

## ORIGINAL RESEARCH

# Onychomycosis in older adults: The age and associated factors affecting the complete cure rate

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### ABSTRACT

**Background:** Limited studies exist on the factors associated with a complete cure of onychomycosis in older adults.

**Objectives:** To determine the age and factors associated with a complete cure among older adults diagnosed with toenail onychomycosis.

**Methods:** A retrospective cohort study was conducted of 95 older adult patients (aged  $\geq 60$  years) diagnosed with toenail onychomycosis between January 2016 and December 2017. Demographic data, mycological findings, treatments and durations to a complete cure were reviewed.

**Results:** The complete cure rates of the patients aged  $< 70$  years and  $\geq 70$  years were 67.4% and 44.9%, respectively ( $P = 0.027$ ). Patients aged  $\geq 70$  years were significantly higher in male gender, had higher history of smoking, peripheral arterial disease, impaired renal function, antihypertensive drug and amorolfine nail lacquer usage, and polypharmacy. A multivariate analysis revealed that being aged  $\geq 70$  years and having a nail thickness  $> 2$  mm were associated with failure to achieve a complete cure. The median times to a complete cure for older adults aged  $< 70$  years and  $\geq 70$  years were 20 months and 47 months, respectively ( $P = 0.007$ ).

**Conclusions:** An age  $\geq 70$  years was related to a lower cure rate and delays in achieving a complete cure. A nail thickness  $> 2$  mm was a poor prognostic factor for a complete cure. Moreover, very old adults were more likely to suffer side effects arising from the use of systemic antifungal medications.

**Key words:** complete cure, cut-off age, older adults, onychomycosis, risk factors.

### INTRODUCTION

Onychomycosis is one of the common health problems affecting older adults worldwide.<sup>1–4</sup> The majority of cases are toenail onychomycosis, which presents as abnormal toenails, such as nail thickening, discoloration and onycholysis.<sup>5, 4</sup> The most common causative organisms of toenail onychomycosis are dermatophytes (DMPs), followed by nondermatophytes (NDMs) and yeasts.<sup>1–4</sup> Mixed DMP and NDM infections have been detected in approximately 40% of patients with onychomycosis.<sup>5, 6</sup> The condition can be painful and uncomfortable, limits physical activity, and may cause embarrassment if the diseased nails are exposed. Collectively, these effects result in low self-confidence and an impaired quality of life.<sup>7, 8</sup>

The reported prevalence of onychomycosis in older adults ranges from 20% to 50% which is higher than other age groups.<sup>9, 10</sup> Given that the growth in the number of older people in the world is accelerating,<sup>11</sup> the proportion of patients with suspected onychomycosis is highly likely to rise. Older adult patients tend to have poor foot hygiene resulting from many comorbidities (such as eye diseases and arthritis of the hands) and mobility problems.<sup>12</sup> As a consequence, older adults experience foot and nail disorders more frequently than younger people.

The age cut-off for use in defining ‘the elderly’ population group varies. The World Health Organization has set an age of 65 years for this age group.<sup>15</sup> While most

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developed countries tend to use that age, definitions of the elderly in Africa use age cut-offs as low as 50 or 55 years.<sup>14</sup> On the other hand, one Japanese study defined subjects over 70 years of age as elderly.<sup>15</sup> In Thailand, the elderly are defined as people aged 60 years or more.<sup>16</sup> In view of these disparities as well as the very great differences in physiological and functional statuses found among the elderly, treatment decisions should be based on individual needs. Age alone should not be the sole determinant for treatment. To avoid the difficulties presented by the wide heterogeneity in the cut-off age for 'elderly', the current investigation defined subjects over 60 years of age as older adults. However, there are limited data on the age that is associated with a complete cure of onychomycosis among older adults. Therefore, this study set out to determine the age and other factors associated with a complete cure among older adults diagnosed with toenail onychomycosis, as well as the relevant baseline characteristics, including medical comorbidities and prescription-medication usage.

