

Original Research Article

Multimorbidity Burden and Specific Clinical Comorbidities in Onychomycosis: A Retrospective Case-Control Study in an Indonesian Tertiary Referral Hospital

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ABSTRACT

Background: Onychomycosis is the most common chronic fungal disease of the nail unit worldwide. Metabolic, vascular and cutaneous disorders are known risk factors. The added effect of a combined comorbidity burden in tropical outpatient populations remains under-evaluated.

Objective: To describe the spectrum of clinical comorbidities and to analyze the association between cumulative comorbidity burden and onychomycosis among outpatients of a tertiary referral hospital in Indonesia.

Methods: This retrospective case-control study took place at the Dermatology Clinic of Dr. Moewardi General Hospital, Surakarta (January 2020 to June 2026). It enrolled 76 patients. There were 38 mycologically confirmed onychomycosis cases (positive 10% potassium hydroxide mount and/or culture) and 38 outpatient controls without onychomycosis. We recorded demographics, obesity, diabetes mellitus, hypertension, venous insufficiency, psoriasis, HIV/immunosuppression, systemic autoimmune disease, tinea pedis and the total comorbidity count. Bivariate analyses used the chi-square and Fisher exact tests. We calculated odds ratios (OR) with 95% confidence intervals (CI).

Results: Tinea pedis (47.4%), obesity (39.5%), hypertension (36.8%), autoimmune disease (31.6%) and diabetes mellitus (31.6%) were the most common comorbidities among cases. Multimorbidity (≥ 2 comorbidities) was more frequent in cases than in controls (50.0% vs. 15.8%). Patients with no comorbidity were mostly controls (28.9% vs. 7.9%). Cumulative comorbidity burden was associated with onychomycosis (chi-square = 12.01, $p = 0.002$). The OR for ≥ 2 vs. 0 comorbidities was 11.61 (95% CI: 2.41–55.94, $p = 0.002$).

Conclusion: A higher cumulative comorbidity burden was associated with onychomycosis in this single-center case-control study. Management should address coexisting metabolic, vascular and fungal-reservoir conditions alongside antifungal treatment.

All authors have reviewed and approved the final version of the manuscript.

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1. Introduction

Onychomycosis is a chronic, recalcitrant fungal infection of the nail apparatus. It involves the hard keratin nail plate, the vascular nail bed, the proximal and lateral nail folds, and the germinative matrix.¹ Clinicians regard it as the most prevalent nail disease in dermatology. About 50% of all nail disorders and up to 30% of all superficial cutaneous mycoses worldwide are attributed to it.^{2,3} Global prevalence in the adult general population is estimated at 5.5% to 10.0%. Geographic and climatic variation is wide.^{4,5} North American cohorts report 8.7% to 13.8%. European population-based studies give 0.5% in children but above 24.0% in

older groups.^{2,6,7} Southeast Asia is different again. Constant warmth and high humidity in tropical and equatorial regions suit both dermatophytic and non-dermatophytic fungi, and the resulting clinical pattern departs from the temperate European one.

Three groups of organisms cause onychomycosis: anthropophilic dermatophytes, yeasts, and non-dermatophyte molds (NDMs).^{8,9} Dermatophytes have long been the main agents, led by *Trichophyton rubrum*, then the *Trichophyton mentagrophytes/interdigitale* complex and *Epidermophyton floccosum*. In Western literature they account for 60% to 90% of toenail infections.^{5,10} Recent mycology surveys from tropical

and developing countries describe a changing picture.^{9,11} In Southeast Asia, and in Indonesia in particular, *Candida* yeasts (mainly *Candida albicans*, *Candida parapsilosis* and *Candida tropicalis*) and opportunistic NDMs (such as *Aspergillus niger*, *Fusarium solani* and *Scopulariopsis brevicaulis*) make up a growing share of isolates. This is most evident in fingernail onychodystrophy and in patients with occupational water exposure or immunosuppression.^{11,12} Clinically, five classic forms are recognized: distal lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), endonyx onychomycosis (EO) and total dystrophic onychomycosis (TDO).^{13,14} DLSO is by far the most common and occurs in over 80% of cases. Hyphae invade the stratum corneum of the hyponychium and distal nail bed. Subungual hyperkeratosis, progressive onycholysis, yellowish-brown discoloration and eventual crumbling of the plate follow.^{14,15}

Patients and general practitioners have long treated onychomycosis as a cosmetic nuisance or an unavoidable sign of aging. Academic medicine has revised that view.^{15,16} Fungal colonization weakens the physical and immunological barrier of the distal digit. It opens a route of entry for secondary bacterial pathogens, including *Staphylococcus aureus*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa*.¹⁷ Some patients are especially exposed: older adults, patients with peripheral arterial disease and people with poorly controlled diabetes mellitus. In them, untreated onychomycosis often becomes the starting point of severe, limb-threatening infection, such as ascending erysipelas, necrotizing cellulitis, paronychia, deep subungual abscess, osteomyelitis of the distal phalanx and non-traumatic lower extremity amputation.^{16,18} The burden goes beyond infection. Distortion of the nail unit causes chronic pain, impairs walking and limits work. It adds a psychological and social cost that lowers health-related quality of life.^{14,16}

Treatment has advanced. Oral allylamines (terbinafine) and triazoles (itraconazole, fluconazole) are now joined by topical formulations with better nail penetration: ciclopirox 8% lacquer, amorolfine 5% lacquer, efinaconazole 10% solution and tavaborole 5% solution. Real-world outcomes are still disappointing.^{19,20} Complete clinical and mycological cure rarely exceeds 40% to 50% in long-term observational cohorts. Relapse or recurrence occurs in 20% to 50% of patients within 1 to 3 years after treatment stops.^{13,21} Antifungal resistance and poor adherence do not explain all of this. Host-specific systemic and cutaneous factors also matter, because they create conditions in which fungi survive, multiply and re-infect.^{16,18}

Many predisposing conditions are linked to onychomycosis in the literature. They include increasing age, genetic variants in pattern recognition receptors (such as dectin-1 and CARD9), chronic peripheral neuropathy, repeated microtrauma from tight footwear or foot deformities (hallux valgus,

hammer toes), hyperhidrosis, obesity, chronic venous insufficiency (CVI), peripheral arterial occlusive disease, diabetes mellitus, human immunodeficiency virus (HIV) infection, hematological malignancy, and iatrogenic immunosuppression after organ transplantation or during treatment of systemic autoimmune disease.^{16,22–25} Most published studies, however, have examined these factors one at a time. They look at onychomycosis in diabetes alone, or in psoriasis alone, and so miss the reality of multimorbidity.^{22,24–27} In routine outpatient care, chronic diseases rarely occur alone. They cluster within the same patient and can add to tissue fragility, microvascular impairment and cellular immunodeficiency.^{28,29}

Data from Indonesia and the wider Southeast Asian region are thin. Few studies examine how onychomycosis relates to the range of systemic comorbidities.¹¹ Most local reports are small descriptive surveys or case reports that focus on identifying the organism, and they do not systematically assess concurrent non-communicable disease. Tertiary referral centers in urban Indonesia are a suitable place to study the question. They receive patients with advanced, recalcitrant or multisystem disease from primary and secondary facilities. Their outpatients therefore often carry metabolic, vascular and immunological multimorbidity. Describing the quantity and pattern of that burden is needed to understand the systemic side of onychomycosis in tropical developing countries.

