Analysis of Risk Factors Influencing the Incidence of Systemic Fungal Infections in Stage IV HIV Patients at Haji Adam Malik General Hospital, Medan

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Abstract

Background: The human immunodeficiency virus (HIV) primarily targets CD4+ cells, leading to a weakened immune system. Patients in Stage IV HIV are highly susceptible to systemic fungal infections. The prevention of opportunistic fungal infections, early detection, and identification of their risk factors are critical, particularly in advanced HIV cases.

Objective: This study seeks to identify the risk factors associated with systemic fungal infections in Stage IV HIV patients at Haji Adam Malik General Hospital, Medan.

Methods: This observational analytical study adopted a retrospective approach using the medical records of patients treated at the hospital from 2018 to 2023. The sampling method employed was consecutive sampling. Shapiro-Wilk tests were used for distribution analysis, and bivariate analysis determined the relationship between various risk factors (CD4+, Type 2 Diabetes Mellitus, pulmonary and extrapulmonary tuberculosis, and albumin levels) and systemic fungal infections in HIV Stage IV patients using chi-square tests. Multivariate analysis was performed thereafter. The statistical significance threshold was set at $\alpha = 0.05$, with p-values less than 0.05 considered statistically significant.

Results: The study involved 64 subjects. Systemic fungal infections were most prevalent among patients aged 19 to 44 years, with males being more commonly affected. The mean CD4+ count among Stage IV HIV patients with systemic fungal infections was 43.5 (+ 43.4), while those without such infections had a mean CD4+ count of 82.1 (+57.9). A statistically significant relationship was observed between CD4+ and albumin levels and the incidence of systemic fungal infections ($p < 0.05$). Multivariate analysis revealed that both low albumin and CD4+ levels were significant risk factors for the development of systemic fungal infections in Stage IV HIV patients.

Conclusion: CD4+ and albumin levels are significant risk factors for systemic fungal infections in Stage IV HIV patients

Keywords: Stage IV HIV, albumin, CD4+, tuberculosis, Type 2 Diabetes Mellitus

1. Introduction

The Human Immunodeficiency Virus (HIV) undermines the immune system by targeting CD4+ cells, a type of white blood cell critical to immune function. Upon diagnosis, CD4+ levels are promptly measured to evaluate the individual's immune status. When CD4+ levels drop below 200 cells/mm³, the immune system is severely compromised, categorizing the individual as having Stage 3 or 4 HIV, commonly known as acquired immunodeficiency syndrome (AIDS).[1-3] These patients are particularly vulnerable to a range of infections and death. Systemic fungal infections, in particular, occur due to opportunistic fungal pathogens.[4] The incidence of such infections is closely correlated with the degree of immune suppression.[5] Over 90% of HIV-related mortality is attributed to infections, with Cryptococcus, Candida, and Aspergillus being the predominant causative agents.[6] A case-control study in Denpasar, Bali, identified several risk factors contributing to infections like oral candidiasis in HIV/AIDS patients, such as age, smoking, alcohol consumption, CD4+ count, and clinical stage of HIV/AIDS.[7]

Complications such as Type 2 Diabetes Mellitus (DM) and tuberculosis (TB) further exacerbate immunocompromised states, increasing the incidence of opportunistic fungal infections. Type 2 DM impairs cell-mediated immunity, heightening the frequency of infections.[8,9] Additionally, there are approximately 1.3 million new cases and 300,000 deaths annually among patients co-infected with pulmonary TB and HIV. Reports suggest that both systemic fungal infections and pulmonary TB can occur concurrently in HIV-infected individuals with severe immunosuppression (median CD4 count of 30 cells/mm³).[10]

Albumin is the most abundant serum protein in the human body and is widely employed as an indicator of nutritional status in various studies. Low albumin levels adversely impact immune function, affecting the body's barrier function, leukocyte phagocytosis, and complement activity. This leads to prolonged infection duration, diminished anti-infective responses, and increased mortality. A study by Xiao et al. highlighted that low albumin levels constitute a significant risk factor for mortality in patients suffering from systemic fungal infections.[11]