## MATERIALS AND METHODS

This retrospective cohort study was performed on older adult patients (aged  $\geq 60$  years) with DMP toenail onychomycosis who were treated with oral antifungal agents at the Department of Dermatology in a tertiary hospital in Thailand. It excluded fingernail onychomycosis, NDM toenail onychomycosis and *Candida* toenail onychomycosis. The baseline characteristics, clinical signs and symptoms, potassium hydroxide (KOH) examination and fungal culture results, treatment regimens, treatment outcomes, and durations to a complete cure were retrospectively reviewed.

The diagnoses of DMP onychomycosis had been confirmed by microscopic examination in 20% KOH solution and mycological culture in Sabouraud dextrose agar, with and without cycloheximide. Any subsequent nail culture results indicating the presence of an NDM infection after the diagnosis of DMP onychomycosis, but prior to a cure of the DMP onychomycosis, were deemed to indicate mixed onychomycosis. The diagnoses of NDM onychomycosis required a positive microscopic examination and a positive mycological culture for at least two consistent isolations from repeated samplings.<sup>17</sup> A 'complete cure' meant a clinical finding of less than or equal to 10% nail abnormalities and a negative mycological laboratory result.<sup>18</sup>

### Statistical analysis

Descriptive statistics were used to describe the baseline characteristics, clinical signs and symptoms, fungal culture results and treatment choices. Fisher's exact test was employed to compare the categorical variables. Continuous variables with and without normal distribution were analysed by an independent t-test and the Mann-Whitney U-test, respectively. Binary logistic regression with enter method was utilized to determine the factors associated with a complete cure. All variables showing statistical significance (a  $P$  value of  $< 0.2$ ) in a univariate analysis were

included in a multivariate analysis. A  $P$  value of  $\leq 0.05$  in the multivariate analysis was considered statistically significant. The times to a complete cure for different age groups were analysed using Kaplan-Meier survival analysis. All statistical data analyses were performed using PASW Statistics for Windows (version 18.0; SPSS, Chicago, Ill., USA).

## RESULTS

A total of 95 older adult patients diagnosed with DMP toenail onychomycosis were enrolled. Age was classified into five age groups (60–64, 65–69, 70–74, 75–79 and  $\geq 80$  years) to determine the age associated with a complete cure. The age groups 60–64 and 65–69 achieved complete cure rates that were approximately the same or higher than those of the other age groups. Moreover, the older adult patients who were aged  $\geq 70$  years achieved a complete cure significantly less frequently than the patients aged  $< 70$  years ( $P = 0.027$ ). Thus, the factors associated with a complete cure among older adults aged  $< 70$  years and those who were  $\geq 70$  years were analysed.

Most of the cases of toenail onychomycosis (60%) were caused by DMPs alone. The remaining 40% of the cases revealed NDM infections, and they were classified as mixed infections. The causative organisms of the onychomycosis are detailed in Table 1. Comparisons of the demographic data and clinical findings of the patients aged  $< 70$  years and those  $\geq 70$  years are presented in Table 2. A male predominance, a history of smoking,

**Table 1** Causative organisms of toenail onychomycosis of all older adult patients, older adults aged  $< 70$  years, and older adults aged  $\geq 70$  years

	N (%)		
	All patients (N = 95)	Age $< 70$ years (N = 46)	Age $\geq 70$ years (N = 49)
Dermatophytes	57 (60)	27 (58.7)	30 (61.2)
<i>Trichophyton mentagrophytes</i>	34 (35.8)	17 (37)	17 (34.7)
<i>Trichophyton rubrum</i>	20 (21.1)	10 (21.7)	10 (20.4)
<i>Trichophyton tonsurans</i>	2 (2.1)	0	2 (4.1)
<i>Trichophyton raubitschekii</i>	1 (1.1)	0	1 (2)
Mixed infection <sup>†</sup>	38 (40)	19 (41.5)	19 (38.8)
<i>Trichophyton mentagrophytes</i> and <i>Neoscytalidium</i> spp.	22 (23.2)	9 (19.6)	13 (26.5)
<i>Trichophyton rubrum</i> and <i>Neoscytalidium</i> spp.	7 (7.4)	3 (6.5)	4 (8.2)
<i>Trichophyton mentagrophytes</i> and <i>Fusarium</i> spp.	4 (4.2)	4 (8.7)	0
<i>Trichophyton rubrum</i> and <i>Aspergillus</i> spp.	1 (1.1)	1 (2.2)	0
Mix of $> 2$ organisms	4 (4.2)	2 (4.1)	2 (4.1)

<sup>†</sup>Mixed infection of dermatophytes and nondermatophytes.

