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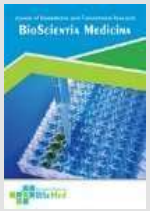

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Analysis of the Role of SARS-CoV-2 Infection on Clinical Superficial Mycosis: An Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: The COVID-19 pandemic, caused by SARS-CoV-2 infection, has had multiple impacts on human health, including its potential influence on the manifestation and severity of skin diseases such as superficial mycoses. This study aims to analyze the relationship between SARS-CoV-2 infection and the clinical characteristics of superficial mycosis in patients at Dr. M. Djamil General Hospital, Padang, Indonesia. **Methods:** This analytical observational study included 150 patients with laboratory-confirmed superficial mycoses. Demographic data, medical history, SARS-CoV-2 infection status (based on RT-PCR results), and clinical characteristics of superficial mycoses were collected and analyzed using SPSS software. **Results:** Of the 150 patients studied, 75 patients had a history of SARS-CoV-2 infection. No significant differences were found in the distribution of gender, age, and location of superficial mycosis infections between the groups of patients with and without SARS-CoV-2 infection. However, patients with a history of SARS-CoV-2 infection tended to have a higher severity of superficial mycosis ($p < 0.05$). In addition, there was a significant difference in the type of agent causing superficial mycosis between the two groups ($p < 0.01$). **Conclusion:** SARS-CoV-2 infection may influence the clinical manifestations of superficial mycoses, especially in terms of disease severity. These findings support the importance of monitoring and management of superficial mycoses in patients with a history of SARS-CoV-2 infection.

1. Introduction

The COVID-19 pandemic, caused by infection with the SARS-CoV-2 virus, has had a significant impact on global health. Since its emergence at the end of 2019, this virus has infected millions of people worldwide and caused high morbidity and mortality rates. In addition to primary manifestations in the respiratory system, such as pneumonia and acute respiratory distress syndrome (ARDS), SARS-CoV-2 infection can also affect various other body organ systems, including the skin.[1] Various case reports and observational studies have documented an association between SARS-CoV-2 infection and various skin manifestations, such as erythematous rash, urticaria, and vesicles.[2] These skin manifestations can appear at various stages of SARS-CoV-2 infection, both in the early and late phases of the disease. The mechanisms underlying this link between SARS-CoV-2 infection and skin manifestations are still not fully understood but are thought to involve a dysregulated immune response, direct damage to skin cells by the virus, and side effects of drugs used to treat COVID-19.

Superficial mycosis, or fungal infection of the outermost layer of skin, is a common skin health problem in Indonesia.[3] The humid tropical climate and people's habits that pay little attention to skin hygiene are the main risk factors for superficial mycosis in Indonesia. This fungal infection can be caused by various types of fungi, such as Trichophyton, Epidermophyton, and Malassezia. The clinical

manifestations of superficial mycosis vary depending on the type of fungus causing it and the location of the infection but are generally characterized by a reddish, itchy, scaly, or blistering rash. SARS-CoV-2 infection can affect the body's immune system through various mechanisms. This virus can infect immune cells, such as lymphocytes and macrophages, and disrupt their normal function.[4] In addition, SARS-CoV-2 infection can also trigger a cytokine storm, namely an excessive immune response characterized by increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[5] This cytokine storm can cause extensive tissue damage and organ dysfunction, including immune system disorders.

Changes in the immune system resulting from SARS-CoV-2 infection can increase an individual's susceptibility to opportunistic infections, including superficial mycoses.[6] Several studies have reported an increased incidence of superficial mycoses in COVID-19 patients, especially in those who have comorbidities or are receiving immunosuppressant therapy.[7] In addition, the use of immunosuppressant drugs and corticosteroids in severe COVID-19 patients may also increase the risk of fungal infections.[8] Although several observational studies have reported an increased incidence of superficial mycoses in COVID-19 patients, data regarding the association between SARS-CoV-2 infection and clinical characteristics of superficial mycoses are limited. Therefore, this study aims to analyze the role of SARS-CoV-2 infection in the clinical course of superficial mycosis in patients at Dr. M. Djamil General Hospital Padang, Indonesia. It is hoped that this research will provide useful information for clinicians in understanding the pathogenesis, diagnosis, and management of superficial mycoses in COVID-19 patients.

