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Developing diagnostic criteria to differentiate fungal foot infections caused by *Neoscytalidium dimidiatum* and dermatophytes

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ABSTRACT

Background: The predisposing factors and clinical presentations of fungal foot infections caused by non-dermatophytes and dermatophytes are challenging to differentiate. Definite diagnoses of non-dermatophyte infections at first visits facilitate their treatment.
Objectives: This study aimed to develop diagnostic criteria to differentiate fungal foot infections caused by *Neoscytalidium dimidiatum* and dermatophytes.
Methods: Diagnostic prediction research based on a retrospective, observational, cross-sectional study. The reviewed patients were aged ≥18 and underwent a mycological examination for fungal foot infections. A fungal culture at the initial visit was the gold standard for determining causative organisms.
Results: Analyses were carried out on the data from 371 patients. *N. dimidiatum* accounted for 184 (49.6%) infections, and dermatophytes caused the remaining 187 (50.4%) cases. Five significant predefined predictors were used to develop the diagnostic criteria and score. They were immunocompetence status, no family history of fungal infections, the absence of pruritus, the absence of other concurrent fungal skin infections, and agricultural work. The lower score cutoff was <8 (sensitivity 97.8% and specificity 25.7%). The higher cutoff was >11 (sensitivity 83.7% and specificity 57.8%). The score showed an area under the receiver operating characteristic curve of 0.755 and was well calibrated.
Conclusions: The criteria and score show promise for clinical use, with acceptable discriminative performance and good calibration. They will help physicians differentiate the causative organisms in patients with fungal foot infections at the first visit, enabling the determination of appropriate antifungal treatment.

1. Introduction

Fungal foot infections are common worldwide, with reported prevalences 0f 3.5%–40.6% among patients visiting health centers

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[1–5]. Diabetes mellitus, peripheral vascular disease, wearing slippers, and repetitive foot injuries have been associated with a higher risk of fungal foot infections [1]. The infections are caused by dermatophytes and non-dermatophyte molds and yeasts [4,6–9]. The prevalence of non-dermatophyte foot infections is reportedly increasing, with studies finding that non-dermatophytes cause between 17% and 58% of fungal foot infections [2,10]. The variation in causative agents may reflect differences in the diagnostic methods employed and in the agents' geographic distribution [1,10,11].

Neoscytalidium dimidiatum is a dematiaceous ascomycete and is usually transmitted to humans from the soil and the environment. The mold is commonly found in tropical countries, including Thailand, Singapore, and Brazil, and it causes nail and superficial skin lesions [1,11–15]. The presence of dematiaceous hyphae in a potassium hydroxide examination of skin lesion scrapings from skin lesions cannot identify causative species. Rather, fungal culture is the gold standard for diagnosis. Unfortunately, only some hospitals have the resources to perform and expertly interpret fungal cultures.

Notably, several studies have reported indistinguishable risk factors and clinical findings of dermatophyte and non-dermatophyte fungal foot infections [1–3,10,16,17]. Regarding treatment and outcomes, topical antifungal medications, such as azoles and allylamines, are the primary treatment for dermatophyte foot infections. Systemic antifungal agents are reserved for patients who do not respond to topical therapy. In contrast to non-dermatophyte foot infections, particularly *Neoscytalidium* infection, which typically resist traditional topical treatment, a combination of topical and systemic antifungal medications or that of topical antifungal and keratolytic medication is recommended as the first treatment for non-dermatophyte foot infections [14,18]. Early diagnosis of non-dermatophyte infections would facilitate their treatment.

This study aimed to elucidate the risk factors, clinical features, and appropriate treatment of patients with *Neoscytalidium dimidiatum* foot infections. Moreover, diagnostic criteria and scores were developed from relevant predictive factors for differentiating between diagnoses of *Neoscytalidium dimidiatum* and dermatophyte foot infections.