**Table 2** Demographic data and characteristics of all older adult patients, older adults aged < 70 years, and older adults aged ≥ 70 years

	<i>N</i> (%)			<i>P</i> value
	All patients ( <i>N</i> = 95)	Age < 70 years ( <i>N</i> = 46)	Age ≥ 70 years ( <i>N</i> = 49)	
Gender				
Male	54/95 (56.8)	16/46 (34.8)	38/49 (77.6)	<0.001*
Female	41/95 (45.2)	30/46 (65.2)	11/49 (22.4)	
Age (years), mean ± SD	70.3 ± 7.5	65.9 ± 2.7	76.3 ± 5.4	–
Smoking ( <i>N</i> = 82)	12/82 (14.6)	2/39 (5.1)	10/45 (25.5)	0.028*
Underlying diseases				
Dyslipidemia	69/95 (72.6)	30/46 (65.2)	39/49 (79.6)	0.167
Hypertension	61/95 (64.2)	25/46 (54.3)	36/49 (75.5)	0.058
Diabetes mellitus	28/95 (29.5)	12/46 (26.1)	16/49 (32.7)	0.508
Peripheral arterial disease ( <i>N</i> = 90)	28/90 (31.1)	8/44 (18.2)	20/46 (45.5)	0.012*
Impaired renal function ( <i>N</i> = 76)	26/76 (34.2)	4/33 (12.1)	22/45 (51.2)	0.001*
Cardiovascular disease	15/95 (15.8)	4/46 (8.7)	11/49 (22.4)	0.092
Cerebrovascular accident	7/95 (7.4)	1/46 (2.2)	6/49 (12.2)	0.112
Medications before starting systemic antifungal therapy				
Statins ( <i>N</i> = 87)	55/87 (65.2)	23/42 (54.8)	32/45 (71.1)	0.126
Antihypertensive drugs ( <i>N</i> = 90)	59/90 (65.6)	24/44 (54.5)	35/46 (76.1)	0.046*
Antidiabetic drugs ( <i>N</i> = 91)	25/91 (25.3)	9/44 (20.5)	14/47 (29.8)	0.545
Antacids/H <sub>2</sub> -antihistamines/PPIs ( <i>N</i> = 92)	28/92 (30.4)	14/44 (31.8)	14/48 (29.2)	0.823
Antidepressants ( <i>N</i> = 94)	4/94 (4.5)	0	4/48 (8.5)	0.117
Benzodiazepines ( <i>N</i> = 92)	12/92 (15)	6/45 (15.3)	6/47 (12.8)	1.000
Immunosuppressive drugs ( <i>N</i> = 95)	2/95 (2.1)	1/46 (2.2)	1/49 (2)	1.000
Anticoagulants ( <i>N</i> = 94)	4/94 (4.5)	1/46 (2.2)	3/48 (6.5)	0.617
Polypharmacy (> 5 medications)	39/95 (41.1)	12/46 (26.1)	27/49 (55.1)	0.004*
Median SCIO	16	16	16	0.967
Clinical characteristic of onychomycosis				
DLSO	94/95 (98.9)	46/46 (100)	48/49 (98)	1.000
PSO	1/95 (1.1)	0	1/49 (2)	
Poor prognosis factors from physical examination				
Nail thickness > 2 mm ( <i>N</i> = 87)	38/87 (45.7)	18/44 (40.9)	20/45 (46.5)	0.668
Foot deformity ( <i>N</i> = 85)	30/85 (36.1)	14/40 (35)	16/45 (37.2)	1.000
Presence of callus/corn ( <i>N</i> = 81)	35/81 (40.7)	17/40 (42.5)	16/41 (39)	0.823
Dermatophytosis at feet	50/95 (52.6)	20/46 (45.5)	30/49 (61.2)	0.102
Oral antifungal agents				
Itraconazole <sup>†</sup>	35/95 (34.7)	17/46 (37.0)	16/49 (32.7)	0.886
Terbinafine <sup>‡</sup>	33/95 (35.7)	15/46 (32.6)	18/49 (36.7)	
Fluconazole <sup>§</sup>	29/95 (30.5)	14/46 (30.4)	15/49 (30.6)	

