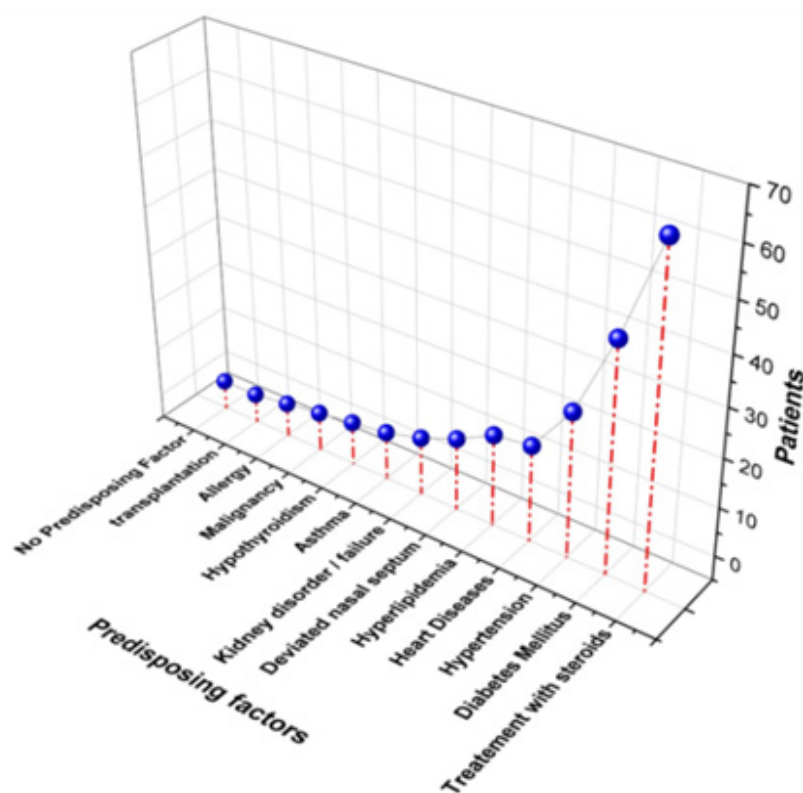


Figure 1. AIFRS Patients' Distinct Medical History

The visible indicators and symptoms that patients display to provide information about the nature of a medical disease are referred to clinical manifestations. The following list of signs of AIFRS represents a spectrum of symptoms that peopleswere encounter. With 22,40 % reporting headaches, this is a prevalent and severe symptom. Specific face pain locations are highlighted by Retro-Orbital Pain, Eyelid Swelling, and Nasal Intonation.

Possible neurological and sensory effects are shown by table 2 and figure 2 which show facial numbness, diminished vision, and loosening of the teeth. Epistaxis and Blindness indicate grave repercussions. Even though are uncommon, dysarthria and seizures highlight the neurological features. Changes in structure are indicated by facial deviation. Recognizing these symptoms contributes to prompt diagnosis and focused therapy, which are essential for managing the complications of AIFRS.



Table 2. Clinical Signs in Patients with AIFRS	
Clinical Manifestation	Patients
Headache	43 (22,40 %)
Restro-Orbital Pain	34(17,71 %)
Eyelid Swelling	17(8,85 %)
Nasal intonation	12(6,25 %)
Facial Numbness	13(6,77 %)
Diminution of vision	20(10,42 %)
Tooth loosening	10(5,21 %)
Epistaxis	9(4,69 %)
Blindness	10(5,21 %)
Dysarthria	16(8,33 %)
Seizure	3(1,56 %)
Facial deviation	5(2,60 %)