2. Materials and methods

2.1. Design and setting

Diagnostic prediction research was conducted. It was based on a retrospective observational cross-sectional study. The reviewed patients attended the dermatology outpatient clinic of an academic university hospital between January 1, 2010 and December 31, 2021. All were ≥18 years of age and underwent a mycological examination for a fungal foot infection. Before this research began, informed consent was obtained, and its protocol was approved by the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand Ethics Committee (Si-328/2022).

2.2. Study population

Patients with suspected fungal foot infections were enrolled. The scales from their foot lesions were examined using a potassium hydroxide preparation and a fungal culture. Direct microscopic examination using 20% potassium hydroxide was employed to detect the presence of fungal hyphae and arthrospores, supporting the diagnosis of fungal foot infection. In addition, fungal cultures were utilized to identify the molds by observing their microscopic and macroscopic characteristics. Sabouraud dextrose agar (SDA) with cycloheximide was employed to grow dermatophytes, while SDA without cycloheximide was used for non-dermatophytes. Chloramphenicol was added to inhibit bacterial growth. The cultures were incubated at a temperature of 27 °C and assessed for fungal growth every 2 weeks over 6 weeks. The identification of fungi was based on the consensus agreement of three experienced fungal microscopists/technicians with over 5 years of expertise in mycological laboratory work. In case of any controversial results, the cultures are further analyzed using molecular methods. The participants were classified into two groups based on the initial culture results: *Neoscytalidium* and dermatophyte foot infection groups. Diagnoses of a *Neoscytalidium* foot infection followed the non-dermatophyte onychomycosis criteria [6]. Two consecutive positive cultures for *Neoscytalidium dimidiatum*, within 1–2 weeks, were used to confirm *Neoscytalidium dimidiatum* as the true pathogen. Diagnoses of a dermatophyte foot infection were based on dermatophyte growth in one culture. Patients were excluded from the analyses if they had a negative mycological culture, a mixed non-dermatophyte and dermatophyte infection, or an infection caused by a non-dermatophyte other than *Neoscytalidium dimidiatum*.

2.3. Data collection and predictors

Demographic data at the baseline visit, including age and gender, were collected. The following predisposing factors for fungal feet infection were reviewed.

- history of previous fungal foot infections
- agricultural work
- using occlusive shoes for >6 h daily
- foot hyperhidrosis for >6 months
- history of using a topical steroid on the feet for >1 week during the previous 3 months
- contact with animals
- walking barefoot

Data on the symptoms at initial visits were collected. The symptoms included pruritus, pain, and clinical findings (for example, the type of fungal foot infection, bilateral or unilateral involvement, and the infection site). Concurrent fungal nail and other skin infections were recorded. The presence of peripheral vascular disease, lymphedema, malalignment of the feet, diabetes mellitus, obesity, or an immunocompromised status were considered comorbidities. Laboratory results were reviewed at the initial visit, the treatment administered, and the clinical outcomes.

2.4. Study size estimation

The sample calculation was from a study comparing the proportions of patients with *Neoscytalidium* and dermatophyte foot infections who worked in agriculture, a factor identified as a potentially significant predictor [12]. The proportions of patients involved in agricultural work were 0.29 and 0.16 in the *Neoscytalidium* and dermatophyte infection groups, respectively. To achieve 80% statistical power and a two-sided alpha error of 0.05, a sample size of 322 patients was required.

2.5. Statistical analysis

Analyses were performed using Stata Statistical Software, release 17 (StataCorp LLC, College Station, TX, USA). Descriptive statistical analysis was used for patients' demographic and clinical characteristics. We described continuous variables using the mean and standard deviation and categorical variables using their frequency and percentage. For comparisons between *Neoscytalidium* and dermatophyte infections, Fisher's exact probability test was used for categorical variables, while an independent *t*-test was used for continuous variables. The area under the receiver operating characteristic (AuROC) curve was used to examine the discriminative ability of each potential predictor. Statistical significance was set at $p < 0.05$.