**Table 2** *Continued*

	N (%)			P value
	All patients (N = 95)	Age < 70 years (N = 46)	Age ≥ 70 years (N = 49)	
Duration of oral antifungal agents (months), mean ± SD				
Itraconazole <sup>†</sup>	10.0 ± 5.9	8.1 ± 4.9	12.0 ± 6.2	0.052
Terbinafine <sup>‡</sup>	7.2 ± 5.1	6.2 ± 5.5	7.9 ± 6.2	0.352
Fluconazole <sup>§</sup>	12.9 ± 6.9	13.0 ± 7.8	12.7 ± 6.3	0.920
Other antifungal treatments				
Urea cream	86 (90.5)	42 (91.3)	44 (89.8)	1.000
5% amorolfine nail lacquer	41 (45.2)	15 (32.6)	26 (55.1)	0.044*
Nail grinding	61 (64.2)	29 (65.0)	32 (65.5)	0.818
Complete cure rate	55/95 (55.8)	31/46 (67.4)	22/49 (44.9)	0.027*

Abbreviations: DLSO, distal lateral subungual onychomycosis; PPIs, proton-pump inhibitors; PSO, proximal subungual onychomycosis; SCIO, the Scoring Clinical Index for Onychomycosis.

\*P value ≤ 0.05

<sup>†</sup>Itraconazole pulse therapy (200 mg twice daily, 1 week each month)

<sup>‡</sup>Terbinafine at a dose of 250 mg per day

<sup>§</sup>Fluconazole at a dose of 200–400 mg once weekly.

**Table 3** Univariate and multivariate analysis of factors affecting complete cure

	N	Cure	(%)	Univariate analysis		Multivariate analysis	
				Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age							
60–69	46	31	(67.4)	2.54 (1.10–5.85)	0.029*	2.75 (1.10–6.87)	0.050*
≥70	49	22	(44.9)	1		1	
Diabetes mellitus							
No	67	39	(58.2)	1.39 (0.57–3.38)	0.465		
Yes	28	14	(50)	1			
Cardiovascular disease							
No	80	46	(57.5)	1.55 (0.51–4.68)	0.440		
Yes	15	7	(46.7)	1			
Nail thickness > 2 mm							
No	49	33	(67.5)	3.54 (1.45–8.60)	0.005*	3.61 (1.44–9.04)	0.006*
Yes	38	14	(36.8)	1		1	
Diagnosis							
Dermatophyte onychomycosis	57	30	(52.6)	1			
Mixed infection <sup>†</sup> onychomycosis	38	23	(60.5)	1.38 (0.60–3.17)	0.448		
Oral antifungal agents							
Itraconazole	33	21	(65.6)	2.00 (0.75–5.48)	0.178		
Terbinafine	32	18	(56.5)	1.47 (0.54–4.00)	0.451		
Fluconazole	30	14	(46.7)	1			

Abbreviations: CI, confidence interval; OR, odds ratio.

