Clinical Research

Clinical and microbiological characteristics of onychomycosis in a tertiary hospital: a cross-sectional study

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ABSTRACT

BACKGROUND Onychomycosis is a common fungal nail infection with a low cure rate. While dermatophytes are the most common causal agent for onychomycosis, the incidence of *Candida* and nondermatophyte mold (NDM) onychomycosis is increasing. This study aimed to analyze the clinical and microbiological characteristics of patients with onychomycosis.

METHODS Patients who visited the Department of Dermatology and Venereology, Cipto Mangunkusumo Hospital, and were diagnosed with onychomycosis from 2017 to 2022 were included. Diagnosis was established through clinical examination, supported by the result of direct microscopic examination with potassium hydroxide.

RESULTS Of 171 patients, 93.6% had onychodystrophy, 65.5% were females, and 62.0% were aged 19–59 years. Most patients had onychodystrophy in more than three nails, affecting fingernails (31.6%) and toenails (34.5%). Interestingly, 84.8% of patients had no history of nail diseases. The median onset of disease was 24.0 (1–1,040) weeks, while the median onychomycosis severity index was 10.0 (2–40). Most cases were caused by *Candida albicans* (48.3%). *Fusarium* was the only NDM documented (2.3%). Some patients were resistant to itraconazole (11.4%) and miconazole (4.5%). Overall, 49.1% of the patients were declared not cured.

CONCLUSIONS *Candida* was the predominant cause of onychomycosis, and onychodystrophy was the dominant feature. Current treatment regimens with systemic or topical antifungal agents did not yield satisfactory results, with more than half of the patients deemed not cured.

KEYWORDS *Candida*, microbiology, molds, onychomycosis, prognosis, tertiary hospital

Onychomycosis is a common fungal infection of the nail that is mostly caused by dermatophytes. It can also be caused by yeasts (*Candida* sp.) and nondermatophyte molds (NDMs), particularly in immunocompromised patients. Although onychomycosis is primarily caused by dermatophytes, the incidence of onychomycosis caused by *Candida* sp. has increased.[1]

The role of *Candida* sp. in the etiology of onychomycosis and the virulence of NDMs in infiltrating nails are still under debate. A previous theory stated that *Candida* infection is the etiology of superficial dermatomycosis only in immunocompromised hosts. However, several studies in the past decade showed that *Candida* also causes onychomycosis in immunocompetent patients, accounting for 58.5% of all onychomycosis cases.[2] Onychomycosis caused by NDMs is difficult to diagnose because NDMs have been considered nail contaminants.[3]

Several cases of onychomycosis due to NDMs have been reported, including those caused by *Aspergillus* sp., *Fusarium*, and *Penicillium* sp. However, the exact cause remains unclear. NDMs and *Candida*

sp. can be primary or secondary pathogens. *Candida* onychomycosis (CO) is mostly caused by *C. albicans* and *C. parapsilosis,* which are often associated with local and systemic immune disorders.[1] Otašević et al[4] reported a 31% prevalence of CO in Serbia, with *C. albicans, C. parapsilosis,* and *Candida* sp. as the three most common causes of CO.

Onychomycosis has mycological, clinical, and complete cure criteria. The most important prognostic factors include patient characteristics, morbidities, nail conditions, and microorganisms. Treating onychomycosis is more difficult than treating other dermatomycoses because of the slow physiological growth of the nails. Therefore, good patient compliance and appropriate treatment are important for good outcomes. Diagnosing onychomycosis is challenging owing to the various diagnostic criteria and associated challenges with its treatment.[5–7]

In 2017, the Department of Dermatology and Venereology, Faculty of Medicine, Cipto Mangunkusumo Hospital, recorded a 15% incidence rate of onychomycosis, with a cure rate of 62.5%.[7] A study in Bali reported an onychomycosis rate of 10.8% in 2016.[8] Considering the relatively low cure rates, particularly in CO cases, this study aimed to analyze the profile of patients with onychomycosis in a tertiary hospital in Jakarta.

METHODS

Study design

This cross-sectional study was conducted at the Department of Dermatology and Venereology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, from January 2017 to December 2022. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital (No: KET-304/UN2.F1/ETIK/PPM.00.02/2022). Secondary data from the medical records were used in this study.

Study participants

The study participants were patients who visited the clinic from 2017 to 2022. The inclusion criteria were patients with onychomycosis with direct microscopic examination data and complete data until treatment completion. Patients without a complete medical record or diagnostic test to support the diagnosis of onychomycosis were excluded. Total sampling was performed using data from the medical records.