Potential predictors for the diagnostic score were selected based on a literature review and variables reaching statistical significance in univariate analysis. A multivariate logistic model included all predictors with a univariate *p*-value <0.05. A full multivariate model without elimination was used to develop the diagnostic score. Each diagnostic factor was allocated a weighted score calculated from the logit coefficient of each predictor. Predictive performances, including model discrimination and calibration, were evaluated using the sum of the scores for the individual factors. The AuROC curve was analyzed to determine discriminative ability. A calibration plot and a Hosmer–Lemeshow goodness-of-fit test were then used to prove the score calibration. A score calibration plot was created by contrasting the sum of the total scores with the observed proportion of *Neoscytalidium* infections within each score stratum.

The patients in the dataset were grouped into three risk categories for *Neoscytalidium* foot infection: low, moderate, and high, to determine the clinical applicability of the proposed score. The score cutoffs were based on sensitivities and specificities suitable for clinical practice. A higher sensitivity with acceptable specificity was required for a lower cutoff, whereas a higher specificity with acceptable sensitivity was needed for a higher cutoff. The positive likelihood ratio (LHR+) with its corresponding 95% confidence interval (CI) was analyzed to determine the ability of each score category to predict *Neoscytalidium* foot infections. Internal validation of the proposed score with bootstrap resampling procedures was used to quantify the optimism of the derived score in diagnosing *Neoscytalidium* foot infections.

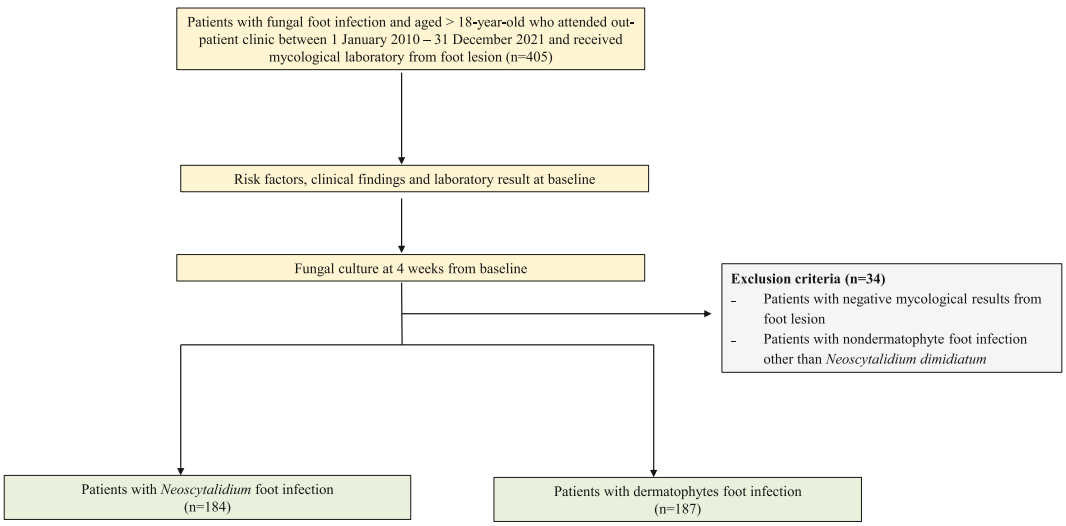

Fig. 1. Study flow diagram of patient details.

3. Results

3.1. Baseline characteristics

A total of 405 patients with fungal foot infections were enrolled. Thirty-four patients were subsequently excluded due to having yeast, *Fusarium,* and *Aspergillus* infections (Fig. 1). The remaining 371 patients were included in the analysis. Their mean age was 63.3 (SD ± 12.4) years, and 214 (57.5%) were male. *Neoscytalidium dimidiatum* was the causative agent in 184 cases (49.6%) and dermatophytes in 187 cases (50.4%). Among the 187 patients with dermatophyte foot infections, *Trichophyton interdigitale* predominated (101 cases; 54%), followed by *T. rubrum* (81 cases; 43.3%), *T. tonsurans* (three cases; 1.6%) and *Microsporum canis* (two cases; 1.1%). The demographic data, risk factors, and clinical characteristics of the patients with *Neoscytalidium dimidiatum* and dermatophyte

Table 1
Baseline demographic data, risk factors, and clinical characteristics of patients with *Neoscytalidium dimidiatum* and dermatophyte foot infections.