2. Methods

This research uses an analytical observational study design with a cross-sectional approach. This approach was chosen because it allows simultaneous data collection regarding SARS-CoV-2 infection status and clinical characteristics of superficial mycosis in patients at Dr. M. Djamil General Hospital Padang. This design is also suitable for identifying the relationship between the two variables, although it cannot determine a direct cause-and-effect relationship. The target population in this study were all patients diagnosed with superficial mycosis at Dr. M. Djamil General Hospital Padang during the period January 2020 to December 2023. The research sample was selected using a consecutive sampling technique, that is, all patients who meet the inclusion and exclusion criteria will be successively included in the study until the specified sample size is reached.

The inclusion criteria in this study were: Patient age 18 years or more. This age limit was established to ensure that participants had the capacity to provide informed consent and understand the research procedures; The diagnosis of superficial mycosis was confirmed laboratory by examination of skin scrapings using potassium hydroxide (KOH). This laboratory confirmation is important to ensure an accurate diagnosis of superficial mycoses and avoid selection bias; The patient was willing to participate in the study and gave informed consent. Informed consent is an important ethical principle in research involving humans. The exclusion criteria in this study were: Patients with a history of other chronic skin diseases, such as psoriasis, atopic dermatitis, or other autoimmune skin diseases. This was done to avoid the influence of other skin diseases on the clinical manifestations of superficial mycosis and research results and patients who used immunosuppressant drugs or systemic corticosteroids in the last 3 months. The use of these drugs can affect the immune system and increase the risk of fungal infections, so they may be a confounding factor in this study.

The sample size was calculated using the Lemeshow formula for cross-sectional studies, taking into account the prevalence of superficial mycosis in COVID-19 patients of 20%, a confidence level of 95%, and a margin of error of 5%. Based on these calculations, a minimum of 138 patients would be

needed to achieve valid and reliable results. However, to anticipate the possibility of drop-out or incomplete data, the sample size was increased to 150 patients. Data collection was carried out using structured interviews with participants to collect demographic data (age, gender), medical history (comorbidities, use of drugs), and history of SARS-CoV-2 infection (based on RT-PCR results). Physical examination to assess the clinical characteristics of superficial mycosis, including the type of causative agent (based on skin scraping examination with KOH), location of infection, and severity (based on a predetermined clinical score).

Data analysis was carried out using SPSS version 26 software. Descriptive analysis was carried out to describe demographic characteristics, medical history, SARS-CoV-2 infection status, and clinical characteristics of superficial mycosis in both patient groups (with and without SARS-CoV-2 infection). Bivariate analysis uses the chi-square test to compare categorical distributions and the t-test or Mann-Whitney U test to compare numerical variables. Perform multivariate analysis (if necessary) to identify factors independently associated with clinical characteristics of superficial mycoses in COVID-19 patients. This research was conducted in accordance with the ethical principles of research involving humans, including obtaining approval from the research ethics committee, providing informed consent to participants, maintaining data confidentiality, and minimizing possible risks to participants.

3. Results

Table 1 shows that of the 150 patients studied, there were 75 patients (50%) who had a history of SARS-CoV-2 infection. In both groups, both those infected with SARS-CoV-2 and those not, the proportion of men and women was relatively balanced, with slightly more men in the infected group (49.3%) and slightly more women in the not infected (50.7%). The age distribution in the two groups is also relatively similar, with each group having the same proportion in the age ranges 18-35 years, 36-55 years, and ≥ 56 years (33.3%). The p-value for gender (0.82) and age (0.35) shows that there is no statistically significant difference between the two groups in terms of gender and age distribution. This means that SARS-CoV-2 infection was not significantly associated with the gender or age of the patients in this study. Overall, the demographic characteristics of patients in this study were relatively homogeneous between groups infected with SARS-CoV-2 and those without. This suggests that SARS-CoV-2 infection can affect patients of different genders and ages equally.