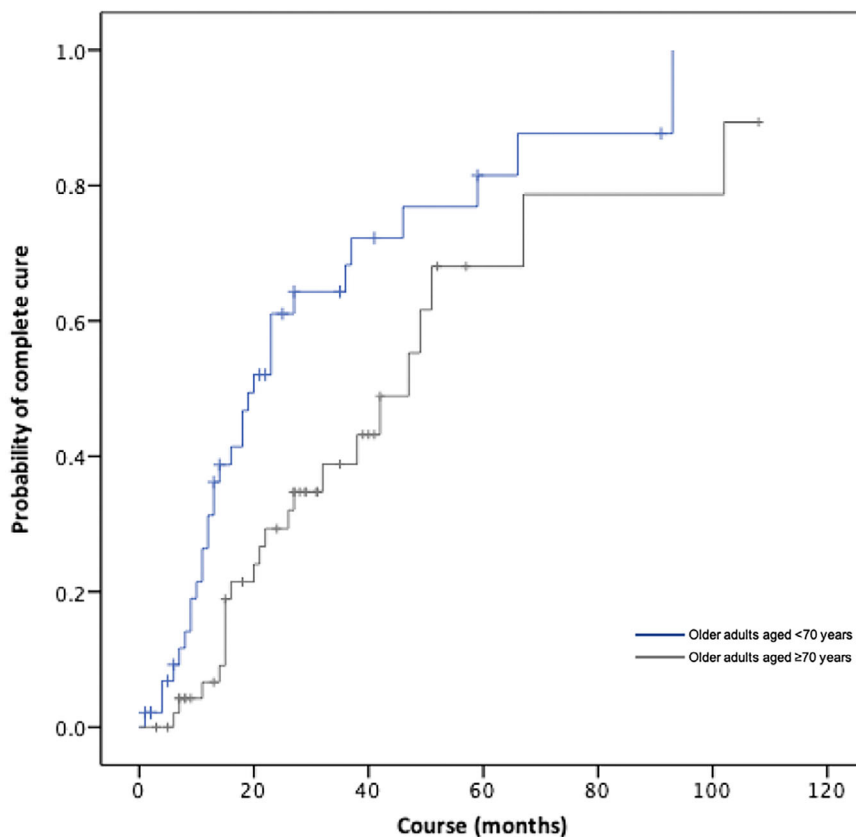
\*P value ≤ 0.05

<sup>†</sup>Mixed infection of dermatophytes and nondermatophytes.

peripheral arterial disease, an impaired renal function, the use of antihypertensive drugs and polypharmacy were significantly found in the patients aged ≥ 70 years. The treatment regimens (doses and durations) of the patients aged < 70 years were like those of the patients aged ≥ 70 years, except that the usage of 5% amorolfine nail lacquer was significantly higher among the patients aged ≥ 70 years.

The values for the Scoring Clinical Index for Onychomycosis of the two age groups at baseline were not significantly different. As to the complete cure rate, older adults aged ≥ 70 years achieved a 44.9% complete cure rate, which was statistically lower than that for older adults aged < 70 years (67.4%; *P* = 0.027).

The Kaplan–Meier survival analysis (Figure 1) revealed that the median times to a complete cure for patients aged



**Figure 1** A Kaplan–Meier survival analysis (one minus survival function) demonstrating the durations until a complete cure of onychomycosis. The median durations—when 50% of older adults aged <70 years and 50% of those aged  $\geq 70$  years had a complete cure—were 20 months and 47 months, respectively ( $P = 0.007$ ).

< 70 years and  $\geq 70$  years were 20 months and 47 months, respectively ( $P = 0.007$ ). As to the multivariate analysis (Table 3), a non-complete cure was found to be associated with two factors: being aged  $\geq 70$  years (adjusted odds ratio, 2.75; 95% CI, 1.10–6.87;  $P = 0.050$ ) and a nail thickness of  $> 2$  mm (adjusted odds ratio 3.61; 95% CI, 1.44–9.04;  $P = 0.006$ ).