The novelty of this study lies in its STROBE-guided case-control design. It goes beyond single-variable associations. It quantifies the effect of cumulative comorbidity burden, defined as the total count of co-occurring chronic diseases, on the occurrence of onychomycosis at an Indonesian tertiary referral center. It also analyzes specific multi-disease combinations across metabolic, vascular, cutaneous and autoimmune domains. In doing so it offers local data on how comorbidities co-occur in patients with onychomycosis in a tropical developing setting. The primary objective was to characterize the demographic profile and the spectrum of specific comorbidities in patients with onychomycosis compared with controls without it. We also tested a hypothesis. Cumulative multimorbidity burden, we proposed, is associated with onychomycosis among outpatients at Dr. Moewardi General Hospital in Surakarta, Indonesia, over a 6-year window.

2. Methods

2.1. Study design and setting

This was an observational analytic retrospective case-control study. It is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies.³⁰ Data came from the electronic medical record (EMR) databases of the Outpatient Clinic of Dermatology and Venereology at Rumah Sakit Umum Daerah (RSUD) Dr. Moewardi in Surakarta, Central Java,

Indonesia. The observation window covered 78 consecutive months (6.5 years), from January 1, 2020 to June 30, 2026. RSUD Dr. Moewardi is a fully accredited tertiary referral and academic teaching hospital affiliated with the Faculty of Medicine, Universitas Sebelas Maret. It serves as the main referral center for an urban, suburban and rural catchment population of more than 6 million residents in southern Central Java and the neighboring Special Region of Yogyakarta.

2.2. Ethical approval and patient safeguards

The research design, protocol amendments and data abstraction methods were submitted to the Health Research Ethics Committee (Komisi Etik Penelitian Kesehatan / KEPK) of RSUD Dr. Moewardi, which reviewed and approved them. The committee issued ethical certification under Document No. 1.478/VIII/HREC/2026. The study followed the ethical principles for medical research involving human subjects set out in the World Medical Association Declaration of Helsinki (1975, as revised in 2013) and national Indonesian health research regulations. All patient-level data were de-identified and pseudonymized before statistical computation. Full names, national citizenship registration numbers (NIK), civil servant registration numbers (NIP), residential addresses, telephone contacts and institutional medical record numbers were permanently replaced with standardized alphanumeric study codes, so participants stayed confidential. The design was retrospective and used existing electronic medical records, with no physical intervention or contact with human subjects. For these reasons the ethics committee granted a waiver of individual written informed consent.

2.3. Participants and eligibility criteria

The cohort comprised two well-defined, mutually exclusive groups. Cases were adult patients with confirmed onychomycosis. Controls were adult outpatients without onychomycosis. Both groups came from the same clinic and period, which limits referral and temporal selection bias.

Inclusion criteria for the case group were as follows. (1) Age ≥ 18 years at first clinical presentation. (2) A documented diagnosis of onychomycosis made by a credentialed dermatology and venereology specialist on characteristic nail changes (discoloration, subungual hyperkeratosis, onycholysis or crumbling of the plate). (3) Objective mycological confirmation, by direct potassium hydroxide (KOH 10%) microscopy showing fungal hyphae, arthroconidia or pseudohyphae and/or by a positive fungal culture yielding a recognized pathogenic fungus on Sabouraud dextrose agar. (4) A complete, verifiable electronic medical record with baseline clinical and demographic data. Cases were excluded in three situations. These were clinical onychodystrophy without positive laboratory confirmation (for example traumatic or other non-mycotic nail dystrophy), grossly incomplete records in which the diagnostic or comorbidity history was missing, and acute post-traumatic nail avulsion without a primary fungal cause.

Controls were chosen by consecutive non-probability sampling. They were adult patients (aged ≥ 18 years) who attended the same Dermatology and Venereology Outpatient Clinic at RSUD Dr. Moewardi during the same period (January 2020 to June 2026) for non-mycotic, non-ungual skin conditions. Examples were common benign dermatological disorders such as acne vulgaris, viral verrucae, seborrheic dermatitis, and allergic or irritant contact dermatitis. Three requirements applied. Controls had to show no clinical onychodystrophy or active fungal nail infection, be adults (≥ 18 years), and have complete electronic medical records. Patients with unconfirmed nail abnormalities, or with an active superficial cutaneous fungal infection outside the scalp or body, were removed from the control pool. This kept the comparison group free of onychomycosis.

2.4. Operational definitions of variables

The primary dependent variable was confirmed onychomycosis (dichotomous: yes vs. no). The primary independent variable was cumulative comorbidity burden. It was defined as the total count of co-occurring, physician-diagnosed chronic systemic or dermatological disorders recorded in the electronic medical record, and was grouped into three tiers: 0 comorbidities (free of chronic disease), 1 comorbidity (single disease burden) and ≥ 2 comorbidities (complex multimorbidity).

Secondary independent variables were demographic factors and ten specific clinical comorbidities, each defined by standard diagnostic criteria. (1) Age was recorded in completed years. It was grouped into three strata: young adults (18–39 years), middle-aged adults (40–59 years) and older adults (≥ 60 years). (2) Biological sex was classified as male or female. (3) Obesity followed the World Health Organization (WHO) Western Pacific Regional criteria for Asian adults. This meant body mass index (BMI) ≥ 25.0 kg/m², calculated as weight in kilograms divided by height in meters squared. (4) Diabetes mellitus followed American Diabetes Association (ADA) guidelines. It required fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), 2-hour post-prandial glucose ≥ 200 mg/dL (11.1 mmol/L), glycated hemoglobin (HbA1c) $\geq 6.5\%$ (48 mmol/mol), or current outpatient treatment with oral antihyperglycemic drugs or subcutaneous insulin. (5) Systemic hypertension followed the 2017 ACC/AHA guidelines. It meant documented systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg on repeated outpatient measurements, or active antihypertensive treatment. (6) Chronic venous insufficiency (CVI) of the lower extremities was identified on physical examination as CEAP (Clinical, Etiological, Anatomical, Pathophysiological) clinical class C2 or higher. Signs were varicose veins, persistent dependent ankle edema, venous eczema/stasis dermatitis or lipodermatosclerosis, supported by vascular clinical notes. (7) Cutaneous psoriasis was diagnosed by board-certified dermatologists from sharply demarcated erythematous plaques with silvery micaceous scales. Histopathology confirmed it when indicated. (8) HIV infection/immunosuppressive status

meant laboratory-confirmed reactive HIV serology (national three-test algorithm) or documented severe iatrogenic immunosuppression. (9) Systemic autoimmune diseases were chronic multisystem inflammatory conditions diagnosed by standard American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and autoimmune blistering dermatoses such as pemphigus vulgaris. They had to need chronic maintenance therapy with systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs). (10) Tinea pedis was a concurrent superficial dermatophyte infection of the plantar, interdigital or lateral foot skin. It was diagnosed clinically and confirmed by positive direct 10% KOH examination showing fungal hyphae.

2.5. Laboratory mycological evaluation

Diagnostic confirmation of onychomycosis followed standard mycological laboratory protocols. These conform to the clinical guidelines of the German Society of Dermatology (DDG) and the British Association of Dermatologists.^{31,32} Before specimens were taken, the affected nail plate and the surrounding periungual skin were cleaned with sterile gauze soaked in 70% isopropyl alcohol. This removed environmental bacteria and superficial saprophytes. Subungual hyperkeratotic debris was collected with sterile surgical curettes from the most proximal advancing border of the lesion beneath the nail plate. Dystrophic nail fragments were cut with sterile heavy-duty nail nippers.