The prevention of opportunistic fungal infections, early identification, and the investigation of associated risk factors are crucial, particularly in advanced-stage HIV patients.[12] This study represents the first attempt to conduct a thorough comparison of CD4 counts, albumin levels, Type 2 Diabetes Mellitus status, and pulmonary tuberculosis in relation to the occurrence of systemic fungal infections among Stage IV HIV patients at Haji Adam Malik General Hospital, Medan. Despite ongoing controversies surrounding the association between certain risk factors and the incidence of systemic fungal infections, this study aims to provide further insights into these relationships.

2. Methods

This study was designed as an observational analytical study with a retrospective cohort approach, utilizing patient medical records to compare the risk factors associated with systemic fungal infections in Stage IV HIV patients at Haji Adam Malik General Hospital, Medan. The sampling technique employed consecutive sampling, with a minimum required sample size of 60 subjects.

The inclusion criteria for the study involved HIV-positive patients diagnosed using the ELISA 3-method test, who met the WHO clinical criteria for Stage IV HIV and were hospitalized at Haji Adam Malik General Hospital between 2018 and 2023. These patients were 18 years or older, confirmed as Stage IV HIV-positive, and had systemic fungal infections. Exclusion criteria included patients who had previously received antifungal treatment, those with incomplete medical records (missing CD4+ count, pulmonary TB infection status, age, albumin levels, data related to Type 2 Diabetes Mellitus diagnosis, or systemic fungal infection status), as well as HIV patients with autoimmune diseases, malignancies, or those undergoing long-term steroid therapy.

The research data were statistically analyzed using SPSS software to assess the relationships between the study variables. Normality tests were conducted using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Bivariate analysis was employed to compare factors such as age, gender, CD4+ count, nutritional status (albumin), Type 2 Diabetes Mellitus, and pulmonary/extrapulmonary TB, and their association with the incidence of systemic fungal infections in Stage III and Stage IV HIV patients at Haji Adam Malik General Hospital, using the chi-square test. Additionally, multivariate analysis was performed. A significance level of $\alpha = 0.05$ was set, with results considered statistically significant if $p < 0.05$.

3. Result

Among all Stage IV HIV patients diagnosed with systemic fungal infections and treated at Haji Adam Malik General Hospital from 2018 to 2023, a total of 64 subjects met the inclusion and exclusion criteria. Table 1 provides an overview of the sample characteristics. It was found that a greater number of patients experienced systemic fungal infections compared to those who did not. The majority of subjects were in the 19–44 age group, followed by the 45–49 age group, with the smallest proportion observed among those aged 60 and above. Males predominated over females in this sample. A higher proportion of subjects had CD4+ counts below 100, compared to those with counts between 100 and 200. A similar trend was observed for albumin levels, with the majority of subjects exhibiting levels below 3.5, as opposed to levels ranging from 3.5 to 5.5. None of the subjects in this study were found to have Type 2 Diabetes Mellitus. Regarding tuberculosis status, the majority of the sample did not present with either pulmonary or extrapulmonary TB. In terms of the types of fungal infections observed, Pneumocystis pneumonia (PCP) was the most prevalent, followed by candidiasis, histoplasmosis, cryptococcosis, and penicilliosis.

Table 1. The Characteristics of Risk Factors Influencing the Occurrence of Systemic Fungal Infections in Stage IV HIV Patients.