Clinical characteristics	*Neoscytalidium dimidiatum* (n = 184)	Dermatophytes (n = 187)	Odds ratio (95% CI)	*p*-value	AuROC (95% CI)
Age (years)	66.4 (10.9)	64.2 (13.6)	1.02 (0.99–1.03)	0.078	0.54 (0.48–0.59)
Male	105 (57.1)	109 (58.3)	0.95 (0.63–1.44)	0.812	0.49 (0.44–0.54)
Risk factors					
- Agricultural work	78 (42.4)	52 (27.8)	1.91 (1.24–2.94)	0.003*	0.57 (0.52–0.62)
- Use of occlusive shoes >6 h/days	16 (8.7)	26 (13.9)	0.59 (0.31–1.14)	0.116	0.47 (0.44–0.51)
- Hyperhidrosis of feet	49 (26.6)	47 (25.3)	1.07 (0.67–1.71)	0.765	0.51 (046–0.55)
- Use of topical corticosteroids on the feet within the previous 3 months	7 (3.8)	9 (4.8)	0.78 (0.29–2.15)	0.633	0.49 (0.46–0.52)
- Contact with animals	74 (40.2)	80 (42.8)	0.90 (0.60–1.36)	0.616	0.49 (0.44–0.54)
- Barefoot walking in public places	47 (25.5)	35 (18.7)	1.49 (0.91–2.44)	0.114	0.53 (0.49–0.58)
- Obesity (BMI >30)	21 (11.4)	21 (11.2)	1.02 (0.54–1.94)	0.956	0.5 (0.46–0.53)
- Family history of fungal infections	7 (3.8)	30 (16)	0.21 (2.06–11.31)	<0.001*	0.43 (0.41–0.47)
Underlying diseases					
- Immunocompetent status	182 (98.9)	172 (92.0)	7.9 (1.8–35.2)	0.006*	0.53 (0.51–0.56)
- Peripheral vascular disease	40 (21.7)	41 (21.9)	0.99 (0.6–1.62)	0.965	0.5 (0.46–0.54)
- Atherosclerosis	15 (8.1)	15 (8.0)	1.02 (0.48–2.15)	0.963	0.5 (0.47–0.53)
- Malalignment of the feet	51 (27.7)	57 (30.5)	0.87 (0.56–1.37)	0.558	0.49 (0.44–0.53)
- Dyslipidaemia	98 (53.3)	96 (51.3)	1.08 (0.72–1.62)	0.711	0.51 (0.46–0.56)
- Diabetes mellitus	54 (29.4)	50 (26.7)	1.14 (0.72–1.79)	0.576	0.51 (0.47–0.56)
Symptoms at baseline					
- Pruritus	22 (12.0)	58 (31.0)	0.3 (0.18–0.52)	<0.001*	0.4 (0.36–0.45)
- Pain	1 (0.5)	3 (1.6)	0.34 (0.04–3.25)	0.346	0.49 (0.48–0.51)
Feet examination					
- Type of infection					
- Moccasin	176 (96.7)	183 (97.9)	0.48 (0.14–1.62)	0.239	0.49 (0.47–0.51)
- Interdigital	20 (10.9)	25 (13.4)	0.79 (0.42–1.48)	0.462	0.49 (0.45–0.52)
- Vesiculobullous	12 (6.5)	23 (12.3)	0.5 (0.24–1.03)	0.061	0.47 (0.44–0.5)
Both feet infection	109 (59.2)	109 (58.3)	1.04 (0.69–1.57)	0.468	0.5 (0.45–0.55)
Concurrent toenail infection	135 (73.4)	148 (79.1)	0.73 (0.45–1.17)	0.192	0.47 (0.43–0.51)
Other concurrent skin infection	2 (1.1)	42 (22.5)	0.04 (0.01–0.16)	<0.001*	0.39 (0.36–0.42)

Numbers are n (%) or mean ± SD. Abbreviations: AuROC, area under the receiver operating characteristic curve; BMI, body mass index.

infections are summarized in Table 1. The patients with *Neoscytalidium* infections were older than those with dermatophyte infections (mean ages, 66.4 vs 64.2 years; $p = 0.078$). *Neoscytalidium* foot infections were significantly associated with patients engaged in agricultural work ($p = 0.003$). Dermatophyte infections were statistically associated with a family history of fungal infections, an immunocompromised status, pruritus symptoms, and other concurrent skin infections. Regarding laboratory results, no dematiaceous hyphae were detected in any foot lesion specimens.