Specimens were divided into two equal portions. The first portion went to direct potassium hydroxide (KOH) examination. Nail clippings and subungual scales were mounted on a clean glass slide in 10% to 20% aqueous KOH, gently heated over a low flame without boiling to speed keratin dissolution, and left for 15 to 30 minutes. Experienced laboratory mycologists screened the slides under light microscopy at low power (100×) and high power (400×). They looked for septate, branching hyphae, chains of arthroconidia, or budding yeast blastoconidia with pseudohyphae. The second portion was inoculated onto primary isolation media. One was Sabouraud dextrose agar (SDA) with 0.05 mg/mL chloramphenicol to suppress bacteria and 0.5 mg/mL cycloheximide to inhibit saprophytic environmental molds. The other was plain SDA without cycloheximide,

which allows recovery of non-dermatophyte molds and yeasts. Culture tubes were incubated aerobically at 25°C to 28°C and checked twice weekly for up to 4 weeks. Colonies that grew were examined macroscopically for morphology, pigmentation and growth rate, and microscopically in lactophenol cotton blue tease mounts to identify diagnostic microconidia and macroconidia.

2.6. Statistical analysis

Statistical computation used IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA), and was verified with Python scientific computing libraries (SciPy 1.14, Statsmodels 0.14). Demographic characteristics and clinical comorbidities were tabulated descriptively. All primary endpoints were categorical and are given as absolute frequencies (n) and relative percentages (%).

Bivariate comparisons between onychomycosis cases and controls used Pearson's chi-square (χ^2) test of independence for 2×2 and 2×3 contingency tables. When the expected frequency was < 5 in more than 20% of cells, the two-tailed Fisher's exact test was used instead. Association strength and direction were expressed as odds ratios (OR) with 95% confidence intervals (CI) calculated by the logit (Woolf) method. Some tables had zero cells: in controls for tinea pedis, systemic autoimmune diseases and chronic venous insufficiency. A standard cross-product ratio cannot be computed in that case. We therefore applied the Haldane-Anscombe continuity correction. A constant of 0.5 was added to all four cells of the 2×2 table, so finite log-odds estimates and standard errors could be computed. Multivariable logistic regression was then explored to assess comorbidity burden while adjusting for baseline age and sex. Significance was set a priori at a two-tailed alpha of $p < 0.05$ for all inferential tests.

3. Results

3.1. Cohort composition

Over the 6.5-year period from January 2020 to June 2026, 76 outpatients met the eligibility criteria and entered the final analytical dataset. The cohort included 38 patients (50.0%) with clinically and mycologically confirmed onychomycosis (the case group) and 38 outpatients (50.0%) with non-mycotic dermatological disorders seen in the same period (the control group) (Table 1).

Table 1. Distribution of onychomycosis cases and control subjects

Group	Frequency (n)	Percentage (%)
Onychomycosis (Cases)	38	50.0
Non-onychomycosis (Controls)	38	50.0
Total	76	100.0

Notes: Values represent absolute frequencies (n) and relative percentages (%).

3.2. Cumulative comorbidity burden in the cohort

Across all 76 participants, underlying chronic disease was common (Table 2). Only 14 patients (18.4%) had no comorbid condition (0 comorbidity). The largest group,

37 patients (48.7%), had exactly one verified comorbid disease. About one-third of the cohort, 25 patients (32.9%), had complex multimorbidity. This meant two or more (≥ 2) chronic systemic or cutaneous disorders at once.

Table 2. Overall distribution of cumulative comorbidity burden among all enrolled participants (N = 76)

Comorbidity Burden	Frequency (n)	Percentage (%)
0 Comorbidity	14	18.4
1 Comorbidity	37	48.7
≥2 Comorbidities (Multimorbid)	25	32.9
Total	76	100.0

Notes: Categorization of comorbidity count per individual patient across the entire cohort.

3.3. Demographic profiles and age-sex associations

Baseline demographic data and the comparison of individual comorbidities between cases and controls are shown in Table 3. The onychomycosis group had peaks in the youngest and oldest age strata. Young adults aged 18–39 years made up 44.7% (n = 17). Middle-aged adults aged 40–59 years made up 18.4% (n = 7), and older adults aged ≥60 years 36.8% (n = 14). Controls leaned toward younger ages. In that group, 68.4% (n = 26) were 18–39 years, 23.7% (n = 9) were 40–59 years, and only 7.9% (n = 3) were aged ≥60 years. In bivariate analysis, older adults aged ≥60 years had higher odds of onychomycosis than the young adult reference group (OR = 7.14, 95% CI: 1.78–28.62, p = 0.003).

Sex distribution differed significantly between the groups. Women formed the majority of cases, 60.5% (n

= 23), and men 39.5% (n = 15). The control group was mostly male (76.3%, n = 29), with women at 23.7% (n = 9). Cross-tabulation showed that female sex was associated with almost fivefold odds of onychomycosis in this outpatient dermatology population (OR = 4.94, 95% CI: 1.83–13.31, Pearson χ^2 = 10.58, p = 0.001).

3.4. Individual comorbidity distributions

Individual comorbid conditions differed sharply between onychomycosis patients and controls (Table 3 and Figure 1). Tinea pedis was the most common comorbid condition among cases, recorded in 47.4% (n = 18). No control had tinea pedis (0.0%, n = 0). The difference was highly significant on the two-tailed Fisher's exact test (p < 0.001). With the Haldane-Anscombe continuity correction the estimated odds ratio was 69.49 (95% CI: 3.98–1213.03), an estimate that rests on a zero cell in the control group and is therefore imprecise.

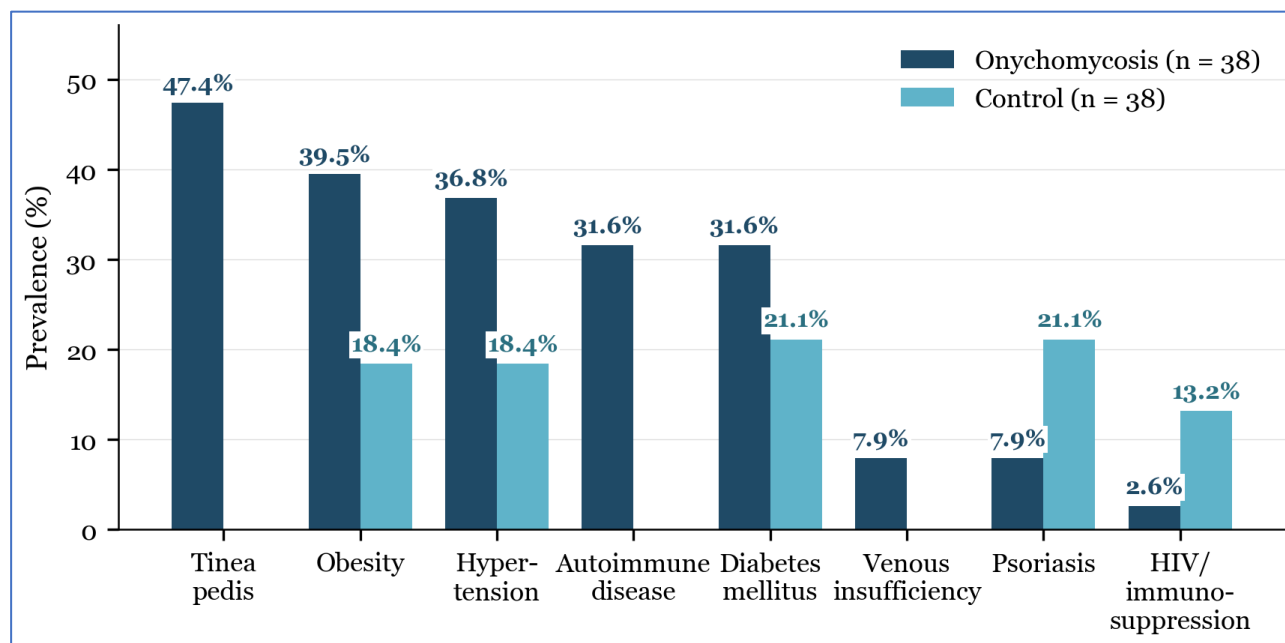


Figure 1. Prevalence of comorbid conditions in patients with onychomycosis versus controls. Bars show the percentage of patients with each condition in each group (n = 38 per group); there is no control bar for tinea pedis, autoimmune disease and venous insufficiency (0.0%).