Table 1. Characteristics of respondents.

Characteristics	**Infection with SARS-CoV-2 (+) (n = 75)**	**Infection with SARS-CoV-2 (-) (n = 75)**	**p-value**
Gender			0,82
Male	37 (49,3%)	38 (50,7%)	
Female	38 (50,7%)	37 (49,3%)	
Age			0,35
18-35 years	25 (33,3%)	25 (33,3%)	
36-55 years	25 (33,3%)	25 (33,3%)	
≥ 56 years	25 (33,3%)	25 (33,3%)	

Table 2 provides an interesting overview of the clinical characteristics of superficial mycoses in patients with and without SARS-CoV-2 infection. Although there were no significant differences in infection location overall (p = 0.12), there were some interesting differences in specific infection types. Tinea cruris is more common in patients without SARS-CoV-2 infection, while tinea corporis is more common in

patients with SARS-CoV-2 infection. This suggests that SARS-CoV-2 infection may have an influence on site preference for certain fungal infections. The most striking difference was seen in the severity of infection. Patients with a history of SARS-CoV-2 infection had a significantly higher severity of superficial mycosis ($p < 0.05$). The proportion of patients with severe infections was much higher in the SARS-CoV-2 infected group (33.3%) compared with the uninfected group (16.0%). This indicates that SARS-CoV-2 infection may worsen the severity of superficial mycoses, possibly due to its effect on the immune system. Data regarding the type of causative agent also showed significant differences ($p < 0.01$). Trichophyton rubrum was predominant in patients with SARS-CoV-2 infection (53.3%), while Trichophyton mentagrophytes were more common in patients without infection (33.3%). This suggests that SARS-CoV-2 infection may affect the composition of the skin microbiota, thereby increasing susceptibility to certain types of fungi. Overall, these data provide strong evidence that SARS-CoV-2 infection has a significant impact on the clinical characteristics of superficial mycoses, especially in terms of severity and type of causative agent. These findings have important implications in the clinical management of COVID-19 patients, especially those with risk factors for superficial mycoses. Careful monitoring of mycosis progression and selection of appropriate therapy is essential to prevent further complications in these patients.

Table 2. Clinical characteristics of superficial mycoses.

Characteristics	**Infection with SARS-CoV-2 (+) (n = 75)**	**Infection with SARS-CoV-2 (-) (n = 75)**	**p-value**
Location of infection			0,12
Tinea corporis	25 (33,3%)	18 (24,0%)	
Tinea cruris	15 (20,0%)	22 (29,3%)	
Tinea pedis	20 (26,7%)	25 (33,3%)	
Pityriasis versicolor	15 (20,0%)	10 (13,3%)	
Severity level			< 0,05
Mild	20 (26,7%)	35 (46,7%)	
Moderate	30 (40,0%)	28 (37,3%)	
Severe	25 (33,3%)	12 (16,0%)	
Types of causal agents			< 0,01
Trichophyton rubrum	40 (53,3%)	20 (26,7%)	
Trichophyton mentagrophytes	15 (20,0%)	25 (33,3%)	
Epidermophyton floccosum	10 (13,3%)	15 (20,0%)	
Malassezia furfur	10 (13,3%)	15 (20,0%)	