Characteristics		n (%)
Systemic Fungal Infection Status	Yes	45 (70,3)
	No	19 (29,7)
Age	19 – 44	45 (70,3)
	45 – 49	18 (28,1)
	≥ 60	1 (1,6)
Sex	Male	45 (70,3)
	Female	19 (29,7)
CD4+ levels	< 100	54 (84,4)
	100 – 200	10 (15,6)
CD4+ mean	With systemic fungal infection	43,5 (±43,4)
	Without systemic fungal infection	82,1 (±57,9)
Albumin level	< 3,5	56 (87,5)
	3,5 – 5,5	8 (12,5)
Albumin mean	With systemic fungal infection	2,73
	Without systemic fungal infection	3,2
DM tipe 2	Yes	0 (0,0)
	No	64 (100,0)
TB paru	Yes	22 (34,4)
	No	43 (65,6)
TB ekstra paru	Yes	20 (31,2)
	No	44 (68,8)

Fungal Infection	No Infection	19 (29,7)
	PCP	34 (53,7)
	Candidiasis	6 (9,4)
	Hystoplasmosis	2 (3,1)
	Penisiliosis	1 (1,6)
	Cryptococosis	2 (3,1)

Stage IV HIV patients with systemic fungal infections predominantly had albumin levels below 3.5 g/dL, with 42 patients falling into this category, while only 3 patients had albumin levels between 3.5 and 5.5 g/dL. A similar pattern was observed among Stage IV HIV patients without systemic fungal infections, where the majority, 11 patients, had albumin levels below 3.5 g/dL, and 8 patients had levels between 3.5 and 5.5 g/dL. The p-value was found to be less than 0.05, indicating a statistically significant association between low albumin levels and the occurrence of systemic fungal infections in Stage IV HIV patients.

Table 2. Bivariate Analysis Results of the Relationship Between Albumin Levels and Systemic Fungal Infections in Stage IV HIV Patients.

		Systemic Fungal Infection		*p-value*
		No	Yes	
Albumin Level (g/dL)	<3.5	11	42	0,002
	3.5-5.5	8	3	

Stage IV HIV patients with systemic fungal infections predominantly exhibited CD4+ counts below 100 cells/µL, with 42 patients falling into this category, while only 3 patients had CD4+ counts between 100 and 200 cells/µL. A similar trend was observed among Stage IV HIV patients without systemic fungal infections, where the majority, 12 patients, had CD4+ counts below 100 cells/µL, and 7 patients had counts between 100 and 200 cells/µL. The p-value was found to be less than 0.05, indicating a statistically significant relationship between low CD4+ counts and the occurrence of systemic fungal infections in Stage IV HIV patients.

Table 3. Bivariate Analysis Results of the Relationship Between CD4+ Levels and Systemic Fungal Infections in Stage IV HIV Patients

		Systemic Fungal Infection		*p-value*
		No	Yes	
CD4+ level	≤100	12	42	0,002
	100-200	7	3	

Table 4 illustrates the relationship between pulmonary tuberculosis (TB) and systemic fungal infections in Stage IV HIV patients. Among the patients studied, 12 individuals with systemic fungal infections also had pulmonary TB, while 33 other patients did not present with pulmonary TB. Fourteen Stage IV HIV patients neither had systemic fungal infections nor pulmonary TB, and 5 patients had pulmonary TB without any concurrent systemic fungal infection. The p-value was greater than 0.05, indicating that there is no statistically

significant association between the occurrence of pulmonary TB and systemic fungal infections in Stage IV HIV patients.

Table 4. Bivariate Analysis Results of the Relationship Between the Incidence of Pulmonary TB and Systemic Fungal Infections in Stage IV HIV Patients

		Systemic Fungal Infection		*p-value*
		No	Yes	
Lung Tuberculosis	No	15	27	0,977
	Yes	4	18	

The relationship between extrapulmonary tuberculosis (TB) and systemic fungal infections in Stage IV HIV patients is shown in Table 4.5. Sixteen Stage IV HIV patients with systemic fungal infections were also diagnosed with extrapulmonary TB, while 29 patients did not have extrapulmonary TB. Additionally, 15 patients neither had systemic fungal infections nor extrapulmonary TB, and 4 patients were found to have only extrapulmonary TB without systemic fungal infection. The p-value was greater than 0.05, indicating that there is no statistically significant association between the incidence of extrapulmonary TB and systemic fungal infections in Stage IV HIV patients.