Data collection

Data were acquired from manual and electronic medical records. Sociodemographic and clinical data included sex, age, comorbidities, history of nail diseases (e.g., previous nail trauma, nail infection, or nail dystrophy), number of involved nails, clinical manifestations, onset, and onychomycosis severity index (OSI). The diagnosis was established through clinical examination, supported by direct microscopic examination before and after potassium hydroxide (KOH) treatment. The primary diagnostic criteria were onychodystrophy, nail discoloration, and onycholysis with pseudohyphae, blastospores, yeast cells, and hyphae. The severity of onychomycosis was defined with OSI, which sums up the multiplication of the involvement area and proximity to the matrix with the presence of subungual hyperkeratosis >2 mm or dermatophytoma.[9] As OSI was implemented in 2020, some participants did not have OSI data. Most patients used national health insurance, leading to limited funding for culture and antifungal sensitivity tests; therefore, only a few patients underwent these tests. Cultures were performed on Sabouraud dextrose agar, and antifungal sensitivity testing was performed for all cultures based on clinical and laboratory standards institute guidelines using ketoconazole, itraconazole, fluconazole, and miconazole.[10,11] Data were acquired from the mycology laboratory of the Department of Parasitology, Faculty of Medicine, Universitas Indonesia. Mycological cure was defined as a negative result on culture or direct microscopic examination.

Statistical analyses

Data were analyzed using SPSS software version 20.0 (IBM Corp., USA). Categorical data are presented as frequencies and percentages. Continuous data with non-normal distribution are presented as medians (min–max). The association between categorical data was analyzed using the chi-square test. $p<0.05$ was considered significant.

RESULTS

Of the 199 documented onychomycosis cases, only 171 were included in this study (Table 1). The laboratory findings are shown in Table 2.

The treatment regimen is shown in Supplementary Figure 1. Most patients were treated with topical

ketoconazole cream, whereas itraconazole was the most used systemic agent. The clinical outcome is shown in Figure 1. Most patients achieved a clinical cure (51.5%), whereas 44.4% of the patients did not achieve a mycological cure. Overall, 49.1% of patients were declared not cured.

Table 1. Sociodemographic and clinical characteristics of the patients

Characteristics	n (%) (N = 171)
Male sex	59 (34.5)
Age (years), median (min–max)	51.0 (9–88)
9–18	7 (4.1)
19–59	106 (62.0)
60–88	58 (33.9)
Comorbidities	
None	44 (25.7)
One comorbidity	91 (53.2)
More than one comorbidity	36 (21.1)
History of nail diseases	
Yes	26 (15.2)
No	145 (84.8)
Number of involved fingernails	
None	59 (34.5)
1	26 (15.2)
2–3	32 (18.7)
>3	54 (31.6)
Number of involved toenails	
None	42 (24.6)
1	27 (15.8)
2–3	43 (25.1)
>3	59 (34.5)
Overall involved fingers	
1	26 (15.2)
2–3	55 (32.2)
>3	90 (52.6)
Clinical manifestations*	
Onychodystrophy	160 (93.6)
Onycholysis	79 (46.2)
Nail discoloration	
Yellowish	126 (73.7)
Greenish	6 (3.5)
Blackish	18 (10.5)
Onset (weeks), median (min–max)	24.0 (1–1,040)
OSI, median (min–max)†	10.0 (2–40)

OSI=onychomycosis severity index
*One patient may have two clinical manifestations; †only 54 patients had OSI score data

None of the characteristics were significantly associated with the clinical outcomes, except onycholysis (Table 3). Patients with onycholysis had a 2.2 times higher risk of not achieving a cure (95% confidence interval = 1.166–4.370) than those without onycholysis.

Table 2. Laboratory findings in patients with onychomycosis

Laboratory findings	n (%) (N = 171)
Direct microscopic examination with KOH (n = 171)	
Blastospore	158 (92.4)
Yeasts	7 (4.1)
Hyphae	3 (1.8)
None	3 (1.8)
Number of colonies (n = 60)	
None	12 (20.0)
10 colonies	6 (10.0)
15 colonies	2 (3.3)
20 colonies	40 (66.7)
Culture result (n = 62)	
C. albicans	29 (48.3)
C. parapsilosis	8 (13.3)
Fusarium	4 (6.7)
C. glabrata	3 (5.0)
Trichosporon sp.	3 (5.0)
C. tropicalis	1 (1.7)
Rhodotorula sp.	1 (1.7)*
C. dubliniensis	1 (1.7)†
None	12 (20.0)
Antifungal sensitivity test (n = 44)	
Fluconazole	44 (100.0)
Ketoconazole	44 (100.0)
Miconazole	42 (95.5)
Itraconazole	39 (88.6)

