Site-Based Comparative Analysis of Sample Collection Through Direct Biopsy and Nasal Swabs for Early Diagnosis of Post-COVID Rhinomaxillary Fungal Infection Using Potassium Hydroxide Mounting: A Retrospective Cohort Study

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Abstract
Aim To perform site-based comparative analysis for samples collected from the nasal region and oral cavity subjected to microscopic detection of fungal hyphae in KOH mount in a group of patients with rhinomaxillary mucormycosis.
Methodology Forty patients fulfilled eligibility criteria. The diagnostic outcome of detection of fungal hyphae from the KOH samples obtained was the primary endpoint of the study. Based on this, the samples were grouped into three groups viz—oral, nasal and both. The secondary outcome was to check if there was any diagnostic delay in these three groups of patients.
Results The mean number of days for delayed diagnosis for oral site involvement was 56.33 ± 37.53, for nasal involvement was 32.86 ± 19.53 and for both oral and nasal involvement was 22.00 ± 12.94. This difference was statistically significant at p = 0.03. The mean delay in diagnosis was significantly less when both oral and nasal regions are involved as compared to the only oral region involved at \( P = 0.01 \).
Conclusion To avoid the chance of delayed diagnosis or false-negative results, it is best to collect samples from both nasal tissues and the most representative site in the den-toalveolar segment depending on the extensiveness of the disease.

Keywords Zygomycosis · Mucormycosis · Delayed diagnosis · Corticosteroids · KOH

Introduction
Mucormycosis (previously called zygomycosis) is a rare but serious angioinvasive infection caused by a group of fungi called mucormycetes. When inhaled, spores of these ubiquitous fungi can infect the lungs, and paranasal air sinuses and may even involve the brain and eyes. Mucormycosis mainly affects people who are immunocompromised and in patients already infected with other diseases. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population. The prevalence of the disease has risen in the past several decades, possibly because of the increased use of steroids, cytotoxic drugs, and other immunosuppressive medical therapies (such as bone marrow transplants) or simply because of the increased recognition lately [1]. The current trend indicates a surge in the disease burden in those with pre-existing diabetes, systemic corticosteroids, and patients infected and/or recovered from SARS-CoV-2 (COVID-19) infection. India had reported a recent surge in mucormycosis cases with an estimated prevalence of 140 per million population, which is about 80 times higher than the prevalence in developed countries. Being an aggressive, life-threatening infection requires prompt diagnosis and early treatment for successful management.

The diagnosis of mucormycosis itself is challenging as the clinical approach to diagnosis lacks sensitivity and specificity [2]. Definitive diagnosis is performed by...
Various specimens can be considered for microscopy depending upon the clinical manifestations and the site of infection. Direct microscopy of a fresh tissue sample with a few drops of potassium hydroxide (KOH) helps to identify the typically broad, hyaline, ribbon-like, irregular fungal hyphae with wide-angle branching. This is accompanied by tissue necrosis and angioinvasion of the fungi giving us a presumptive diagnosis. Early treatment with specific antifungal drugs is of utmost importance to reduce the morbid state.

In our clinical setting, many patients suspected to have rhinomaxillary mucormycosis were found KOH negative on multiple nasal pus swabs and nasal biopsies despite being clinically symptomatic and with radiographically subtle changes not suggestive of evident necrosis where debridement or surgical exploration is not indicated. This led to delayed diagnosis and thereby led to a more destructive lesion at a later stage. However, when subjected to alveolar bone biopsies and sinus biopsies, samples detected fungal hyphae.

This study aimed to perform a site-based comparative analysis for samples collected from the nasal region (swabs, biopsy) and oral cavity (sinus lining, alveolar bone from extracted socket) subjected to microscopic detection of fungal hyphae in KOH mount for early diagnostic screening in a group of patients suspected for rhinomaxillary mucormycosis based on the history in the endemic.