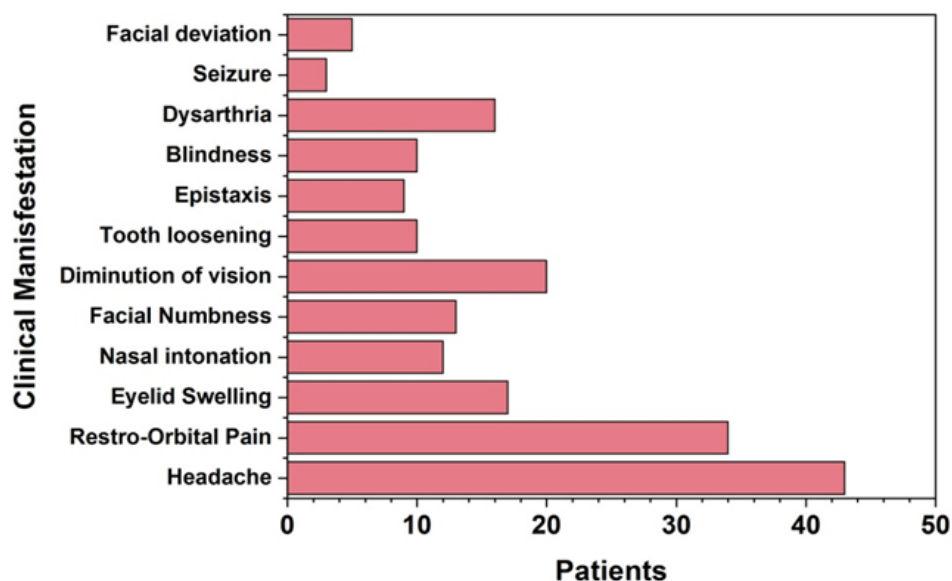


Figure 2. Neurological effects of AIFRS

Table 3 and figure 3 presented to explain the use of antifungal drugs in patients, which are therapeutic treatments, intended to fight fungal infections. 30,21 % of patients received amphotericin B, a broad-spectrum antifungal that is used to treat serious infections. At 22,40 %, nystatin is used to treat infections of the mucosa. The range of 11,46 % to 20,83 % for propionate, casposporin, and voriconazole shows the variety of antifungal treatments available, taking into account factors like patient circumstances and particular fungal strains.

Fluconazole is an effective antifungal with 6,25 % potency. The selection of these drugs reflects a customized approach to care, considering factors including the kind and severity of the disease, the characteristics of the patient, and medication interactions. A wide range of antifungal medications available, it is crucial to have tailored treatment plans for AIFRS to maximize benefits and reduce side effects.

Table 3. Patient Treatment Antifungal Drug Distribution	
Antifungal medication	Patients
Amphotericin B	58(30,21 %)
Nystatin	43(22,40 %)
Voriconazole	40(20,83 %)
Caspofungin	22(11,46 %)
Posaconazole	17(8,85 %)
Fluconazole	12(6,25 %)

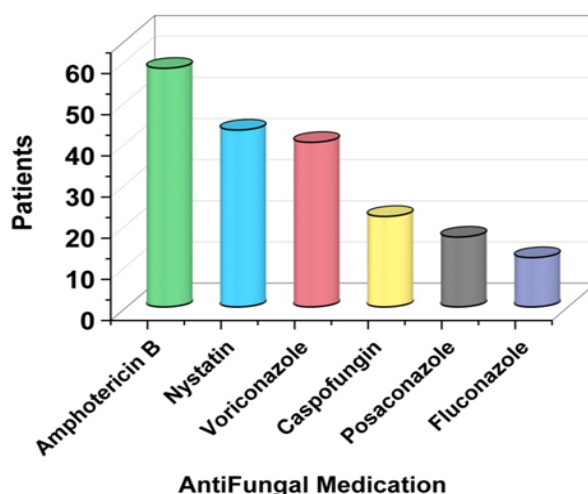


Figure 3. Antifungal Medication Distribution in AIFRS Patients

AIFRS symptoms were experienced by individuals during the course of their disease, as shown in the table 4 and figure 4 data that were supplied. Within the cohort, the distribution shows the different durations of disease. 26,04 % of patients had symptoms for one to fifteen days, which is a majority that represents instances with shorter durations. Notably, 22,92 % of the patients had symptoms that lasted for 16 to 30 days, indicating a longer duration.

The following groups, which span 11,46 % to 7,81 %, identify patients whose stays exceed 105 days. This wide range of duration highlights the variability of the disease's temporal expression, suggested to vary degrees of severity and therapeutic responsiveness. For doctors to assess the course of disease, choose the best course of action and assess the effectiveness of treatment across a range of time periods, must have an understanding of the length of the illness. It helps the patient management plans based on the unique temporal progression of the ailment and provides insightful information about the dynamic nature of AIFRS.

Table 4. AIFRS patients' period of illness	
Duration of illness (days)	Patients
1 day - 15 days	50 (26,04 %)
16 days - 30 days	44 (22,92 %)
31 days - 45 days	22(11,46 %)
46 days - 60 days	37(19,27 %)
75 days - 90 days	24(12,50 %)
91 days - 105 days	15(7,81 %)

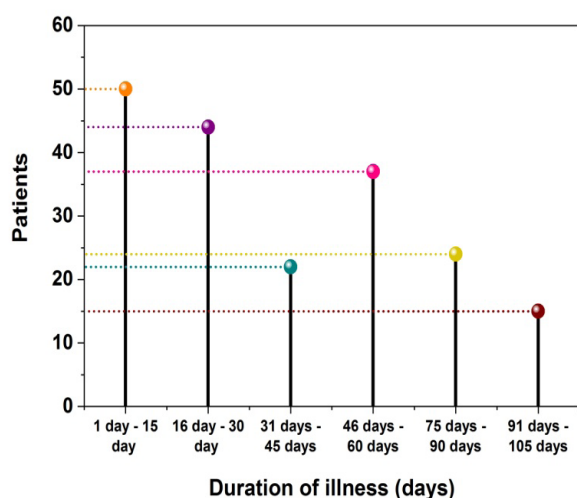


Figure 4. Temporal Manifestation of Symptoms of AIFRS

The age distribution of patients with AIFRS is shown in table 5 and figure 5. A breakdown of instances by age group is provided by the data, which sheds illumination on the condition's demographic distribution. Notably, the biggest cohort (13,02 %) is composed of people aged 50 to 59, suggesting a possible age-related vulnerability.