**Rhodotorula* was identified with *C. parapsilosis* in one patient; †*C. dubliniensis* was identified with *C. albicans* in one patient

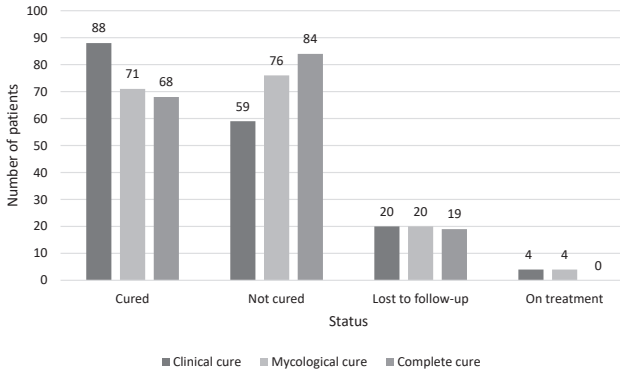

Figure 1. Clinical outcome of the patients

Table 3. Association between sociodemographic and clinical characteristics with clinical outcomes

Determinants	Clinical outcomes		*p*
	Cure, n (N = 68)	Not cured, n (N = 84)	
Male sex	23	31	0.693§
<60 years	44	59	0.468§
History of nail diseases	8	15	0.299§
Etiologic agents*			0.212¶
Yeasts	65	81	
NDM	0	2	
Morphological of fungi†			0.702§
Blastospores	62	78	
Yeast	4	2	
Hyphae	0	3	
None	2	1	
Comorbidities			0.381§
None	17	22	
One comorbidity	39	40	
More than one comorbidity	12	22	
Clinical manifestation‡			
Onychodystrophy	66	75	0.112¶
Onycholysis	23	45	**0.015**§
Nail discoloration			
Yellowish	52	60	0.483§
Greenish	1	4	0.381¶
Blackish	5	13	0.123§
Number of involved fingers			0.991§
1	10	13	
2–3	22	27	
>3	36	44	

NDM=nondermatophyte mold
*Etiologic agents were only identified in 148 because four patients did not have any culture growths; †using direct examination with KOH; ‡one patient may have two clinical manifestations; §chi-square test; ¶Fischer's exact test

Both yeasts and NDMs caused onychodystrophy. The most common species causing onychodystrophy was *C. albicans* (Table 4).

Of the four NDM cases, two were lost to follow-up, and the rest did not achieve a complete cure. Specifically, one patient only achieved a mycological cure, while the other achieved only a clinical cure. All patients were females aged 26–72 years. One patient had a history of AIDS, two had a history of autoimmune disease, and one had no comorbidities.

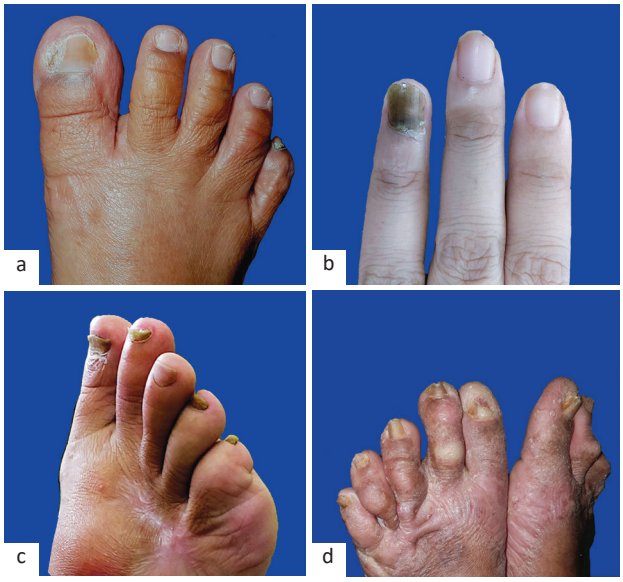

Figure 2. Clinical findings. (a) *Fusarium* onychomycosis showing onychodystrophy and yellowish nail discoloration on the first toenail; (b) *Candida glabrata* onychomycosis showing onychodystrophy and blackish nail discoloration on the second fingernail; (c) *C. parapsilosis* onychomycosis showing onychodystrophy, onycholysis, and yellowish nail discoloration on the first, second, fourth, and fifth toenails; (d) *Trichosporon* onychomycosis showing onychodystrophy, onycholysis, and yellowish nail discoloration on all toenails

Three of the four patients had a history of nail disease prior to onychomycosis. All patients showed onychodystrophy and nail discoloration in nails 2–10 (Figure 2). Direct microscopic examination showed blastospores and pseudohyphae in two patients, whereas the others had hyphae. Only one sample showed sensitivity toward oral antifungal agents, whereas the others were resistant to one azole agent. All patients were administered ketoconazole cream once daily for a treatment duration ranging from 4 to 55 weeks.