Materials and Methods

This study was approved by our Institutional Ethics Committee (AIIMSPR/RC/P/2021/385). Data of all patients admitted to the Department of Dentistry were retrospectively studied for 5 months. All the patients with suspected mucormycosis who were subjected to the KOH mount from both nasal swabs/nasal endoscopic biopsies and biopsies from alveolar bone/dental extraction sockets/ maxillary sinus lining were eligible to be included in the study. These cases in India surged shortly as a sequel to COVID-19 infection, so the study participants included had a history of COVID-19 infection. The diagnostic outcome of the detection of fungal hyphae from the KOH samples was the primary endpoint of the study. Based on this, the samples were grouped into three groups viz—Group I: Oral being patients positive for biopsies from the necrotic alveolar bone, sinus lining; Group II: Nasal being patients positive for biopsies from nasal tissues and pus swabs and Group III: Both being patients positive for biopsies from the nasal and oral cavity.

The secondary outcome was to check if there was any diagnostic delay in these three groups of patients. Diagnostic delay was defined as the combined patient delay (time from first symptoms until presentation to a health practitioner) and professional delay (time from first presentation to microscopic detection of fungal elements) in days. Any delay over 30 days was considered to be a significant addition to the disease burden.

The characteristics studied were the extent of clinical disease by assessing extraoral, intraoral and nasal endoscopic findings, radiographic evidence of disease involving rhinomaxillary complex, the duration for establishing diagnosis after first clinical symptom (diagnostic delay), host factors like uncontrolled random blood glucose, postoperative evidence of recurrent infection and incidence of wound dehiscence after total surgical debridement. Patients with missing data ailing the study outcomes were excluded from the study.

Two data abstractors were appointed to review data retrospectively. The first investigator determined the procedure or location of the biopsy site for each patient along with clinical and radiographic data in the present case record format. The second investigator recorded the KOH laboratory results (outcome) for the patients satisfying the eligibility criteria. Names were redacted from the reports by a third person before outcome data abstraction to avoid any form of bias. Thus, the possibility of selection and reporting bias was eliminated. All the demographic and quantitative data were presented as degrees of distribution and graphs.

Statistical Analysis

Association among variables like diagnostic delay were examined using the Kruskal–Wallis test followed by Mann–Whitney post hoc test based on the site involved. All categorical data were assessed by the Chi-square test for each group. A p-value of <0.01 was considered to be statistically significant.

Results

Over the study period, 85 patients were admitted to the Department of Dentistry for treatment of rhinomaxillary mucormycosis. Of these, 40 patients fulfilled the eligibility criteria, and data of these patients were recorded. Any missing data essential to establishing primary outcomes were excluded.

Patients were divided into three groups based on KOH mount results from oral positive, nasal positive and both positive groups. The characteristics of patients are given in Table 1. The mean age of patients for Group I was 47.33 ± 13.34 years, for Group II was 46.71 ± 8.44 years and for both sites were 49.00 ± 12.00 years. Males were more predominantly distributed [57.1 – 71.4%] in all three KOH-specific sites as compared to females [14.3 – 42.9%].
Table 1  Patient characteristics in each group

Age and gender distribution based on KOH-specific sites

| Variable | Category | Oral | Nasal | Both | P-value |
|----------|----------|------|-------|------|---------|
|          | Mean     | SD   | Mean  | SD   | Mean    | SD     |
| Age      | Mean     | 47.33| 13.34 | 46.71| 8.44    | 49.00  | 12.00  | 0.93<sup>a</sup> |
| Range    | 27–73    |      | 36–61 | 34–62|         |        |        |                 |
| n        | %        | n    | %     | n    | %       |        |        |                 |
| Gender   | Males    | 15   | 71.4% | 6    | 85.7%   | 4      | 57.1%  | 0.50<sup>b</sup> |
|          | Females  | 6    | 28.6% | 1    | 14.3%   | 3      | 42.9%  |                 |

Mean age distribution based on KOH specific sites

Genderwise distribution based on KOH specific sites

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Oral Nasal Both

Males Females

71.4% 85.7% 57.1%

28.6% 14.3% 42.9%
However, there was no significant difference observed in the mean age ($p=0.93$) as well as gender distribution ($p=0.50$) of the patients for KOH-specific sites (Table 1). Hence, each study group was homogenous.