Systemic autoimmune diseases that required chronic immunosuppressive therapy, including systemic lupus erythematosus, rheumatoid arthritis and pemphigus vulgaris, were recorded in 31.6% (n = 12) of onychomycosis patients and in 0.0% (n = 0) of controls. The association was strong (Fisher's exact p < 0.001; continuity-corrected OR = 36.32, 95% CI: 2.06–640.41) and may reflect the effect of therapeutic immune

suppression; the estimate rests on a zero cell and the duration and dose of treatment were not analyzed.

Metabolic and vascular disorders were well represented in cases. Obesity (BMI ≥ 25.0 kg/m²) was found in 39.5% (n = 15) of cases and 18.4% (n = 7) of controls, a statistically significant association (Pearson χ^2 = 4.09, p = 0.043; OR = 2.89, 95% CI: 1.01–8.23). Systemic hypertension was recorded in 36.8% (n = 14) of cases and 18.4% (n = 7) of controls. The odds ratio of

2.58 approached significance (Pearson $\chi^2 = 3.22$, $p = 0.073$; 95% CI: 0.90–7.40). Diabetes mellitus was diagnosed in 31.6% ($n = 12$) of cases and 21.1% ($n = 8$) of controls, giving an odds ratio of 1.73 (95% CI: 0.61–4.88, $p = 0.297$).

Chronic venous insufficiency (CVI) of the lower extremities was recorded in 7.9% ($n = 3$) of onychomycosis cases. No control had it (0.0%, $n = 0$; Fisher's exact $p = 0.240$; continuity-corrected OR = 7.59,

95% CI: 0.38–152.20). Cutaneous plaque psoriasis went the other way: 7.9% ($n = 3$) of onychomycosis patients and 21.1% ($n = 8$) of controls (OR = 0.32, 95% CI: 0.08–1.32, $p = 0.103$). HIV infection/severe immunosuppression was seen in 2.6% ($n = 1$) of cases and 13.2% ($n = 5$) of controls (OR = 0.18, 95% CI: 0.02–1.61, Fisher's exact $p = 0.089$). The hospital's dedicated sexually transmitted infection and immunodeficiency clinic may explain this referral pattern.

Table 3. Baseline demographic characteristics and clinical comorbidity prevalence in onychomycosis patients versus control subjects

Variable	Onychomycosis (n = 38)	Control (n = 38)	Total (N = 76)	Odds Ratio (95% CI)	p-value
Age Category					
18–39 years	17 (44.7%)	26 (68.4%)	43 (56.6%)	Reference	—
40–59 years	7 (18.4%)	9 (23.7%)	16 (21.1%)	1.19 (0.37–3.80)	0.770
≥60 years	14 (36.8%)	3 (7.9%)	17 (22.4%)	7.14 (1.78–28.62)	0.003*
Sex					
Male	15 (39.5%)	29 (76.3%)	44 (57.9%)	Reference	—
Female	23 (60.5%)	9 (23.7%)	32 (42.1%)	4.94 (1.83–13.31)	0.001*
Specific Comorbidities					
Obesity (BMI ≥ 25 kg/m ²)	15 (39.5%)	7 (18.4%)	22 (28.9%)	2.89 (1.01–8.23)	0.043*
Diabetes Mellitus	12 (31.6%)	8 (21.1%)	20 (26.3%)	1.73 (0.61–4.88)	0.297
Hypertension	14 (36.8%)	7 (18.4%)	21 (27.6%)	2.58 (0.90–7.40)	0.073
Chronic Venous Insufficiency	3 (7.9%)	0 (0.0%)	3 (3.9%)	7.59 (0.38–152.20)†	0.240‡
Psoriasis	3 (7.9%)	8 (21.1%)	11 (14.5%)	0.32 (0.08–1.32)	0.103
HIV / Immunosuppression	1 (2.6%)	5 (13.2%)	6 (7.9%)	0.18 (0.02–1.61)	0.089‡
Autoimmune Diseases	12 (31.6%)	0 (0.0%)	12 (15.8%)	36.32 (2.06–640.41)†	<0.001*‡
Tinea Pedis	18 (47.4%)	0 (0.0%)	18 (23.7%)	69.49 (3.98–1213.03)†	<0.001*‡

Notes: *Statistically significant ($p < 0.05$). †Odds ratio calculated with Haldane-Anscombe continuity correction due to zero cell count. ‡p-value derived from two-tailed Fisher's exact test; other p-values from Pearson's chi-square test. Odds ratios for age groups are against the 18–39-year group; 95% confidence intervals were calculated by the logit (Woolf) method.

3.5. Multimorbidity combination patterns

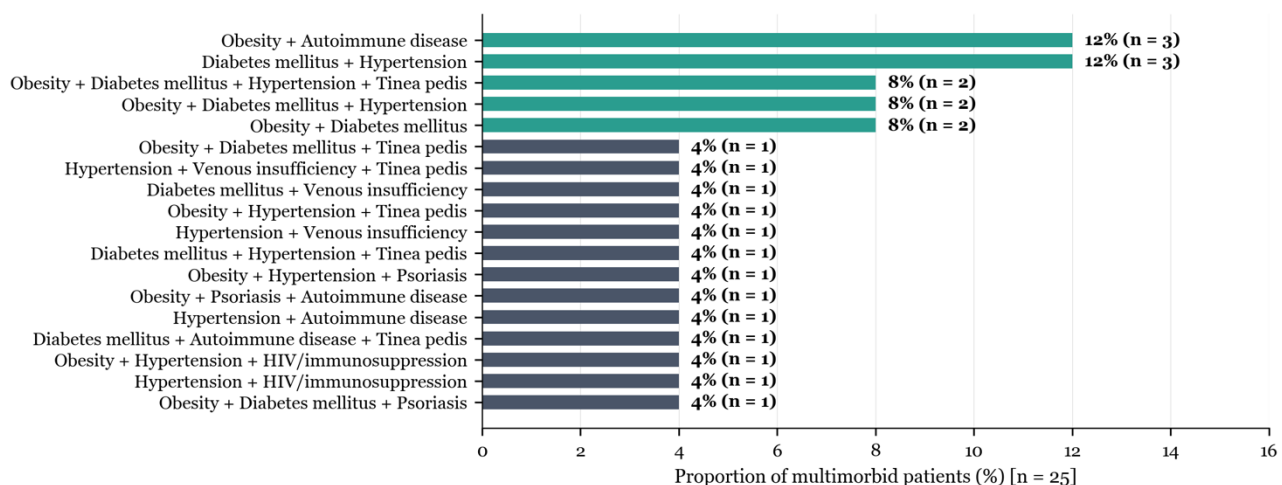
The 25 patients with complex multimorbidity (≥2 co-existing comorbid disorders) showed many overlapping disease combinations (Table 4 and Figure 2). The two most frequent pairs were obesity with autoimmune disease and diabetes mellitus with systemic hypertension, each present in 12.0% ($n = 3$) of multimorbid individuals. Some combinations were complex. Obesity, diabetes mellitus, hypertension and

tinea pedis occurred together in 8.0% ($n = 2$) of multimorbid patients. The triad of obesity, diabetes mellitus and hypertension, and the pair of obesity and diabetes mellitus, each accounted for 8.0% ($n = 2$). Other combinations occurred in single patients (4.0% each): hypertension and venous insufficiency with tinea pedis, diabetes with venous insufficiency, obesity with hypertension and psoriasis, and diabetes with autoimmune disease and tinea pedis.