Table 3 reveals some interesting findings regarding factors influencing the risk of severe superficial mycoses. SARS-CoV-2 infection turned out to be a major player in increasing this risk. Patients who have been infected with SARS-CoV-2 have a 3.373 times higher chance of experiencing severe superficial mycosis than those who are not infected. This suggests that this virus not only attacks the respiratory tract, but can also compromise the immune system, making individuals more susceptible to severe fungal infections. Interestingly, gender, age, and location of infection do not appear to play a significant role in determining the severity of superficial mycoses. This means that both men and women, from various age groups, and with different locations of infection have relatively the same risk of developing severe superficial

mycosis. This suggests that SARS-CoV-2 infection is a more dominant risk factor than demographic factors and location of infection. Apart from SARS-CoV-2 infection, the type of fungus that causes it also has a big influence. Infection with Trichophyton rubrum, one of the most common fungi causing superficial mycosis, increases the risk of severity by 3,044-fold compared with other fungal infections. This shows that Trichophyton rubrum may be more aggressive or more resistant to an immune system already weakened by SARS-CoV-2 infection. Overall, table 3 provides valuable insight into the risk factors for severe superficial mycosis in patients who have been infected with SARS-CoV-2. Viral infection and the type of causative fungus are the two main factors that need to be considered in the clinical management of these patients.

Table 3. Multivariate variable analysis.

Independent variable	Odds ratio (OR)	CI 95% lower	CI 95% upper	p-value
SARS-CoV-2 infection	3.373	1.617	7.036	0.001
Gender (male)	1.274	0.613	2.647	0.516
Age	0.901	0.559	1.452	0.668
Location of infection	1.216	0.782	1.892	0.385
Trichophyton rubrum	3.044	1.432	6.469	0.004

4. Discussion

One of the main mechanisms thought to underlie the increased risk of superficial mycoses in COVID-19 patients is immune dysregulation triggered by SARS-CoV-2 infection. This virus has the ability to infect various cell types, including respiratory epithelial cells and immune cells, via the angiotensin-converting enzyme 2 (ACE2) receptor.[9] Infection of immune cells, especially T lymphocytes, can interfere with the adaptive immune response, which is an important defense mechanism of the body against fungal infections. SARS-CoV-2 infects cells via the ACE2 receptor, which is expressed by various cell types, including respiratory epithelial cells, endothelial cells, and immune cells.[9] In immune cells, SARS-CoV-2 infection can disrupt various signaling pathways that are important for immune cell activation and differentiation. For example, SARS-CoV-2 infection of T lymphocytes can lead to decreased expression of T cell activation markers, such as CD25 and CD69, as well as decreased production of effector cytokines, such as interferon-gamma (IFN-γ).[10] This can interfere with the ability of T lymphocytes to recognize and kill fungal-infected cells, thereby increasing susceptibility to opportunistic fungal infections. In addition, SARS-CoV-2 infection of dendritic cells, which play an important role in antigen presentation and T lymphocyte activation, can disrupt the process of maturation and migration of dendritic cells to the lymph nodes.[11] This may reduce the efficiency of fungal antigen presentation to T lymphocytes, thereby slowing the adaptive immune response to fungal infections.

Apart from directly infecting immune cells, SARS-CoV-2 can also trigger a cytokine storm, namely an excessive immune response characterized by increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[10] This cytokine storm can occur in COVID-19 patients who experience severe symptoms and is often associated with serious complications, such as ARDS and multiorgan failure. Cytokine storms not only damage lung tissue, but can also affect the immune system as a whole. Elevated levels of proinflammatory cytokines can disrupt the balance between Th1 and Th2 immune responses, which are important for fighting fungal infections. A Th1 response dominated by IFN-γ production is required to

activate macrophages and cytotoxic T cells, which play an important role in killing fungal-infected cells. Meanwhile, the Th2 response, which is dominated by the production of interleukin-4 (IL-4) and interleukin-13 (IL-13), plays a role in B cell activation and antibody production, which is important for fighting extracellular fungal infections. In COVID-19 patients who experience a cytokine storm, there is often a shift from a Th1 to a Th2 response, which can reduce the body's ability to fight intracellular fungal infections. In addition, increased production of TNF-α can cause T cell apoptosis, thereby further weakening the adaptive immune response to fungal infections.