**Correlation Between Intraoral Findings and the KOH-Specific Sites**

The test results revealed that the gingival lesions and dental mobility showed a near equal correlation with all three KOH-specific sites, ranging from 42.9 to 57.1% and 66.7 to 85.7%, respectively. However, no significant correlation was observed between gingival lesions, dental mobility and KOH-specific sites. Incidentally, a few cases showed a positive expression of maxillary mobility in the oral site as compared to other sites, but there was no significant correlation found between the three KOH-specific sites (Table 2).

**Correlation Between Radiographic Findings of Bony Erosions and the KOH-Specific Sites Using Chi-Square Test**

The test results revealed that the bony erosions in the radiographic findings were predominantly found to be confined to the maxillary bone without alveolar bone involvement [42.9 – 47.6%] in all three KOH-specific sites. The bony erosions localisation in maxillary bone with alveolar bone involvement and those that are confined to maxillary and zygomatic bone showed an equal distribution [28.6%] in group II and group III patients as compared to 42.9% and 9.5% in group 1, respectively. However, no significant correlation was observed between bony erosions in radiographic findings and the three group sites (Table 3).

| Variable               | Category | Oral | Nasal | Both | $P$-value |
|------------------------|----------|------|-------|------|-----------|
|                        |          | $n$  | $\%$  | $n$  | $\%$     |           |
| Gingival Lesions       | Present  | 11   | 52.4% | 4    | 57.1%    | 0.86      |
|                        | Absent   | 10   | 47.6% | 3    | 42.9%    |           |
| Dental Mobility        | Present  | 14   | 66.7% | 5    | 71.4%    | 0.63      |
|                        | Absent   | 7    | 33.3% | 2    | 28.6%    |           |
| Maxillary Mobility     | Present  | 2    | 9.5%  | 0    | 0.0%     | 0.49      |
|                        | Absent   | 19   | 90.5% | 7    | 100.0%   |           |

![Intra oral findings and the KOH specific site](image-url)
Correlation between Endoscopic Findings and the KOH-Specific Sites Using Chi-Square Test

The test revealed that only nasal crusting was predominant in the nasal site [28.6%], whereas nasal crusting and pus discharge were more predominantly encountered [71.4%] when both oral and nasal KOH-specific sites were involved. A relative proportion of patients was negative for endoscopic findings for group I (19.3%) and group II (14%). The data on the endoscopic findings were not available for all sites [14.3% to 42.9%]. However, no significant correlation was observed between endoscopic findings and KOH-specific sites (Table 4).

Comparison of Mean Duration of Delay in Diagnosis Based on the Site Involved Using Kruskal–Wallis Test Followed by Mann–Whitney Post hoc Test

The test results showed that the mean number of days for delayed diagnosis for oral site involvement was 56.33 ± 37.53, for nasal involvement was 32.86 ± 19.53 and for both oral and nasal involvement was 22.00 ± 12.94 days. Multiple comparisons between groups revealed that the mean delay in diagnosis was significantly less when both oral and nasal regions were involved as compared to the only oral region involved at $p = 0.01$. However, no significant differences were observed between other combinations (Table 5).

Discussion

Mucormycosis species being ubiquitous and an uncommon commensal in human paranasal sinuses and oral cavity turns pathogenic only if the host immunity is compromised. This can occur due to various reasons including prolonged steroidal therapy, immunocompromised patients, uncontrolled diabetes, malignancies such as lymphomas and leukaeemias, renal failure and in patients infected with COVID-19 infection [4]. In the present study, 70% of participants tested Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) positive, 10% were symptomatic but tested negative,
and 12.5% had no COVID-19 association. Immune dysregulation caused by the SARS-CoV-2 virus and the use of broad-spectrum antibiotics and corticosteroids particularly in patients with poorly controlled diabetes with ketoacidosis were proposed to be the cause of infection [4].