## DISCUSSION

Onychomycosis is an important health problem among older adults. This study demonstrated that the complete cure rate for people aged  $\geq 70$  years was significantly lower than that for individuals aged < 70 years. Specifically, an age  $\geq 70$  years was found to be a significant factor contributing to a declined rate of complete cure. This age also correlated with the cut-off age previously documented as being associated with frailty.<sup>19, 20</sup> Frailty is a clinical state of increased vulnerability arising from aging-associated physical decline. It is associated with unfavourable clinical outcomes as well as increased rates of comorbidities and mortality for older adults.<sup>19, 20</sup> In Thailand, a study demonstrated that frailty was related with the age of 72 years, which is quite close to the age associated with a complete cure identified by the present investigation.<sup>19</sup>

Therefore, the issue of onychomycosis among older adults should be of concern, especially with individuals aged  $\geq 70$  years.

Earlier work on patients with toenail dermatophytosis who were receiving terbinafine found that the complete cure rates at 48 months were 36.5% and 28% for patients aged < 65 and  $\geq 65$  years, respectively.<sup>21</sup> Similarly, the current study revealed that older adults aged  $\geq 70$  years had a lower cure rate and a longer median time to a complete cure than older adults aged < 70 years. Treatment of onychomycosis in older adults is notoriously difficult, which may result from the slower growth rate of nails, foot trauma, and poor peripheral circulation.<sup>5, 22, 25</sup> Our investigation found that older adult patients aged  $\geq 70$  years had more significant peripheral circulatory problems than the younger patients; this difference may have had a negative effect on their treatment outcomes.

The baseline characteristics of the older adult patients aged < 70 years were generally like those of the patients aged  $\geq 70$  years. However, there was a greater male predominance, more frequent history of smoking, higher incidence of peripheral arterial disease and impaired renal function, greater use of antihypertensive drugs, and more extensive polypharmacy among the patients aged  $\geq 70$  years. Statins and antihypertensive drugs were used by

more than half of the patients in that age group. It should be noted that simvastatin is contraindicated in combination with itraconazole as the latter medication may inhibit the CYP3A4-mediated mechanism. If that occurs, there is a marked increase in serum concentrations of simvastatin, resulting in rhabdomyolysis.<sup>24</sup> No patients in the present study used lovastatin, astemizole, terfenadine, cisapride, midazolam or triazolam, which are also contraindicated to itraconazole.<sup>25</sup> Thus, identification of current medication usage prior to prescribing systemic antifungal treatment for patients with onychomycosis is important to avoid drug interactions and side effects, especially in the case of older adult patients who are predisposed to renal function decline or to experience polypharmacy.<sup>26, 27</sup>

In this study, the patients aged  $\geq 70$  years used 5% amorolfine nail lacquer significantly more frequently than those aged  $< 70$  years. The explanation may be that the older adult patients aged  $\geq 70$  years had a higher incidence of impaired renal function and a higher degree of comorbidities, resulting in more extensive polypharmacy. Consequently, the oral antifungal therapy was used carefully and less frequently in patients aged  $\geq 70$  years than those aged  $< 70$  years. Another study reported that thickening of the nail plate negatively affected the complete cure rate (odds ratio, 1.67; 95% CI, 0.90–3.01), although the results did not demonstrate a statistically significant difference.<sup>28</sup> However, the current work revealed that a nail thickness of  $> 2$  mm was a poor prognostic factor for a complete cure. This may be explained by a difficulty in achieving a sufficient concentration of drugs in thick nails. Adjunctive nail grinding is therefore necessary to reduce nail thickness and enhance treatment efficacy.<sup>29, 30</sup>

This study had some limitations. Firstly, due to the nature of a retrospective study, some data were unfortunately missing. Moreover, this study was undertaken at a tertiary hospital, which is more likely to deal with high severities of diseases. Finally, long-term follow-up may be needed to ensure that a complete cure is achieved in older adults.

In summary, an age equal to, or more than, 70 years can be considered a prognostic factor for a lower cure rate and a delay in the complete cure of toenail onychomycosis. The older adults in this study frequently had impaired renal function, poor peripheral circulation and polypharmacy; all such factors should therefore be considered before making treatment decisions. Moreover, a nail thickness of more than 2 mm was associated with poor treatment outcomes.

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#### ETHICAL APPROVAL

The research was approved by the Siriraj Institutional Review Board (Si. 392/2020).

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