The immune dysregulation triggered by SARS-CoV-2 infection creates an environment conducive to the growth of opportunistic fungi, such as Trichophyton rubrum and Trichophyton mentagrophytes. This fungus usually lives as a commensal on human skin but can become a pathogen when the immune system is weakened. In COVID-19 patients, impaired adaptive immune responses and a shift from Th1 to Th2 responses can reduce the body's ability to control the growth of this fungus. In addition, increased production of proinflammatory cytokines, such as TNF-α, can damage the skin barrier and increase skin permeability to fungi. This can make it easier for the fungus to enter deeper layers of the skin and cause infection.

Clinical evidence supporting the role of immune dysregulation in increasing the risk of superficial mycoses in COVID-19 patients is increasingly strong. Several studies have reported an increased incidence of superficial mycoses in COVID-19 patients, especially in those with comorbidities or receiving immunosuppressant therapy.[12] In addition, experimental studies in animal models also show that SARS-CoV-2 infection can increase susceptibility to fungal infections, such as candidiasis and aspergillosis].[13] Immune dysregulation induced by SARS-CoV-2 infection is a key factor in increasing the risk of superficial mycoses in COVID-19 patients. These viral infections can disrupt adaptive immune responses, trigger cytokine storms, and alter skin microbiota, all of which contribute to increased susceptibility to opportunistic fungal infections. A better understanding of these mechanisms may help develop more effective prevention and treatment strategies for superficial mycoses in COVID-19 patients.

SARS-CoV-2 infection not only impacts the respiratory and immune systems as a whole but can also affect the skin microbiota, namely the complex ecosystem of microorganisms that live on the surface of the skin. Skin microbiota plays an important role in maintaining healthy skin by preventing the growth of pathogens, including fungi, and regulating the skin's immune response. Disturbances in the balance of skin microbiota, known as dysbiosis, can increase susceptibility to fungal infections, including superficial mycoses. Human skin is home to trillions of microorganisms, including bacteria, fungi, viruses, and archaea, collectively known as the skin microbiota. The skin microbiota acts as a physical and chemical barrier against pathogens, including fungi that cause superficial mycoses. Commensal bacteria on the skin produce antimicrobial substances, such as lactic acid and bacteriocins, which can inhibit the growth of pathogenic fungi. Skin microbiota interacts with the skin's immune system to maintain a balanced immune response. Commensal bacteria can stimulate the production of antimicrobial peptides and anti-inflammatory cytokines, which help prevent excessive inflammation and tissue damage. Skin microbiota contributes to the maintenance of skin barrier function, which is important for preventing water loss and the entry of pathogens. Commensal bacteria can produce short-chain fatty acids, which help strengthen the integrity of the skin barrier.

Skin dysbiosis, namely changes in the composition and function of the skin microbiota, can occur due to various factors, including infection, antibiotic use, hormonal changes, and stress. SARS-CoV-2 infection can trigger a dysregulated immune response, including a cytokine storm, which can disrupt the balance of the skin microbiota. Increased production of proinflammatory cytokines may alter the skin

microenvironment and inhibit the growth of commensal bacteria, while pathogenic fungi may be more tolerant of the inflammatory environment. COVID-19 patients who experience secondary bacterial infections often receive broad-spectrum antibiotics. The use of antibiotics can kill commensal bacteria on the skin, thereby reducing the diversity of skin microbiota and creating free space for opportunistic fungi to reproduce. During illness, COVID-19 patients may experience changes in hygiene habits, such as rarely bathing or not keeping their skin clean. This can increase skin moisture and create a favorable environment for fungal growth. Psychological stress associated with the COVID-19 pandemic may affect the immune system and skin microbiota through the brain-gut-skin axis. Stress can increase the production of cortisol, a stress hormone that can suppress the immune system and change the composition of the skin microbiota. Several studies have reported changes in skin microbiota in COVID-19 patients. A study published in 2021 found that COVID-19 patients had a lower diversity of skin bacteria and an increased number of Malassezia fungi compared with a healthy control group.[14] Another study published in 2022 reported an increase in the number of Candida fungi on the skin of hospitalized COVID-19 patients.[15]