DISCUSSION

In the present study, most patients were female, with a median age of 51.0 years (ranged 9–88 years). Similarly, a previous study reported a preponderance of females and older patients with onychomycosis.[7,12,13] Onychomycosis is more prevalent in women due to increased water exposure, particularly during activities such as laundry and dishwashing.[7] However, men also have a significant risk of onychomycosis, despite no clear explanation.[13] Older age is associated with onychomycosis due to a decrease in immune responses, poor vascularization, and declining nail

Table 4. Association between causal agent and clinical manifestation

	Clinical manifestation				
	Onychodystrophy	Onycholysis	Yellowish nail discoloration	Greenish nail discoloration	Blackish nail discoloration
Type*					
Blastospore and pseudohyphae	147	76	116	5	18
Yeast cell	7	3	4	1	0
Hyphae	3	0	3	0	0
Species†					
C. albicans	27	13	26	1	2
C. parapsilosis	7	5	6	0	0
Fusarium	4	2	4	0	0
Trichosporon	3	2	3	0	0
C. glabrata	3	0	1	2	1
C. dubliniensis	1	1	1	0	0
C. tropicalis	1	0	1	0	0
Rhodotorula	1	0	1	0	0
No growth	12	3	10	1	1

*Based on clinical and direct examination results (171 patients were performed direct examination with KOH); †based on culture (62 patients)

growth.[7] However, the present study reported a higher prevalence of onychomycosis in the productive age group than in the elderly. This might be explained by the greater awareness of the adult population and higher exposure to water during work or religious practices, as Muslims pray 5 times daily.[7]

Half of the patients had one comorbidity, and almost all had no history of nail disease. Comorbidities are often associated with onychomycosis. The most common comorbidities associated with onychomycosis are diabetes mellitus (DM), poor peripheral vascularization, psoriasis, and immunodeficiency. A history of nail trauma also commonly predisposes patients to onychomycosis.[14] Cho et al[13] reported that, in addition to knee osteoarthritis, patients with onychomycosis were also diagnosed with hypertension, DM, dyslipidemia, and hypothyroidism. Although nail trauma was not mentioned, 1.2% of the patients had a history of toe trauma.[13] A previous study in Indonesia reported that most patients with onychomycosis had no comorbidities and no history of nail disease; however, the most common comorbidities identified were other skin diseases, endocrine diseases, and other systemic diseases.[7] In Italy, 77% of patients with onychomycosis had comorbidities, including DM, immunodeficiency, and peripheral vascular diseases.[15] In the present study, the development of onychomycosis was not significantly linked to a history of nail disorders; however, comorbidities might play an important role in its development.

In the present study, most of the patients had onychomycosis in more than three nails, which aligns with a previous study in Jakarta.[7] A study on the onychomycosis in elderly patients showed that 43% had more than one toenail involvement.[15] A study in Italy also reported that more than 50% of the patients presented with involvement of multiple nails in both fingers and toes.[16] Multiple nail involvement is implicated in choosing treatment for the patients since moderate-to-severe onychomycosis should be treated with systemic agents, while mild-to-moderate cases can be treated with topical agents alone.[5] In the present study, some patients did not receive systemic agents due to the presence of comorbidities and the use of other oral medications, which could lead to potential drug interactions.

In line with previous studies,[7,15] the present study found that onychodystrophy was the most common clinical manifestation of onychomycosis. Onychodystrophy is an abnormal nail appearance, both in thickness and growth, caused by various disorders, including fungal infections,[17] with a median disease onset of 24.0 weeks. A previous study in Indonesia reported that most patients had an onset period of <6 months.[7]

Direct microscopic examination showed that almost all patients had blastospores, and *C. albicans*

was identified as the most common fungus grown in culture media. This result aligns with a previous study in India, which reported *C. albicans* as the most common fungal isolate from patients with onychomycosis.[12] Meanwhile, several studies have reported dermatophytes as the most common cause of onychomycosis.[18,19] *Candida* is a well-known organism residing in the normal flora of human skin, mucous membranes, and nails.[5]