Factors attributable to COVID-19-related mucormycosis include hyperglycemia, sera response to infection, altered adipose tissue sensitivity and β-cell destruction, altered mucosal clearance and local immunity, and use of immune-mediated therapies (Corticosteroids, Tocilizumab, etc.). Additionally, mucosal erosion secondary to aggressive use of steam inhalation or the use of high flow oxygen has also been considered as a factor promoting fungus colonisation.

Uncontrolled diabetic patients and patients under corticosteroid usage normally present with the reduced capability of the host in combating fungal infections. It can lead to impaired ciliary motility of the nasal mucosa thereby leading to ineffective phagocytosis of the invading organisms, instead providing them with an excellent substrate for proliferation. The presence of ketone reductase in the fungi helps them thrive through critical situations when there is ketoacidosis and metabolic acidosis [5].

Infection is caused by asexual spore formation. In an immunocompromised host, when airborne spores settle on the oral or nasal mucosa, germination will follow and hyphae will develop as polymorphonuclear leukocytes are less effective in removing the invading hyphae. Hyphae then begin to invade arteries, wherein they propagate within the vessel walls and lumens causing thrombosis, ischaemia, and infarction with dry gangrene of the affected tissues. Later haematogenous spread to other organs can occur leading to the spread of the infection [5]. Due to their relatively bigger dimensions as compared to other species, they are easily retained in the paranasal sinuses.

Table 4 Correlation between endoscopic findings and the KOH-specific site using Chi-square test

| Variable          | Oral      | Nasal     | Both       | P-value |
|-------------------|-----------|-----------|------------|---------|
|                   | n         | %         | n          | %       | n          | %       |         |
| Endoscopic findings | Nasal crusting | 4 | 19.0% | 2 | 28.6% | 0 | 0.0% | 0.18 |
|                   | Pus discharge noted | 4 | 19.0% | 1 | 14.3% | 1 | 14.3% |
|                   | Both      | 5 | 23.8% | 0 | 0.0% | 5 | 71.4% |
|                   | Absent    | 4 | 19.0% | 1 | 14.3% | 0 | 0.0% |
|                   | Data not available | 4 | 19.0% | 3 | 42.9% | 1 | 14.3% |

Endoscopic findings and the KOH specific site

![Endoscopic findings and the KOH specific site](image)
The time lapse between the onset of symptoms and diagnostic procedures was proved to be associated with mortality [6]. Chamilos et al. demonstrated that delayed antifungal therapy increases mortality in patients with haematologic malignancy that have invasive mucormycosis infection. They emphasised the importance of not just the timely administration of antifungal agents, but also aggressive diagnostic strategies [7]. According to Jeong et al., timely debridement of necrotic tissue can reduce the extent of infecting moulds and improve the penetration of antifungal agents to the site of infection [6]. In the absence of reliable diagnostic tools except for direct examination and culture of infected tissues, molecular approaches are currently just in the phase of trial and economic feasibility is difficult in developing countries like India with an overburdened health management system.