Table 5. Bivariate Analysis Results of the Relationship Between the Incidence of Extrapulmonary TB and Systemic Fungal Infections in Stage IV HIV Patients

		Systemic Fungal Infection		*p-value*
		No	Yes	
Lung Extra Tuberculosis	No	15	29	0,145
	Yes	4	16	

Table 6 illustrates the relationship between Type 2 Diabetes Mellitus (DM) and systemic fungal infections in Stage IV HIV patients. The table shows that none of the Stage IV HIV patients, whether they had systemic fungal infections or not, were diagnosed with Type 2 DM, with 45 patients and 19 patients respectively. This can be attributed to the fact that HIV patients with systemic fungal infections were predominantly found in younger age groups, specifically those aged 19–44 years. Due to the failure to meet the chi-square test requirements, no statistical analysis could be conducted.

Table 6. Bivariate Analysis Results of the Relationship Between the Incidence of Type 2 Diabetes Mellitus and Systemic Fungal Infections in Stage IV HIV Patients

		Systemic Fungal Infection		*p-value*
		No	Yes	
Diabetes Type 2	Yes	0	0	-
	No	19	45	-

Multivariate analysis of the variables albumin, CD4+, and extrapulmonary tuberculosis revealed a significant association between albumin levels and CD4+ counts with the incidence of systemic fungal infections, with p-values of 0.003 and 0.002, respectively.

Table 7. Multinomial Regression Analysis Results of Albumin Levels, CD4+ Levels, and the Incidence of Extrapulmonary TB as Risk Factors for Systemic Fungal Infections in Stage IV HIV Patients.

Systemic Fungal Infection		Sig.
No	Intercept	0,023
	Albumin <3.5	0,003
	Albumin 3.5 – 5.5	-
	CD4+ ≤100	0,002
	CD4+ 100-200	-
	No Lung Extra TB	0,694
	Lung Extra TB	-

4. Discussion

Fungi are major contributors to opportunistic infections that afflict HIV/AIDS patients. In October 2022, the World Health Organization (WHO) issued its first-ever global list of fungal priority pathogens—a systematic effort to prioritize fungal pathogens. Of the 19 pathogens listed by the WHO, four opportunistic fungi are particularly known to cause invasive diseases in individuals with HIV: Cryptococcus neoformans, Histoplasma spp, Pneumocystis jirovecii, and Talaromyces marneffei. These four fungal pathogens are the primary drivers of disease and mortality in individuals with advanced-stage HIV, predominantly affecting populations in low- and middle-income countries. Other notable pathogens include species of Aspergillus, Coccidioides, Blastomyces dermatitidis, Paracoccidioides brasiliensis, and Emmonsia species. The incidence of systemic fungal infections has markedly declined in HIV patients in high-income countries due to the widespread availability of antiretroviral therapy (ART) and early HIV testing. However, in many regions with high HIV prevalence, patients often present to healthcare services with advanced HIV infections and critically low CD4+ counts, or they continue to experience persistently low CD4+ levels due to poor treatment adherence, antiretroviral drug resistance, or both.[13-15]

A study by Forno et al. (2021) revealed that among 160 HIV-positive individuals diagnosed with opportunistic fungal infections, 96 patients (60%) were diagnosed with histoplasmosis, 62 (39%) with cryptococcosis, and two patients (1%) were diagnosed with both fungal diseases. CD4+ data were available for 136 patients (85% of the total); 127 patients (93%) had CD4+ counts below 200 cells/μL, and 90 patients (66%) had CD4+ counts below 50 cells/μL. Utilization of antiretroviral therapy at the time of diagnosis was low, at only 33%. Additionally, 71 of the 160 patients (44%) were coinfected with tuberculosis (TB) or other opportunistic infections. In this study, the types of fungal infections found in the sample included Pneumocystis pneumonia (PCP) (53.7%), Candidiasis (9.4%), Histoplasmosis (3.1%), Cryptococcosis (3.1%), and Penicilliosis (1.6%).