Table 4. Distribution of specific co-occurring comorbidity combinations among multimorbid patients (≥ 2 comorbidities, $n = 25$)

Comorbidity Combination Pattern	Number of Patients (n)	Percentage (%)
Obesity + Autoimmune Disease	3	12.0
Diabetes Mellitus + Hypertension	3	12.0
Obesity + Diabetes Mellitus + Hypertension + Tinea Pedis	2	8.0
Obesity + Diabetes Mellitus + Hypertension	2	8.0
Obesity + Diabetes Mellitus	2	8.0
Obesity + Diabetes Mellitus + Tinea Pedis	1	4.0
Hypertension + Venous Insufficiency + Tinea Pedis	1	4.0
Diabetes Mellitus + Venous Insufficiency	1	4.0
Obesity + Hypertension + Tinea Pedis	1	4.0
Hypertension + Venous Insufficiency	1	4.0
Diabetes Mellitus + Hypertension + Tinea Pedis	1	4.0
Obesity + Hypertension + Psoriasis	1	4.0
Obesity + Psoriasis + Autoimmune Disease	1	4.0
Hypertension + Autoimmune Disease	1	4.0
Diabetes Mellitus + Autoimmune Disease + Tinea Pedis	1	4.0
Obesity + Hypertension + HIV/Immunosuppression	1	4.0
Hypertension + HIV/Immunosuppression	1	4.0
Obesity + Diabetes Mellitus + Psoriasis	1	4.0
Total Multimorbid Patients	25	100.0

Notes: Data represent specific multimorbidity combinations documented in the 25 patients presenting with two or more comorbid conditions.

**Figure 2.** Specific co-occurring comorbidity combinations among patients with ≥ 2 comorbidities. Bars show the proportion of the 25 multimorbid patients (cases and controls combined) with each combination.

3.6. Cumulative comorbidity burden and onychomycosis

A central finding was a statistically significant relationship between cumulative comorbidity burden and onychomycosis (Table 5 and Figure 3). In the case cohort, half of the patients (50.0%, $n = 19$) had multimorbidity (≥ 2 comorbidities). Another 42.1% ($n =$

16) had exactly one comorbidity. Only 7.9% ($n = 3$) had no comorbid disease. Controls looked different. Just 15.8% ($n = 6$) had ≥ 2 comorbidities, 55.3% ($n = 21$) had one, and 28.9% ($n = 11$) had none. Pearson's chi-square test showed a highly significant difference in the distribution of comorbidity burden between the groups ($\chi^2 = 12.007$, $df = 2$, $p = 0.002$).

Table 5. Association between cumulative comorbidity burden and the occurrence of onychomycosis

Group	0 Comorbidity (n, %)	1 Comorbidity (n, %)	≥ 2 Comorbidities (n, %)	Total (n, %)	Chi-Square (χ^2)	p-value
Onychomycosis (Cases)	3 (7.9%)	16 (42.1%)	19 (50.0%)	38 (100.0%)	12.007	0.002*
Control (Non-onychomycosis)	11 (28.9%)	21 (55.3%)	6 (15.8%)	38 (100.0%)		
Total Cohort	14 (18.4%)	37 (48.7%)	25 (32.9%)	76 (100.0%)		

Notes: *Statistically significant ($p < 0.05$). Percentages within rows represent proportion within the diagnostic group. Odds Ratio for ≥ 2 vs. 0 comorbidity = 11.61 (95% CI: 2.41–55.94, $p = 0.002$); Odds Ratio for ≥ 2 vs. < 2 comorbidities = 5.33 (95% CI: 1.81–15.69, $p = 0.003$).

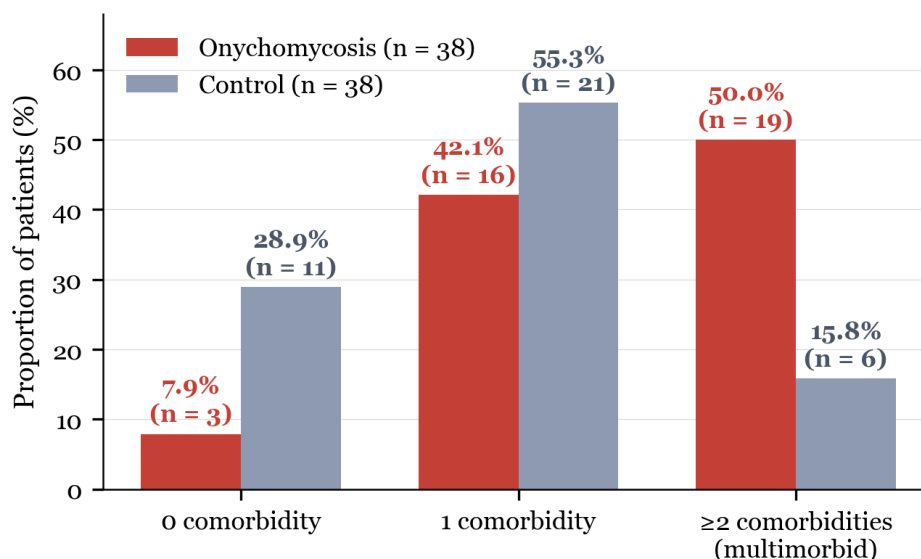


Figure 3. Cumulative comorbidity burden in patients with onychomycosis versus controls (chi-square = 12.01, $p = 0.002$).

Risk estimation showed higher odds with multimorbidity (Figure 4). Patients with complex multimorbidity (≥ 2 comorbidities) had 11.61-fold higher odds of onychomycosis than patients without comorbid conditions (OR = 11.61, 95% CI: 2.41–55.94, Fisher's exact $p = 0.002$). Compared with all patients

who had fewer than two comorbidities (<2 , meaning the 0 and 1 comorbidity strata together), multimorbid patients kept a 5.33-fold higher odds of onychomycosis (OR = 5.33, 95% CI: 1.81–15.69, $p = 0.003$). These findings show higher odds of onychomycosis with two or more comorbidities, in unadjusted comparisons.