3.2. Multivariate analysis and modeling

The significant diagnostic predictors identified in the univariate analysis were subjected to multivariate analysis (Table 2). Each predictor in the final model was assigned a weighted score based on each factor's logit coefficient. Scores were approximated to the nearest whole number. The sum of the transformed scores ranged from 2 to 12, and the overall mean score of all patients was 10.0 ± 2.2. There was a significant difference in the mean scores of patients with *Neoscytalidium dimidiatum* infections and those with dermatophyte infections (11.0 ± 1.1 vs 9.1 ± 2.6; $p < 0.001$).

Two cutoffs were used to group the patients with fungal foot infections into three risk categories for *Neoscytalidium* foot infections: low, moderate, and high (Table 3). The lower cutoff score was <8, with a sensitivity of 97.8% (95% CI, 94.5–99.4) and a specificity of 25.7% (95% CI, 19.6–32.6). The higher cutoff was >11, with a sensitivity of 83.7% (95% CI, 77.5–88.7) and a specificity of 57.8% (95% CI, 50.3–64.9). The prevalence of *Neoscytalidium dimidiatum* foot infections and the LHR + for each category are detailed in Table 3. The confidence intervals of LHR + for the risk categories did not overlap. The score showed acceptable criteria to distinguish patients with *Neoscytalidium dimidiatum* and those with dermatophyte infections, based on an AuROC at 0.755 (95% CI, 0.71–0.80; Fig. 2A). After internal validation with the bootstrap procedure, the test AuROC was 0.753 (95% CI, 0.70–0.80). Regarding score calibration, the Hosmer–Lemeshow goodness-of-fit statistic revealed a non-significant result (no statistical evidence of lack-of-fit; $p = 0.772$), representing an almost perfect fit of the model to the observed data. The score calibration plot also showed good agreement between the calculated score and the observed risk for a *Neoscytalidium dimidiatum* foot infection. The predicted risk scores and the observed risks for a *Neoscytalidium dimidiatum* foot infection are illustrated in Fig. 2B to represent the relative number of patients for each score.

4. Discussion

This study developed diagnostic criteria and scores that facilitate the differential diagnosis of *Neoscytalidium dimidiatum* from dermatophyte foot infections, thereby guiding appropriate management. The significant diagnostic predictors for *Neoscytalidium dimidiatum* foot infections were patient involvement in agricultural work, an immunocompetent status, the absence of pruritus, other concurrent fungal skin infections, or a family history of fungal infections. The score shows promise for clinical use, with acceptable discriminative performance and good calibration.

As shown in this study, working in agriculture or having contact with soil or an environment contaminated with *Neoscytalidium dimidiatum* predisposes to foot infection [1,7]. Contact with soil may also present an additional risk for geophilic dermatophyte infections; however, such dermatophytes rarely cause foot infections [1,2,19]. Close contacts or family members with histories of fungal infections have been reported in high proportions (72%–80%) of patients with dermatophyte infections [20–22]. Genetic susceptibility and close contact with family members or transmission through fomites or the environment may cause chronic and recurrent dermatophyte infections [20]. However, there have been limited reports on genetic predisposition or familial infections related to non-dermatophyte molds, especially *Neoscytalidium dimidiatum*.

Dysregulation of the host immune response was reported to be associated with dermatophyte infections [20,23,24]. The present study found that an immunocompromised status is a risk factor for dermatophyte infections, similar to previous studies. Conversely, non-dermatophytes, especially *Neoscytalidium dimidiatum*, are highly virulent in invading the skin and nails [1,6,8]. Hence, irrespective of an individual's immunocompetent status, aggressive non-dermatophytes can cause superficial, deep skin and nail infections [13,25].