Successful management of this deadly disease is early diagnosis and early treatment which includes a combination of medical and surgical debridement. Knowing the importance of early diagnosis, which is the most challenging aspect of mucormycosis management, we were left with the option of microscopic examination of tissue specimens in patients who were clinically suspected to have a fungal infection. Commonly patients with rhinomaxillary infection presented with mobile tooth (70%), numbness in the infraorbital region (40%), palatal ulceration (25%), blurred vision (7.5%), nasal discharge (20%), intraoral pus draining sinus tract or fistula (65%), exposed bone [alveolar (20%), palatal (5%), both (7.5%) and absent (67.5%)] with common history of COVID-19 infection. Most of the patients were hospitalised under oxygen and were usually given steroids to combat the deadly viral infection. Computed tomography and magnetic resonance imaging revealed thickening of the maxillary sinus (right—5%, left—10%), any two sinuses (47.5%), three sinuses (32.5%) and all paranasal sinuses in 5% of the cases. Subtle erosive changes of the maxillary bone (80%) with alveolar bone involvement and without alveolar erosion were seen in 35% and 45% of the cases, respectively. Changes extending to zygomatic bone were seen in 15% of the cases.

### Table 5 Comparison of mean duration of delay in diagnosis based on the site involved using Kruskal–Wallis test followed by Mann–Whitney post hoc test

| Sites  | N   | Mean  | SD    | Min | Max  | P-value<sup>a</sup> | Sig. Diff | P-value<sup>b</sup> |
|--------|-----|-------|-------|-----|------|----------------------|-----------|----------------------|
| Oral   | 21  | 56.33 | 37.53 | 10  | 120  | 0.03*                | O vs N    | 0.20                 |
| Nasal  | 7   | 32.86 | 19.53 | 7   | 62   | O vs B               | 0.01*     |                      |
| Both   | 7   | 22.00 | 12.94 | 10  | 43   | N vs B               | 0.40      |                      |

<sup>a</sup> P-value derived by Kruskal–Wallis test  
<sup>b</sup> P-value derived by Mann–Whitney post hoc test
Infection usually starts in the nasal cavity and spreads to the paranasal sinuses. Bhandari et al., in 2021 stated that the humid environment of the nose and paranasal sinuses favour the growth and invasion of fungi. Early implantation of fungi is common in the maxillary sinus with a mass of fungal growth called a fungal ball and with no evidence of bone erosion. The most common site involved in mucor is middle turbinate, followed by middle meatus and septum. In undiagnosed or untreated cases, the infiltration of the bone is common [8].

When the infection extends through the nasal turbinates, the orbit frequently becomes involved, and orbital cellulitis, extraocular muscle paresis, proptosis and chemosis are commonly found. Extension of the infection posteriorly into the brain results in the formation of abscesses and necrosis of the frontal lobes. When the disease invades inferiorly into the mouth, a black, necrotic eschar is often found on the palate, this finding is highly suggestive of the presence of invasive mucormycosis [9].

In the present setup, various tissue specimens were sent for microscopic examination (using KOH stain) and fungal culture. Swabs were sent from nasal mucosa, sinus tract or tissue specimen from necrotic bone or suspected tissue from paranasal sinus with the aid of endoscopy. Few of these showed fungal elements giving way for hospitalisation and definitive treatment, while some turned negative despite clinically evident disease leading to delayed medical management. Multimodal therapy is key to reducing the disease burden which involves both surgical debridement and systemic antifungal therapy. Without antifungal therapy, the disease burden and recurrence increase even after performing surgical debridement.

Harrill et al., stated that the median time from the symptom onset to diagnosis was 7 months [1]. In the present study, the mean number of days for delayed diagnosis among various study groups was 56.33 ± 37.53, 32.86 ± 19.53 and 7 months [1]. In the present setup, various study groups were sent for microscopic examination (using KOH stain) and fungal culture. Swabs were sent from nasal mucosa, sinus tract or tissue specimen from necrotic bone or suspected tissue from paranasal sinus with the aid of endoscopy. Few of these showed fungal elements giving way for hospitalisation and definitive treatment, while some turned negative despite clinically evident disease leading to delayed medical management. Multimodal therapy is key to reducing the disease burden which involves both surgical debridement and systemic antifungal therapy. Without antifungal therapy, the disease burden and recurrence increase even after performing surgical debridement.