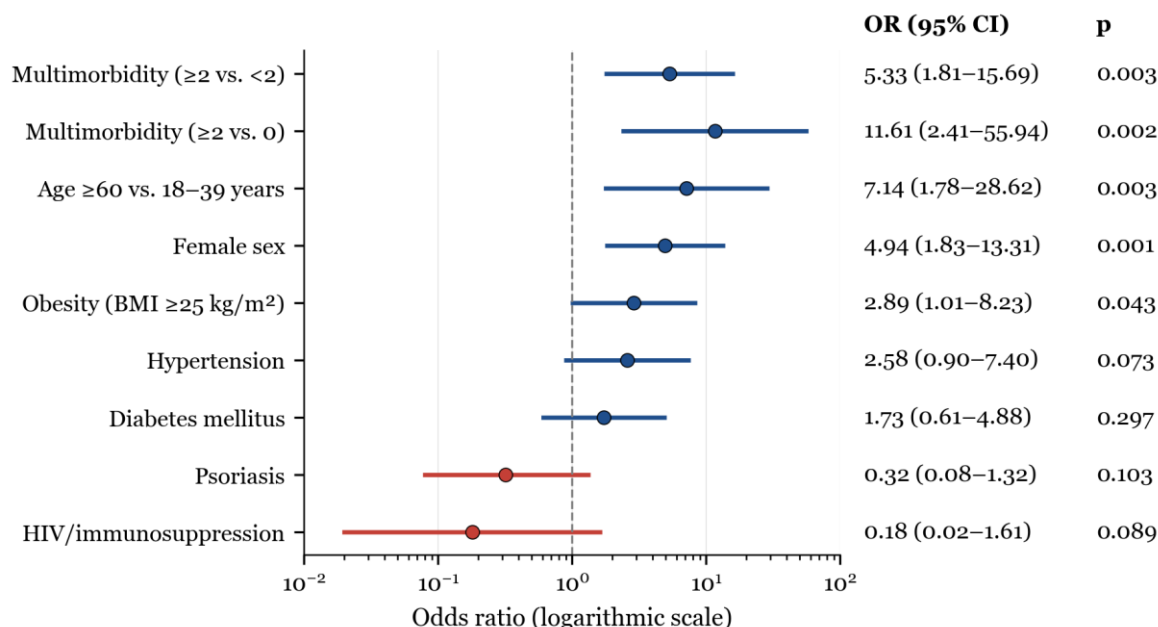


Figure 4. Forest plot of the association between clinical factors and onychomycosis (odds ratios with 95% confidence intervals, logarithmic scale). Odds ratios for age are against the 18–39-year group; p-values for multimorbidity are from Fisher's exact test and the others from Pearson's chi-square test.

4. Discussion

4.1. Principal findings

This study found that, in a tropical tertiary referral setting, onychomycosis was associated with a higher cumulative comorbidity burden. Half of all patients with mycologically confirmed onychomycosis had two or more concurrent systemic or cutaneous disorders. Their odds of fungal nail disease were 11.61-fold higher than in individuals without chronic comorbidities ($p = 0.002$). Five conditions stood out as the main co-occurrences: tinea pedis (47.4%), obesity (39.5%),

systemic hypertension (36.8%), systemic autoimmune diseases (31.6%) and diabetes mellitus (31.6%). The results challenge the traditional view of onychomycosis as an isolated, purely superficial cosmetic disorder. They place it instead as an important cutaneous sentinel of multisystem metabolic, vascular and immunological dysregulation.

4.2. Comparison with international cohorts

The high prevalence of multimorbidity in our Indonesian cohort agrees with recent large international analyses. Albuquer *et al.* (2023) conducted

a case-control study of 15,760 onychomycosis patients in the United States All of Us Research Program. Patients with onychomycosis had higher odds of several chronic systemic diseases: obesity (OR = 2.59), peripheral vascular disease (OR = 3.04), chronic venous insufficiency (OR = 3.38), diabetes mellitus (OR = 3.28) and HIV infection (OR = 1.80).²⁹ Shah *et al.* (2024) analyzed 119,662 onychomycosis admissions in the US National Inpatient Sample. Systemic hypertension was the most frequent comorbid condition (60.8%), followed by fluid/electrolyte disorders (25.5%), chronic pulmonary disease (22.7%), uncomplicated diabetes (22.3%) and obesity (15.1%).³³ Multivariate regression in that national study showed large risk elevations for concurrent tinea pedis (OR = 111.99), venous insufficiency (OR = 6.92), HIV (OR = 4.37), psoriasis (OR = 3.67), obesity (OR = 2.41) and complicated diabetes mellitus (OR = 2.05).³³ In Spain, Navarro-Pérez *et al.* (2024) found in a cross-sectional study that diabetes mellitus raised the risk of onychomycosis almost threefold (OR = 2.754, 95% CI: 1.652–4.679, $p < 0.001$). Polymicrobial and mixed fungal infections predominated among diabetic individuals.²⁴ In South Africa, Pezisa *et al.* (2026) studied 103 mycologically confirmed onychomycosis patients in a tertiary hospital. Systemic comorbidities were present in 53.4%, led by hypertension (29.1%) and diabetes mellitus (18.4%).³⁴ In Mexico, Araiza-Santibáñez *et al.* (2016) investigated 138 geriatric onychomycosis cases. At least one comorbidity was present in 68.8%, and hypertension (36.2%) and diabetes (35.5%) dominated.³⁵ The close agreement between these varied international cohorts and our findings from Surakarta shows that cumulative comorbidity is a universal, cross-continental driver of fungal nail colonization.

4.3. Mechanisms of fungal nail invasion

To understand why hosts with multimorbidity are so susceptible, the biochemistry of fungal invasion of the nail apparatus needs to be examined. The nail plate is a dense, specialized barrier. About 80% to 90% of it consists of hard, sulfur-rich alpha-keratins, stabilized by

many intra- and intermolecular disulfide bonds between cysteine residues.^{1,36} Fungi that colonize this hostile substrate, mainly dermatophytes such as *Trichophyton rubrum*, secrete a large set of enzymes known as the keratinolytic degradative cascade.³⁷ Monod *et al.* (2022) and Martinez-Rossi *et al.* (2021) showed that hyphae cannot directly cleave native, disulfide-crosslinked hard keratin. Invasion starts with a sulfitolysis step driven by the fungal sulfite efflux pump (encoded by the Ssu1 gene).³⁶ The secreted sulfite is a reducing agent. It cleaves keratin disulfide bridges (cystine) into cysteine and S-sulfocysteine, unravels the tightly coiled polypeptide chains and exposes cleavage sites.

After sulfitolysis has unfolded the keratin, dermatophytes secrete a wide set of endo- and exo-proteases. These digest the exposed polypeptide backbones. The main virulence factors are subtilisin-like serine proteases (Sub3, Sub4, Sub7) and fungalisins (the metalloproteases Mep3, Mep4 and Mep5).³⁷ Fungi also release aspartic proteases (Saps) and leucine aminopeptidases (Laps), which hydrolyze oligopeptides to free amino acids. Fungal oligopeptide transporters take these up to feed mycelial growth. Dermatophytes also express cell-surface adhesins and hydrophobins that bind human corneocytes with high affinity. They then secrete an exopolysaccharide matrix that builds resilient biofilms in the subungual space.^{38,39} Biofilms may impede the penetration of host immunoglobulins and topical antifungal drugs, which may contribute to the therapeutic recalcitrance seen in chronic infection.³⁸

4.4. Pathophysiological pathways

The following mechanisms are drawn from the literature; none was measured in this study. In a host with multimorbidity, this enzymatic machinery may meet a nail microenvironment that is impaired in several physiological domains: metabolic, microvascular, biomechanical and immunological (Figure 5).