With corresponding percentages of 13,02 % and 14,06 %, the age categories of 40 to 49 and 70 years, beyond it have notable presence. However, the lack of instances in the age ranges of 20 to 29 points to possible age-related trends. It is essential to comprehend the age distribution to identify demographic predispositions, guide healthcare planning and can be identify age-specific risk factors linked to AIFRS.

Table 5. Age Distribution of Patients with AIFRS	
Age wise Distribution	Patients
0 years- 20 years	40 (20,83 %)
20 years- 29 years	30 (15,63 %)
30 years- 39 years	25 (13,02 %)
40 years- 49 years	25(13,02 %)
50 years- 59 years	25 (13,02 %)
60 years -69 years	20 (10,42 %)
70 years and above	27 (14,06 %)

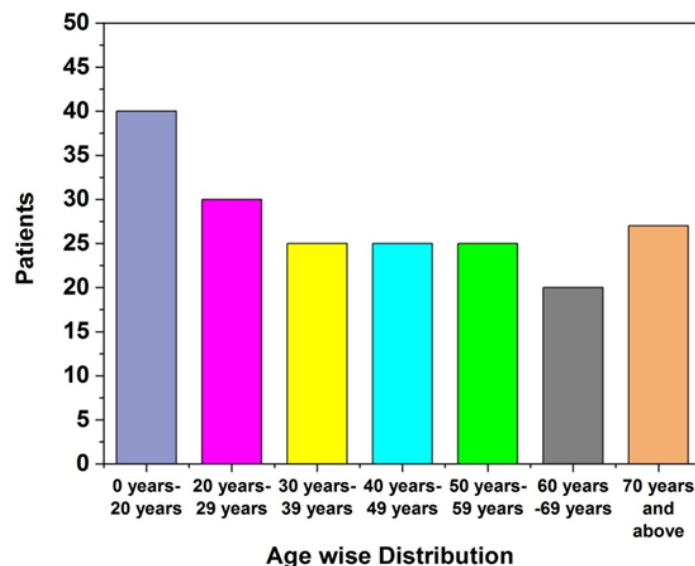


Figure 5. Age wise distributors

## DISCUSSION

The research on AIFRS in COVID-19 inpatients offers an examination of a challenging medical situation that has drawn more attention as a result of the pandemic. The conversation covers a range of topics, providing insight into the clinical, epidemiological and therapeutic implications of AIFRS in relation to COVID-19. It has inherent challenges with AIFRS diagnosis, particularly when dealing with COVID-19. Due to their common symptoms (headaches and nasal congestion), invasive fungal infections and COVID-19 respiratory manifestations need a sophisticated approach to differentiate them. The quick development of IFRS symptoms highlights the need of increased clinical awareness and underscores the necessity of early detection. The predisposing variables analysis highlights the high rate of steroid therapy in the patient group and highlights its possible contribution to immune system dysregulation. The incidence of ailments including cardiovascular disease, hypertension and diabetes mellitus complicates the understanding of underlying health problems linked to AIFRS. The clinical manifestations of AIFRS shed light on the range of symptoms that patients may encounter. Results provide a solid foundation for better diagnosis and treatment methods in this complex medical situation by advancing the knowledge of epidemiological trends, clinical symptoms and therapeutic approaches.

## CONCLUSION

The research clarified the way of fungal rhinosinusitis interacts with COVID-19 inpatients. The results highlight



customized treatment approaches and highlight the need of early detection. Patient management requires a complex and individualized approach due to the multiple nature of predisposing variables and the changing clinical spectrum. The research drop illumination on the multifaceted aspects of AIFRS, emphasizing the importance of mycological investigations in identifying the causative fungi and guiding effective treatment strategies. The predominance of males and the high prevalence of steroid usage as a predisposing factor underscore the need for targeted preventive measures and awareness campaigns. The diversity of clinical manifestations, ranging from common symptoms like headaches to severe neurological complications, necessitates vigilant monitoring and prompt intervention. The choice of antifungal medications, including broad-spectrum agents like Amphotericin B, highlights the individualized nature of treatment plans based on fungal susceptibility. The varied duration of illness emphasizes the dynamic nature of AIFRS, requiring tailored patient management approaches. The age distribution findings suggest potential age-related vulnerabilities, warranting further investigation. Overall, the research contributes valuable insights into the clinical, mycological and demographic facets of AIFRS, providing a foundation for improved diagnostics, treatment and public health strategies. Developing efficient diagnostic techniques for early AIFRS diagnosis and looking into the long-term effects on COVID-19 survivors are important topics of research. Comprehensive AIFRS treatment requires evaluating the efficacy of preventative interventions, including vaccination, in populations at high risk.

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## FINANCING

The authors did not receive financing for the development of this research.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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