OSI is a valid and reliable scoring for assessing onychomycosis severity, with a value of 10 indicating moderate onychomycosis.[9] The present study reported varying onychomycosis severity with OSI ranging from 2 to 40. Notably, the median OSI was 10.0, which was lower than that reported in previous studies in China, Egypt, and Germany.[20–22]

Topical medications are recommended for mild-to-moderate onychomycosis, whereas oral medications are recommended for moderate-to-severe onychomycosis. Most patients in this study received a topical ketoconazole cream, whereas itraconazole was the most commonly used systemic agent. A similar study in the same institution reported itraconazole pulse-dose therapy as the mainstay treatment for onychomycosis.[7] Itraconazole acts by inhibiting the lanosterol 14α-demethylase with broad spectrum activity toward *Candida,* dermatophytes, and NDMs. It had a 47% complete cure rate for fingernail onychomycosis and a 14% complete cure rate for toenail onychomycosis, which was lower than the complete cure rate of terbinafine (59% and 38% for fingernail and toenail onychomycosis, respectively).[6] However, azole was used as the mainstay treatment because most cases were caused by *Candida*, which responds better to itraconazole than terbinafine. Nail lacquers are not commonly used because of their high cost and limited availability.

All patients were sensitive to fluconazole and ketoconazole; however, some were resistant to itraconazole and miconazole. Resistance to antifungal agents is increasing worldwide, including in Indonesia, and is caused by poor compliance to treatment, suboptimal treatment, incorrect diagnosis, and genetic mutations. Several genes, such as ERG11, CDR1, MDR1, and CDR2, play a role in the development of azole resistance.[23,24] The present study only assessed microbiological resistance without assessing clinical resistance because it was a cross-sectional study. Susceptibility testing is necessary for effective treatment strategies and patient prognosis. However, some patients could not afford the test because they were not covered by the national health insurance.

Most patients in this study did not achieve a complete cure for onychomycosis. This result aligns with a previous study that also reported a poor cure rate of onychomycosis.[6] Factors contributing to this poor cure rate are high resistance rate, possible *Candida* colonization, female sex, older age, comorbidities, involvement of more than three nails, and presence of dystrophic onychomycosis.[7,25] Therefore, developing new treatment strategies is necessary to improve onychomycosis cure rates.

NDMs are also a significant factor in onychomycosis, with a worldwide prevalence of 2–22%. The main challenge is the diagnosis and prognosis of the disease.[3] In the present study, the patients had either comorbidities or a history of nail disease; this aligns with a previous study that suggested NDMs cannot destroy the keratin but can act as secondary intruders. *Fusarium* causes distal lateral subungual onychomycosis, superficial white onychomycosis, and proximal subungual onychomycosis.[3] However, this study did not analyze the onychomycosis type due to a lack of data and found that onychodystrophy and nail discoloration were the prominent features of NDM onychomycosis.

Direct microscopic examination revealed blastospores and pseudohyphae in half of the patients, while the other half showed hyphae. *Fusarium* is known to produce nonpigmented septated hyphae, while blastospores and pseudohyphae are produced by *Candida*.[26] This suggests that *Candida* might have colonized the infected nails as *Candida* is an opportunistic pathogen in human nails.[7] Further examination with culture showed that three out of four samples were resistant to an azole agent, which aligns with the literature reporting *Fusarium*'s resistance to antifungal agents. *Fusarium* also has a poor therapeutic response, with limited choices for successful therapy.[23,27] Hence, as seen in this study, the treatment duration is usually long. Nevertheless, the patients were given an unstandardized therapy, ketoconazole cream, due to cost limitations. The recommended therapies for *Fusarium* onychomycosis are itraconazole and terbinafine,[3] which are not covered by the national health insurance.

In contrast to Widaty et al,[7] the present study identified onycholysis as the only characteristic

associated with clinical outcomes of onychomycosis. This difference may be attributed to different study populations. Onycholysis occurs because of damage to the nail isthmus, which is the most resilient area for the adhesion of the nail bed and nail plate. Onycholysis is difficult to treat;[28] therefore, patients with onycholysis are less likely to be cured than those without onycholysis.

This study had several limitations. Only 60 patients had culture results, and some were lost to follow-up. We also did not assess onychomycosis type (i.e., distal lateral subungual onychomycosis, endonyx, total dystrophic onychomycosis, etc.) or clinical resistance owing to a lack of data; therefore, only microbiological resistance was documented. Future studies with larger sample sizes and more comprehensive diagnostic tests are warranted.

In conclusion, *Candida* was the predominant cause of onychomycosis, with onychodystrophy as the dominant feature. Current treatment regimens with systemic or topical antifungal agents did not yield satisfactory results, with more than half of the patients deemed not cured.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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