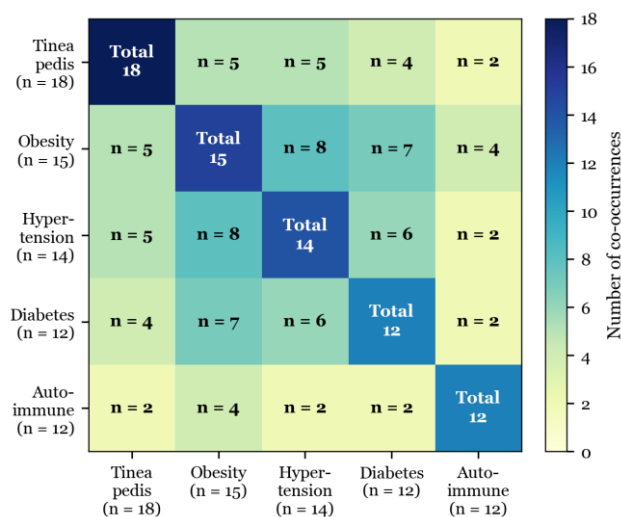


Figure 5. Comorbidity co-occurrence matrix in patients with onychomycosis. Cells show the number of patients with both conditions; diagonal cells show the number of patients with each condition.

Obesity, biomechanics and inflammation. Obesity (BMI ≥ 25.0 kg/m²) was present in 39.5% of our cases (OR = 2.89, $p = 0.043$) and is a strong biomechanical and systemic driver of fungal disease. In a post hoc analysis of clinical trial data, Elewski and Tosti (2015) classified 73.5% of onychomycosis patients as overweight or obese. Obese individuals had lower complete cure rates than normal-weight peers (15.9% vs. 22.0%, $p = 0.05$).⁴⁰ Excess body weight changes foot biomechanics. It flattens the longitudinal and transverse plantar arches, raises forefoot contact pressure and increases shear forces on the distal toes during push-off.²³ This chronic mechanical stress causes subclinical subungual microhemorrhages and repeated microtrauma to the hyponychial epithelial seal. The resulting micro-fissures let dermatophyte arthroconidia penetrate. Systemically, as reviewed by Ouchi *et al.* (2011) and Spatocco *et al.* (2026), adipose tissue acts as an active endocrine organ. It secretes pro-inflammatory adipokines (leptin, resistin) and downregulates anti-inflammatory adiponectin.^{41,42} The resulting chronic low-grade systemic inflammation (raised circulating TNF- α , IL-6 and C-reactive protein) dysregulates cell-mediated immunity and weakens the host's Th1/Th17 cutaneous antifungal defense. Excess soft tissue, limited joint mobility and redundant abdominal aprons also make daily foot inspection and digital hygiene difficult in obese individuals. Moist skin-on-skin friction between crowded toes then creates a macerated, hyperhidrotic microclimate that favors fungal germination.

Diabetic microangiopathy and neuropathy. Diabetes mellitus was recorded in 31.6% of our onychomycosis cases. It is a recognized major metabolic predisposing condition. Sustained hyperglycemia causes non-enzymatic glycation of long-lived structural proteins, and advanced glycation end-products (AGEs) accumulate in tissue.^{43,44} AGEs bind their cell-surface receptor (RAGE) on microvascular endothelial cells and pericytes. This starts intracellular oxidative stress, nuclear translocation of NF- κ B and heavy transcription of pro-fibrotic cytokines. The capillary basement membrane thickens. Perivascular hyalinization and luminal narrowing follow, the hallmarks of diabetic microangiopathy.^{18,43} Nutritive blood flow to the distal digits falls, with local capillary rarefaction and hypoxia at the nail bed. Delivery of circulating effector leukocytes, complement components and systemic antifungal drugs falls with it.

Diabetic sensorimotor polyneuropathy adds to the problem. It dulls protective pain and temperature sensation in the distal toes. Repeated, unnoticed trauma from footwear friction or minor injury can then break the hyponychial seal, and the patient does not react.¹⁸ Hyperglycemia also directly inhibits neutrophil chemotaxis, phagocytosis and the production of reactive oxygen species (ROS) in the oxidative burst. Innate cellular defense against fungal hyphae is blunted. Cutaneous and subungual interstitial fluid in diabetic patients contains more glucose. This feeds invading dermatophytes and *Candida* species and speeds mycelial growth and biofilm consolidation.¹⁸ The effect is twofold. Diabetic patients have higher infection rates,

and they also develop mixed, polymicrobial nail colonization that resists standard antifungal courses.⁴⁵

Vascular stasis and endothelial dysfunction. Systemic hypertension (36.8% in cases, OR = 2.58) and chronic venous insufficiency (7.9% in cases, OR = 7.59) are two further vascular mechanisms that predispose to onychomycosis. Chronic arterial hypertension causes endothelial shear stress, systemic nitric oxide deficiency, medial smooth muscle hypertrophy and peripheral arteriosclerosis. Perfusion pressure in the distal digital capillary loops falls. Chronic venous insufficiency, as studied by Saqib *et al.* (2018) in toenail onychomycosis, produces ambulatory venous hypertension through deep or superficial valvular incompetence.⁴⁶ Raised retrograde hydrostatic pressure dilates post-capillary venules and widens endothelial gap junctions. Plasma macromolecules and red blood cells leak into the perivascular interstitium. Extravasated fibrinogen polymerizes into pericapillary 'fibrin cuffs'. These have been proposed to act as a physical diffusion barrier that obstructs oxygen and nutrient exchange between capillaries and distal keratinocytes.

Chronic interstitial edema and tissue hypoxia follow. They degrade the structure of the distal epidermis and hyponychium.¹⁶ Chronic vascular stasis also slows linear growth of the nail plate. This matters. The outward growth of a healthy nail plate is a natural mechanical clearance mechanism, because it carries distally advancing fungal hyphae away. Any reduction in nail turnover, as in venous stasis and aging, gives fungi more time to move proximally toward the germinative matrix. Deep, recalcitrant infection can then become established.^{9,13}

Autoimmune disease and pharmacological immunosuppression. A large share of onychomycosis cases in our cohort (31.6%, $n = 12$) had a concurrent systemic autoimmune disease ($p < 0.001$). This reflects the specialized tertiary referral role of Dr. Moewardi Hospital. It is supported by Tuchinda *et al.* (2006) in Thailand, who reported a 24.0% prevalence of onychomycosis among patients with autoimmune blistering diseases (OR = 4.39, $p = 0.013$).⁴⁷ Patients in our cohort with systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and pemphigus vulgaris were on chronic immunosuppressive therapy. This included oral corticosteroids (prednisone, methylprednisolone) and non-biologic DMARDs (methotrexate, azathioprine, cyclophosphamide).