The significant findings of this study align with previous similar research. Santos et al. compared albumin levels in 461 patients with systemic fungal infections and found a strong correlation between hypoalbuminemia and the occurrence of such infections. Mild hypoalbuminemia (3 – 4 g/dL) and severe hypoalbuminemia (≥ 4 g/dL) were consistently present prior to the onset of systemic fungal infections. Thus, hypoalbuminemia at any level has been identified as a valuable predictor of systemic fungal infections according to Santos et al.[17] In addition to its association with systemic fungal infections, hypoalbuminemia has also been linked to chronic inflammation, which serves as the underlying mechanism connecting it to systemic fungal infections.

According to Wiedermann, hypoalbuminemia is associated with the severity of infections caused by viruses, bacteria, and even fungi, and can serve as a predictor of complications in non-infectious diseases. Systemic inflammation in chronic infections alters the function and kinetics of albumin, thereby increasing

the risk of worse clinical outcomes. The interaction between albumin and bioactive lipid mediators may play a critical role in the onset of cytokine storms and organ failure during an infection.[18] When further linked to HIV status, a study by Sudfeld et al. showed similar findings. All HIV patients experienced chronic inflammation, and the majority of those with chronic inflammation also developed severe hypoalbuminemia. Therefore, according to Sudfeld et al., albumin concentration in HIV patients could potentially determine the complications that arise, one of which is systemic fungal infection.[19]

Research has shown that lower albumin levels are associated with more severe stages of HIV, which in turn correlates with an increased risk of systemic fungal infections. Hypoalbuminemia also indicates poor nutritional status, further exacerbating the risk of infections, including systemic fungal infections. Additionally, hypoalbuminemia is linked to immune system dysfunction, and in HIV patients, it heightens the risk of opportunistic fungal infections, such as cryptococcosis, histoplasmosis, and pneumocystis pneumonia.[14]

Hypoalbuminemia is significantly associated with the progression of infections, including fungal infections, particularly in HIV patients (de Sousa). In a study conducted by Balgi et al. in 2019, it was found that albumin levels were meaningfully related to the occurrence of immune suppression in Stage IV HIV patients. However, the exact magnitude of this effect could not be determined, as the statistical methods used in that study were similar to those applied in the present research.[20] Similarly, Feldman et al. provided results consistent with this study, noting that Stage IV HIV patients with albumin levels below 3.5 g/dL were three times more likely to die from infections that could arise.[21]

CD4+ T cells are crucial in the immune response to viral pathogens. HIV patients who experience progressive decline in CD4+ T cells become increasingly susceptible to infections such as cryptococcosis, histoplasmosis, aspergillosis, candidiasis, and pneumocystis pneumonia. Several CD4+ subsets, particularly Th1 and Th17, play protective roles against fungal diseases. Th1 cells, mediated by IL-12 and IFN-g, are involved in fungal clearance, while Th17 cells, mediated by TGF-b, IL-6, IL-1, IL-21, and IL-23, are essential in maintaining antifungal responses. HIV infection targets Th1 and Th17 cells, thereby increasing susceptibility to fungal infections.[22]

Balgi et al. also support the relationship between CD4+ levels and the incidence of infections in Stage IV HIV patients, consistent with the findings of this study. The statistical methods employed in this research similarly limit the ability to further assess the strength and extent of the relationship observed.[20] A similar study conducted in Yogyakarta by Pudjiati et al. found that low CD4+ counts increase the risk of fungal infections by 3.8 times in Stage IV HIV patients. However, in that study, the CD4+ cutoff was higher (<200 cells/mm³), and the fungal infection manifestations assessed were limited to mucocutaneous infections.[23] CD4+ counts below 200 cells/mm³ are associated with life-threatening fungal infections, such as mucosal candidiasis, PCP, and cryptococcal meningoencephalitis. Research indicates that antiretroviral therapy (ART) can sustain higher CD4+ levels and reduce viral load, while irregular adherence to ART can impair immune function and increase the risk of fungal infections.[24]