Previous studies have reported that the clinical presentations of fungal foot infections caused by non-dermatophytes and dermatophytes were not distinguishable [12,26]. The vesicular form of fungal foot infections rarely occurred in cases of non-dermatophyte infections. However, one study reported that 9.7% of patients with *Neoscytalidium dimidiatum* foot infections presented with vesicles [1]. Consequently, the present study determined that 6.5% of the *Neoscytalidium dimidiatum* foot infections had vesiculobullous lesions. Nevertheless, this study found that vesiculobullous formation and pruritus were significantly less frequent among *Neoscytalidium*

Table 2
Multivariable regression analysis of predictive factors for differentiating *Neoscytalidium dimidiatum* foot infections from dermatophyte foot infections.

Potential predictors	Odds ratio	95% CI	*p*-value	β	Item score
Doing agricultural work	1.87	1.15–3.07	0.012	0.63	1
No family history of fungal infections	4.29	1.71–10.75	0.002	1.46	2
Immunocompetent status	4.10	0.82–20.5	0.086	1.41	2
No pruritus	3.37	1.89–6.00	<0.001	1.21	2
No other concurrent fungal skin infections	21.95	5.11–94.29	<0.001	3.09	5

Abbreviations: β, beta-coefficient; CI, confidence interval.

Table 3
Distribution of *Neoscytalidium dimidiatum* foot infections, dermatophyte foot infections, and likelihood ratios of *Neoscytalidium dimidiatum* foot infections (LHR+) in low-, moderate-, and high-risk categories.

Risk categories	Score	Prevalence (%)	*Neoscytalidium* infections (n = 184)	Dermatophyte infections (n = 187)	LHR+	95% CI	*p*-value
Low	<8	14.0	4 (2.3)	48 (25.6)	0.08	0.02–0.24	<0.001
Moderate	8–11	61.7	112 (60.7)	117 (62.6)	0.97	0.69–1.37	0.870
High	>11	24.3	68 (37.0)	22 (11.8)	3.14	1.82–5.56	<0.001
Mean ± SD			11.0 (1.1)	9.1 (2.6)			<0.001

Numbers are n (%) or mean ± SD. Abbreviations: CI, confidence interval; LHR+, positive likelihood ratio; SD, standard deviation.

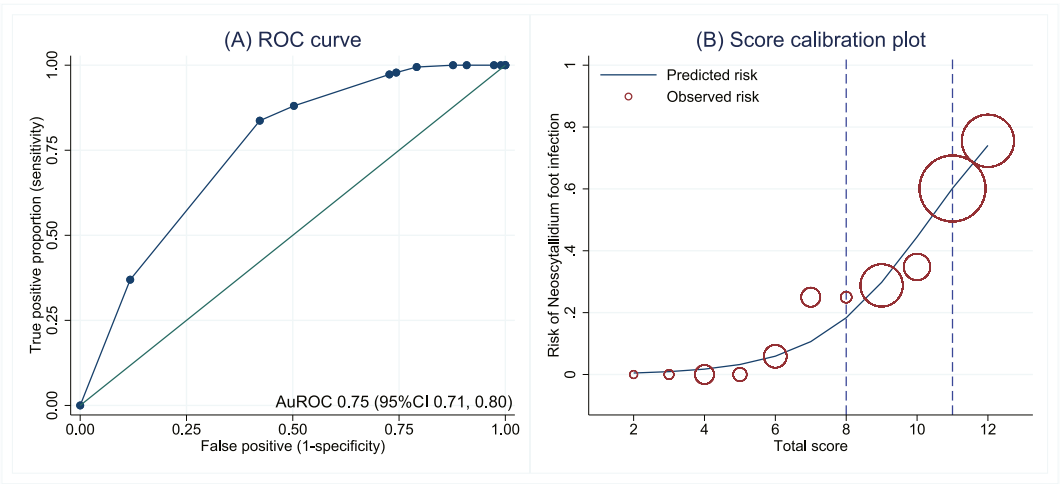

Fig. 2. ROC curve (parametric) and 95% confidence band for predicting *Neoscytalidium* foot infections by the derived score (A). Predicted risk of *Neoscytalidium* foot infections by score (solid line) and observed risk of *Neoscytalidium* foot infections (hollow circles). The circle size depicts the relative number of patients for each score. (B) Abbreviations: AuROC, area under the receiver operating characteristic curve; CI, confidence interval.

dimidiatum infections than dermatophyte infections.