Mechanistically, systemic corticosteroids bind cytoplasmic glucocorticoid receptors and move to the nucleus, where they inhibit the transcription factors NF- κ B and AP-1. Synthesis of pro-inflammatory cytokines (IL-1, IL-2, IL-6, TNF- α and IFN- γ) falls sharply.⁴⁸ Cell-mediated immunity matters even more. It is organized by CD4+ T-helper 1 (Th1) and T-helper 17 (Th17) lineages and is the basis of host defense against mucocutaneous fungal infection. Th17 cells, driven by IL-23 and the master transcription factor ROR γ t, produce the effector cytokines IL-17A, IL-17F and IL-22. These stimulate keratinocytes to upregulate and secrete

antimicrobial peptides, including human beta-defensin 2 (hBD-2), S100A7 (psoriasin) and cathelicidin (LL-37).⁴⁹ The peptides disrupt fungal cell membranes directly and recruit neutrophils to the infection site. Pharmacological suppression of the Th17/IL-17 axis by systemic immunosuppressants removes this antimicrobial shield. Dormant fungal arthroconidia can then germinate unchallenged and invade the hard keratin of the nail unit.⁴⁹

The tinea pedis fungal reservoir. Concurrent tinea pedis was found in nearly half of onychomycosis cases (47.4%, $n = 18$) and in 0% of controls ($p < 0.001$; OR = 69.49). This underlines the role of tinea pedis as an active, persistent fungal reservoir. In their re-analysis of clinical trial data, Elewski and Tosti (2015) found that about 21% of onychomycosis patients had co-existing tinea pedis. Patients who also received antifungal therapy for tinea pedis reached complete nail cure rates almost twice those of patients whose foot skin went untreated (29.4% vs. 16.1%, $p = 0.025$).⁴⁰ Arthroconidia from macerated interdigital spaces or dry, hyperkeratotic plantar skin are shed continuously into socks and shoes. Friction during walking then re-inoculates the hyponychial groove and lateral nail folds. Unless the skin reservoir is fully eradicated, treating the nail unit alone, topically or systemically, leads to early reinfection. This is one reason why untreated tinea pedis is regarded as a source of reinfection of the nail unit.⁴⁰

4.5. Demographic determinants: advanced age and female sex

Two demographic associations stood out in our study: advanced age (≥ 60 years: 36.8% vs. 7.9%, OR = 7.14, $p = 0.0028$) and female sex (60.5% vs. 23.7%, OR = 4.94, $p = 0.001$). The age association agrees with worldwide epidemiological data, including Gupta *et al.* (2022) and Araiza-Santib   ez *et al.* (2016).^{7,35} Nail senescence involves a sharp slowing of linear growth, from about 3.0 mm/month in healthy young adults to under 1.5 mm/month in people over 65 years.⁵⁰ This reduces the rate at which fungal spores are carried out. Older adults also have age-related microvascular stiffening, subungual hyperkeratosis, toe deformities, poorer visual acuity and less joint flexibility. These changes impair routine foot and nail grooming.⁷

The female predominance among our onychomycosis cases (60.5%) contrasts with several Western population surveys that reported higher male prevalence, but it matches other regional tertiary studies.^{11,51} In an Indonesian study at RSUPN Dr. Cipto Mangunkusumo, Jakarta, Widaty *et al.* (2024) found that 65.5% of onychomycosis patients were female.¹¹ Mayengo *et al.* (2025) likewise reported a high prevalence of onychomycosis (57.5%) among women who use nail cosmetics in Uganda.⁵¹ Cultural, occupational and behavioral factors may explain this female excess in outpatient dermatology. In urban Indonesia, adult women spend much time in domestic tasks with prolonged contact with water and harsh detergents (cooking, dishwashing, laundry). These repeatedly hydrate and macerate the nail unit and

weaken the eponychial and hyponychial seals. Gel nail polish, acrylic extensions, aggressive cuticle trimming and salon manicures or pedicures with shared, non-sterile instruments also cause microscopic trauma and chemical etching that make fungal colonization easier.⁵¹ Finally, women tend to be more sensitive to visible skin and nail changes and seek care sooner. Men often ignore subungual thickening until function is impaired.

4.6. Clinical implications

Our results show that cumulative multimorbidity increases susceptibility to onychomycosis. This has implications for clinical dermatology and multidisciplinary care. First, clinicians should drop the outdated view of onychomycosis as an isolated cosmetic issue. It is better treated as an external sign of possible underlying metabolic, vascular or immunological dysfunction. Second, dermatologists who see patients with recalcitrant or multi-digit onychomycosis should screen for comorbidity. This includes blood pressure measurement, glycemic profiling (HbA1c), BMI assessment and a review of vascular and immunological medication. Third, management protocols need restructuring. Treating the nail plate alone is likely to fail if the interdigital tinea pedis reservoir, peripheral edema, glycemic control, weight reduction and foot hygiene are left unaddressed. In diabetic and immunosuppressed patients, routine podiatric screening in primary and tertiary clinics is advisable. It can catch early onychomycosis before it progresses to bacterial cellulitis or limb-threatening ulceration.

4.7. Strengths and limitations

The study has several strengths. These include a 6.5-year observation period in a leading academic tertiary center, strict inclusion criteria that required objective mycological confirmation (10% KOH microscopy and/or fungal culture) in every case, recruitment of controls from the same clinic and period, and a systematic definition of ten discrete comorbid conditions and of the cumulative multimorbidity tiers.

Several limitations must be acknowledged. First, the retrospective design relies on existing electronic medical records. It therefore cannot establish the exact timing of each comorbidity relative to the first fungal inoculation. Second, data came from a single tertiary academic center. Berkson's selection bias may therefore have enriched the cohort with patients who have more complex, severe or numerous chronic illnesses than community populations. Third, fungal identification relied on direct 10% KOH microscopy and conventional culture on Sabouraud dextrose agar. Molecular identification methods, such as real-time PCR or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), were not routinely available. Detailed genotyping of fungal strains and resistance mutations was thus not possible.^{14,31} Fourth, some lifestyle and behavioral variables were not systematically recorded in hospital EMR charts: daily shoe occlusiveness, duration of occupational footwear, sports participation and frequency of salon pedicures. Prospective, multicenter studies with molecular

pathogen identification and standardized behavioral tracking would build on these findings.

5. Conclusions

In conclusion, this retrospective case-control study found a statistically significant association between cumulative multimorbidity burden and onychomycosis in an Indonesian tertiary outpatient setting ($p = 0.002$). The association was large. Patients with multimorbidity (≥ 2 co-existing comorbid disorders) had 11.61-fold higher odds of onychomycosis than individuals free of chronic disease. Tinea pedis, obesity, systemic hypertension, systemic autoimmune disorders and diabetes mellitus were the dominant comorbidities.

These findings suggest that clinicians should consider comorbidity when evaluating onychomycosis. Long-term clinical and mycological cure may need a multidisciplinary approach. It could combine targeted systemic and topical antifungal therapy with eradication of adjacent cutaneous fungal reservoirs (tinea pedis), strict glycemic control, management of vascular edema, and patient education on digital hygiene and protective foot care.

Declarations

Use of Generative Artificial Intelligence. The authors did not use any generative artificial-intelligence tools in writing, analyzing, or preparing this manuscript. All content was produced and verified by the authors, who take full responsibility for its integrity and accuracy.

Author Contributions. N.M.: conceptualization, methodology, supervision, writing – original draft, writing – review & editing. L.P.A.: investigation (electronic medical record data extraction), data curation, writing – original draft (literature search). H.F.Y.: data curation, writing – review & editing. All authors read and approved the final manuscript.

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Conflict of Interest. The authors declare no competing financial, professional, or personal interests.

Ethical Approval. The study protocol received formal ethical approval from the Health Research Ethics Committee (Komisi Etik Penelitian Kesehatan) of RSUD Dr. Moewardi General Hospital under Ethical Clearance Certificate No. 1.478/VIII/HREC/2026, and was conducted in accordance with the Declaration of Helsinki (1975, as revised in 2013).

Patient Consent. A waiver of individual informed consent was granted by the ethics committee because of the retrospective, de-identified nature of the electronic medical record review. Consent for publication is not applicable.

Data Availability. The de-identified datasets analyzed during the current study are available from the corresponding author upon reasonable academic request, in accordance with institutional data transfer and patient confidentiality regulations.

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