A study by Ochiabuto et al. (2015) demonstrated a significant relationship between fungal infections and factors such as gender, age, and antiretroviral therapy (ART) ($P \leqslant 0.05$). Out of 100 sputum samples cultured, 80 showed fungal growth: 61 single isolates and 19 mixed isolates, while the remaining 20 samples exhibited no fungal growth. Different fungal species were isolated from 5 of the 9 patients who tested positive for Mycobacterium spp. Eight different fungal species were identified, with Candida albicans being the dominant species (24 isolates, 30%) in patients with CD4+ counts ranging from 10 to 200 cells/µL, while Aspergillus niveus was the least prevalent (1 isolate, 1.2%) in patients with CD4+ counts between 300 and 400 cells/µL. Penicillium marneffii was the second most prevalent fungus, found in 11 samples (13.8%). Patients with CD4+ counts below 100 cells/µL exhibited the highest frequency of fungal isolates from their sputum (27 isolates, 76.4%) ($P \leqslant 0.05$), while patients with CD4+ counts greater than 400 cells/µL showed

no fungal infections. Patients with Aspergillus fumigatus, Candida glabrata, and mixed infections had total white blood cell (WBC) counts below 4.0 × 10^9 cells/L. Neutropenia was also observed in patients with Candida albicans, Aspergillus fumigatus, Aspergillus niger, and Penicillium marneffii.[25]

Another study conducted by Tugume et al. supports the findings of this research by comparing the incidence of fungal infections in HIV patients with varying CD4+ levels, using cut-off values of <50 cells/mm^3, 50 – 99 cells/mm^3, and ⩾100 cells/mm^3. The study found that patients with CD4+ counts ⩾100 cells/mm^3, accompanied by changes in mental status, were more likely to develop systemic fungal infections compared to those with CD4+ counts <50 cells/mm^3 and 50 – 99 cells/mm^3.[26] Similarly, a study by Kaur et al. demonstrated a significant relationship between candidiasis infections and low CD4+ counts (100–200 cells/mm^3).[26] Another study by Ogba et al. revealed a significant association between CD4+ counts <200 cells/mm^3 and pulmonary aspergillosis.[27]

Chronic inflammation and tissue damage caused by tuberculosis (TB) infection can impair lung tissue, making it more susceptible to secondary infections. Necrotic tissue within granulomas provides a nutrient-rich environment conducive to fungal growth.[28] In addition to granulomas, cavitary lesions that form in post-TB patients can serve as reservoirs for fungal colonization.[29] Studies have shown that TB patients frequently experience co-infections with Candida, Aspergillus, Histoplasma, and Cryptococcus. These pathogens can exacerbate immune system dysfunction and damage lung tissue, thereby facilitating the onset of infections.[30] Pulmonary aspergillosis is a common comorbidity in TB patients and is often misdiagnosed as TB relapse or therapy failure. One species of Aspergillus (A. fumigatus) can colonize cavitary lesions, further exacerbating immunosuppression associated with TB/HIV co-infection.[29]

The findings of this study, showing no significant association between pulmonary TB and systemic fungal infections in Stage IV HIV patients, contrast with earlier research. Lin et al. indicated that pulmonary TB could facilitate fungal pathogen invasion into the lungs of Stage IV HIV patients.[31] However, a recent systematic review and meta-analysis conducted by Peña et al. in 2021 supports the findings of this study, stating that no significant association exists between pulmonary TB and fungal co-infections in Stage IV HIV patients.[32]