Because of the nonspecific clinical signs, a high index of suspicion should be made in the existence of risk factors. Nasal scrapings and fine-needle aspiration cytology were performed to give the diagnostic results which showed fungal hyphae. Swabs were taken, and cultures from sinuses were negative in most of the cases (25%). Thus in the rhinomaxillary group which presents with common disease presentations, we found 52.5% of participants to show fungal hyphae from the oral tissue (necrotic bone or sinus lining via Caldwell Luc), 12.5% from nasal tissue/pus as well as from both tissue specimens with extensive involvement.

Mucorales appear in the tissue as irregularly shaped, broad hyphae with right-angle branching. The hyphae are easily visualised in routine haematoxylin–eosin-stained sections as well as in tissue stained by the periodic acid–Schiff reaction or by Grocott-Gomori methenamine-silver nitrate stains. Hyphae are usually found in the midst of an acute neutrophilic infiltrate along with the hyphal invasion of the blood vessels [9].

In a report to check the diagnostic values of KOH examination, histological examination, culture for onychomycosis and periodic acid–Schiff stain (PAS) were highly specific but poorly sensitive. KOH was highly sensitive but poorly specific and Grocott’s methenamine-silver stain (GMS) was both highly sensitive and specific [10].

Various other techniques for diagnosis include immunohistochemistry, polymerase chain reaction (PCR)-based methods and matrix-assisted laser desorption or ionisation time-of-flight mass spectrometry (MALDI-TOF MS). A study done by combining a semiquantitative method using high-resolution melt analysis and real-time quantitative PCR (RQ PCR) assays showed sensitivity and specificity of 100% and 93%, respectively, and a high negative predictive value (99%) in detecting mucormycetes. Despite their higher sensitivity and specificity, these diagnostic aids are not available in clinical setups in India for it to be used commonly giving way to conventional techniques. Thus, KOH mount setup is feasible for the Indian scenario; however, the sites should be carefully selected to collect suitable samples showing hyphae infiltration in the necrotic tissue helping to predicate the diagnosis at an early stage rendering them to medical management with systemic antifungals.

The limitation of the study is its retrospective temporality with limited sample size. The present study concurs that in the rhinomaxillary mucormycosis group, the fungal spores have two different patterns of invasion evident with oro-nasal signs and symptoms. To avoid the chance of delayed diagnosis or false-negative results, it is best to collect samples from both nasal tissues as well as the most representative site in the dentoalveolar segment depending on the extensiveness of the disease.

**Conclusion**

Effective management of rhinomaxillary mucormycosis involves surgical debridement followed by systemic antifungals. To start antifungal therapy, it is important to establish a diagnosis prior because of the financial burden and nephro-toxicity it imposes. The microscopic examination and its reliability depend on the viability and infiltration of fungal hyphae in the samples obtained. Delayed diagnosis or false-negative results leads to much extensive destruction. Earlier diagnosis leads to better outcome and saves the patient life.

Based on the evidence from our retrospective study, we imply that in cases where in extensive involvements of the
disease, the diagnosis is quite straightforward with reduced diagnosis delay. However, among the cases where the alveolar destruction is less with minimal clinical presentation, nasal swab KOH alone is ineffective in getting diagnosis, and a more aggressive procedures like direct biopsy and translateral exposure with biopsy yielded early diagnosis with less false-negative results which helped us to institute early therapy to our patients with minimal morbidity. Hence, we recommend both nasal swabs and invasive biopsies from oral representative sites to negate the possibility of delayed diagnosis.

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**Availability of data and material** All the research-related data are available to the principal investigator.

**Declarations**

**Conflict of interest** None of the authors have any financial or personal interest associated with this article. No funding has been received by any author for this study.

**Consent to participate** A written informed consent was obtained from all individual participants included in the study.

**Consent for publication** Consent is obtained for publication of this data from the patients.

**Ethical approval** All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by Institutional Ethics Committee at All India Institute of Medical Sciences- Raipur (AIIMSRPR/RC(P)/2021/385).

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