Concerning widespread fungal infections, they are observed more frequently in dermatophyte nail infections than in non-dermatophyte nail infections [12]. Similarly, the current investigation revealed that other concurrent skin infections were observed in patients with dermatophyte foot infections but not in those with *Neoscytalidium* foot infections. Previous reports demonstrated that only 8.6%–9.4% of patients with *Neoscytalidium* infections presented with lesions on their palms, fingers, or groin [7,8]. Whole-body examinations should be performed in all patients with fungal foot infections to facilitate diagnosis and determine the appropriate treatment.

The newly developed diagnostic score shows promise for clinical use. The data for its predictors can be readily obtained in an outpatient setting. The diagnostic score can help physicians categorize patients into risk groups and manage the diseases accordingly. Patients with a low risk for a *Neoscytalidium* foot infection could be treated topically with allylamine, imidazole, ciclopirox, benzylamine, or tolnaftate. Systemic antifungal treatment may help the widespread or concurrent nail infections. Particular care should be taken in patients with a high risk of a *Neoscytalidium* foot infection. A consensus treatment for *Neoscytalidium* infections is yet to be established. In vitro studies showed the antifungal effects of amphotericin B, terbinafine, voriconazole, and luliconazole against *Neoscytalidium dimidiatum* [27,28]. Topical keratolytic and new topical antifungal agents, such as luliconazole, have shown promising outcomes [28]. A combination of terbinafine and topical treatments should be used in refractory cases. Mycological cure should also be monitored carefully.

This study has some limitations. First, the data were collected retrospectively, so bias and missing data could not be avoided. Patients with complete data were included in the analysis to develop the score. Second, fungal culture results at baseline were utilized to determine the causative agents. Molecular methods provide higher sensitivity and rapid detection; however, their high cost has hindered their routine use in general clinical practice. Consequently, we opted to employ the culture method for identifying the type of fungal infection in our study. To mitigate the potential for misclassification bias, we ensured that fungal diagnoses were made by well-trained and experienced microscopists/technicians. In cases where controversial identifications arose from the fungal culture results, molecular methods were used for further specimen identification. Regarding mixed infection, a previous study reported an eclipsed phenomenon, defined as a non-dermatophyte nail infection occurring after a dermatophyte nail infection [29]. Notably, some mixed dermatophyte and *Neoscytalidium* foot infections that subsequently occurred in the current investigation may have been misclassified. Finally, the present study was conducted at a single tertiary-care hospital that handles complex and recalcitrant cases. This means that the prevalence of non-dermatophyte infections may be higher than that at local hospitals. Therefore, the generalization of the

diagnostic score to other clinical settings or populations should be validated before implementation.

5. Conclusions

This study proposes using diagnostic criteria that adopt five simple predictors to differentiate between *Neoscytalidium dimidiatum* and dermatophyte foot infections. The proposed diagnostic score demonstrated acceptable discriminative ability and calibration in determining causative agents, thereby supporting the delivery of appropriate management. A history of agricultural work, a family history of fungal infections, and an immunocompromised status should be evaluated in all patients. Moreover, itch symptoms should be investigated, and a holistic physical examination should be performed to identify any other concurrent skin infections.

Author contribution statement

Charussri Leeyaphan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Chatree Chai-Adisaksopha; Phichayut Phinyo: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Napatra Tovanabutra; Sumanas Bunyaratavej: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Prior presentation

None.

IRB approval status

Reviewed and approved by Siriraj IRB (Si 328/2022).

Reprint requests

Charussri Leeyaphan.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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