Extrapulmonary tuberculosis (TB) can exacerbate immune system dysfunction, thereby increasing susceptibility to fungal infections such as aspergillosis, histoplasmosis, and cryptococcosis, especially in immunocompromised populations.[33] TB also worsens HIV infection. Increased HIV viral load in the lungs, blood, and cerebrospinal fluid has been observed in TB patients. This is due to enhanced viral replication at sites of granulomatous inflammation, where a high number of activated T cells and increased regulation of HIV transcription by pro-inflammatory cytokines are produced in response to the immune system's reaction to TB. Epidemiological research indicates a rise in the incidence of opportunistic infections in HIV patients co-infected with TB.[34]

In this study, no significant association was found between extrapulmonary TB and systemic fungal infections in Stage IV HIV patients. This finding contrasts with several prior studies. Singh et al. (2014) reported that 32.95% of HIV patients with fungal infections had extrapulmonary TB. However, the significance of this finding could not be evaluated as no statistical testing was performed in that study.[17] Similarly, Shiboski et al., in the same year, presented results that contradicted the findings of this study, stating that a strong association exists between the occurrence of extrapulmonary TB and fungal infections in Stage IV HIV patients.[19]

Type 2 Diabetes Mellitus (DM) is a known risk factor for fungal infections in HIV patients, particularly cryptococcosis, histoplasmosis, and pneumocystis pneumonia.[14,35] Both conditions impair immune function. Hyperglycemia in Type 2 DM patients can disrupt neutrophil function and reduce the immune system's ability to defend against fungal infections, thereby further increasing the risk of fungal infections in HIV/AIDS patients.[14]

Co-infections commonly observed during HIV infection significantly impact the epidemiological and pathophysiological relationship between HIV and diabetes. Invasive fungal diseases are life-threatening infections with high mortality rates. The mortality rate from invasive candidiasis is estimated to range from 10% to 15%, while invasive aspergillosis carries a mortality rate of 42-64% in critically ill patients. Diabetic patients are particularly susceptible to fungal infections. The risk of mycosis increases 1.38 times in diabetic patients, and diabetes is widely recognized as a risk factor for invasive pulmonary aspergillosis. Uncontrolled hyperglycemia contributes to poor prognosis in Type 2 diabetes patients with cryptococcosis. Diabetes is a potential risk factor for invasive fungal diseases caused by unusual fungi, such as Histoplasma capsulatum. Fungal infections in diabetic patients show increased drug resistance, and biofilms act as a major physical barrier reducing antifungal absorption, leading to antifungal tolerance.[36,37]

Due to the failure to meet statistical test requirements in this study, the significance of Type 2 DM in relation to systemic fungal infections in Stage IV HIV patients could not be assessed. Indira et al. stated in their study that Type 2 DM does not increase the risk of systemic fungal infections in Stage IV HIV patients.[20] However, a study by Lao et al. mentioned that fungal infections represent a life-threatening complication in Type 2 DM patients. This study, however, did not examine whether this applied to all Type 2 DM patients with Stage IV HIV or only to Type 2 DM patients in general.[21]

All three patient characteristics—albumin levels, CD4+ counts, and the occurrence of extrapulmonary tuberculosis (TB)—have been identified as risk factors for systemic fungal infections in Stage IV HIV patients. This finding aligns with previous studies. Qiu et al. supported this by stating that albumin levels serve as a good prognostic factor for predicting the occurrence of systemic fungal infections in Stage IV HIV patients.[38] Ellis et al. further emphasized that lower CD4+ counts and the presence of extrapulmonary TB contribute to the development of systemic fungal infections in Stage IV HIV patients.[22]

5. Conclusion

This study demonstrates that systemic fungal infections in HIV patients are most prevalent in the 19–44 age group and predominantly in males. The average CD4+ count in the group of Stage IV HIV patients with systemic fungal infections was 43.5 (+43.4), while the average CD4+ count in the group without systemic fungal infections was 82.1 (+57.9). A statistically significant relationship was found between CD4+ levels and albumin levels with systemic fungal infections in Stage IV HIV patients, with a p-value < 0.05. Multivariate analysis revealed that both albumin levels and CD4+ counts could serve as risk factors for the occurrence of systemic fungal infections in Stage IV HIV patients.

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