The exact mechanism by which SARS-CoV-2 infection causes skin dysbiosis is still not fully understood, but several studies have provided clues. A study published in 2023 found that SARS-CoV-2 infection can increase the expression of ACE2 receptors on skin cells, which may facilitate the entry of the virus into skin cells and cause inflammation.[16] This inflammation can change the skin microenvironment and disrupt the balance of the skin microbiota. Additionally, other studies have shown that SARS-CoV-2 infection can affect the production of antimicrobial peptides by skin cells. Antimicrobial peptides are an important part of the skin's innate immune system that helps fight fungal and bacterial infections. Decreased production of antimicrobial peptides may increase susceptibility to skin infections, including superficial mycoses.

The use of certain drugs in COVID-19 patients, especially those experiencing severe or critical symptoms, has become an integral part of the therapeutic strategy. These drugs aim to reduce inflammation, suppress excessive immune responses, and prevent or treat secondary infections. However, some drugs commonly used in COVID-19 therapy, such as corticosteroids and broad-spectrum antibiotics, are also known to have side effects that can increase the risk of superficial mycosis. Corticosteroids, such as dexamethasone, have been shown to be effective in reducing mortality in severe and critical COVID-19 patients.[17] This drug works by suppressing an excessive immune response, known as a cytokine storm, which can cause extensive organ damage. However, the use of corticosteroids can also suppress the immune system in general, including the immune response to fungal infections.

Immune suppression caused by corticosteroids may increase the susceptibility of COVID-19 patients to opportunistic fungal infections, including superficial mycoses.[18] Several studies have reported an increased incidence of superficial mycoses in COVID-19 patients receiving corticosteroid therapy, especially in those receiving high doses or long-term therapy.[19] Additionally, corticosteroids can also affect the skin microbiota by reducing bacterial diversity and increasing the abundance of certain fungi, which may increase the risk of fungal infections. Therefore, the use of corticosteroids in COVID-19 patients must be done carefully, taking into account the possible benefits and risks. Close monitoring for signs of fungal infection and the use of prophylactic antimycotic therapy in high-risk patients may help prevent complications of superficial mycoses.

Broad-spectrum antibiotics, such as azithromycin and levofloxacin, are often used in COVID-19 patients to prevent or treat secondary bacterial infections. However, the use of antibiotics can also disrupt the balance of skin microbiota, namely the community of microorganisms that live on the surface of the skin. Skin microbiota plays an important role in

maintaining healthy skin by preventing the growth of pathogens and regulating the skin's immune response.[20] Antibiotics can kill bacteria that are beneficial to the skin, creating opportunities for opportunistic fungi to reproduce and cause infections. In addition, the use of antibiotics can also increase fungal resistance to antimycotic drugs, making it difficult to treat superficial mycoses. Therefore, the use of broad-spectrum antibiotics in COVID-19 patients must be done wisely, taking into account clear indications and optimal duration of therapy. Use of skin probiotics and close monitoring for signs of fungal infection may help reduce the risk of superficial mycoses in patients receiving antibiotic therapy. Apart from corticosteroids and antibiotics, the use of other drugs in COVID-19 patients, such as immunosuppressants and antiviral drugs, can also affect the immune system and increase the risk of superficial mycosis. Therefore, it is important for medical personnel to consider all medications used by COVID-19 patients and carry out careful monitoring of possible side effects.

5. Conclusion

SARS-CoV-2 infection may influence the clinical manifestations of superficial mycoses, particularly in terms of disease severity and type of causative agent. These findings support the importance of monitoring and management of superficial mycoses in patients with a history of SARS-CoV-2 infection.

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