Prognostic factors impacting clinical outcome following *Malassezia* folliculitis treatment

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Background: *Malassezia* folliculitis (MF) is a chronic disease that develops in the pilosebaceous unit, caused by *Malassezia* species. Patients' characteristics, clinical manifestations, laboratory examination, and treatment choice affect the clinical recovery in patients with MF. This study aimed to identify several potential factors that determine the treatment outcome of MF.

Methods: This retrospective study was conducted at Dr. Cipto Mangunkusumo Hospital, Jakarta, from 2013 to 2017. Eligible patients diagnosed with MF based on clinical and microscopic examinations were included. Clinical outcomes were defined as complete cure or improvement with a decrease in the subjective symptoms (itchiness) and objective symptoms (lesions). Analyses were carried out using STATA version 5.0, and some analyses and graphics were generated in R (version 3.2.2 for Windows), GraphPad Prism version 6.01, and Microsoft Excel.

Results: A total of 30 patients with MF were recruited. Several factors had a significant effect on the clinical outcomes such as predilection site (chest; HR 1.422; 95% CI 1.262–1.696; $P = 0.018$), isolated systemic therapy (HR 1.915, 95% CI 1.441–2.532; $P = 0.002$), and combination therapy (HR 1.858; 95% CI 1.350–2.541; $P = 0.041$).

Conclusion: Lesions in the chest area, isolated systemic antifungal therapy, and combination therapy were associated with good outcomes following antifungal treatment.

Keywords: *Malassezia*, skin infectious diseases, prognosis, antifungal agents

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INTRODUCTION

Malassezia folliculitis (MF), previously known as pityrosporum folliculitis, is a disease that often goes underdiagnosed as another type of folliculitis or acne, leading to irrelevant and prolonged treatment [1,2]. Akaza *et al.* found that *Malassezia restricta*, *M. globosa*, and *M. sympodialis* were the main *Malassezia* species found in MF [3]. *Malassezia* yeasts are normal microbiota associated with human stratum corneum and hair follicles in more than 90% of the healthy population [4]. However, in several conditions, these dimorphic lipophilic yeasts can turn into opportunistic pathogens and cause skin diseases, including pityriasis versicolor, seborrheic dermatitis, and MF [5,6].

MF is characterized by a highly pruritic, follicular papulopustular eruption seen commonly on the upper trunk. It appears in young age groups and is rarely seen in post-middle age groups. The hallmark symptom is pruritus [7–11]. Although MF's clinical presentation might be confused with acne vulgaris (AV), there is no association with comedones [5,12,13]. The diagnosis of MF is based

on clinical suspicion and response to antifungal therapy [11]. Direct microscopic examination using KOH solution with the addition of Parker blue-black ink would be useful for grading the spore load (up to +3) of *Malassezia* [14]. On histopathologic examination, MF shows dilated follicles with excessive round or oval yeast cells. In the periodic acid-Schiff stain, follicular infundibulum with the presence of spores is clearly shown [15].

The exact prevalence of MF worldwide is still unknown. Geographical areas play an important role in the density of *Malassezia* skin colonization [16]. MF tends to have a higher incidence in people living in warm and humid climates [17]. A retrospective study in Japan and Korea reported 44 patients with MF from 2007 to 2013 and 20 patients with MF during the period of 2008–2011 [2,18]. A study conducted in the Philippines from 1988 to 1989 reported 68 patients with MF. Another study in Saudi Arabia reported 62 patients with MF during the period from 1991 to 1993 [1,14].

Besides the huge possibility that MF may go underdiagnosed, its management could be challenging since it has a high recurrence rate [19]. Several host-related factors or baseline factors, such as demographic characteristics, clinical symptoms, grade of spore load from direct microscopic examination, and type of treatment, may affect the recovery rate. As for therapy, it is advisable to use oral antifungal agents, as topical agents do not penetrate well into the hair follicles [11]. To date, there are limited studies on the prognostic factors of MF. Hence, we conducted a study to identify the association between these factors and the outcome following MF treatment.

MATERIALS AND METHODS

This retrospective study was conducted at Dr. Cipto Mangunkusumo Hospital (RSCM), a tertiary hospital in Jakarta, Indonesia, from 2013 to 2017. The Institutional Review Board and Ethical Committee of Faculty of Medicine Universitas Indonesia (No 18-02-0185) approved the study protocol.

Study participants. We included all patients diagnosed with MF at the Dermatology and Venereology Outpatient Clinic based on clinical and microscopic examinations. The diagnosis was established through clinical examination and direct microscopic examination with potassium hydroxide (KOH) solution, with the presence of spores in the latter representing the main diagnostic criterion. Patients treated with topical or systemic antifungals within a month prior to diagnosis, patients with other infections that did not correlate with MF, and those with incomplete medical records (no record of mycological examination, type of therapy, or follow-up) were excluded from the study. Patients were considered lost to follow-up if they missed the clinic visits for one or more consecutive weeks.

Demographic, clinical characteristic, and comorbidity. Data taken from medical records were demographic characteristics (age and gender), patients' complaints (itchiness, history of illness, and history of pityriasis versicolor), clinical examination (presence of follicular papulopustular lesions and comedones), sites of lesions (interscapular, scapula, chest, upper arm, face, or other sites), spore load (up to +3), types of treatment, and comorbidities if present. The grading criteria of spore load by direct microscopic examination (per high power field) was as follows: 1+ (1 to 2 single spores; no clusters), 2+ (small cluster, not more than 6 spores; or 12 spores if dispersed), 3+ (large clusters of 7-12 spores; or 20 spores if dispersed), and 4+ (cluster of 12 spores; or 20 spores and more if dispersed) [9].

Study outcomes. The primary endpoint of this study was complete cure or improvement of subjective symptoms (itchiness) and objective symptoms (lesions) as shown in Figure 1.

Statistical analysis

All data were analyzed using STATA version 15.0. Analysis of association between variables and the duration of follow-up during treatment can be seen from the mathematic model between one variable and others using multivariate analysis (Cox proportional hazards). All independent variables were analyzed using various tests, i.e., proportional hazards (PH) assumption test, through representation or global statistical tests.

RESULTS

In this study, we recruited 30 patients with MF. Univariate baseline patients' characteristics are presented in Table 1. Kaplan Meier curves showing the improvement of clinical outcomes from two of the most influencing factors are presented in

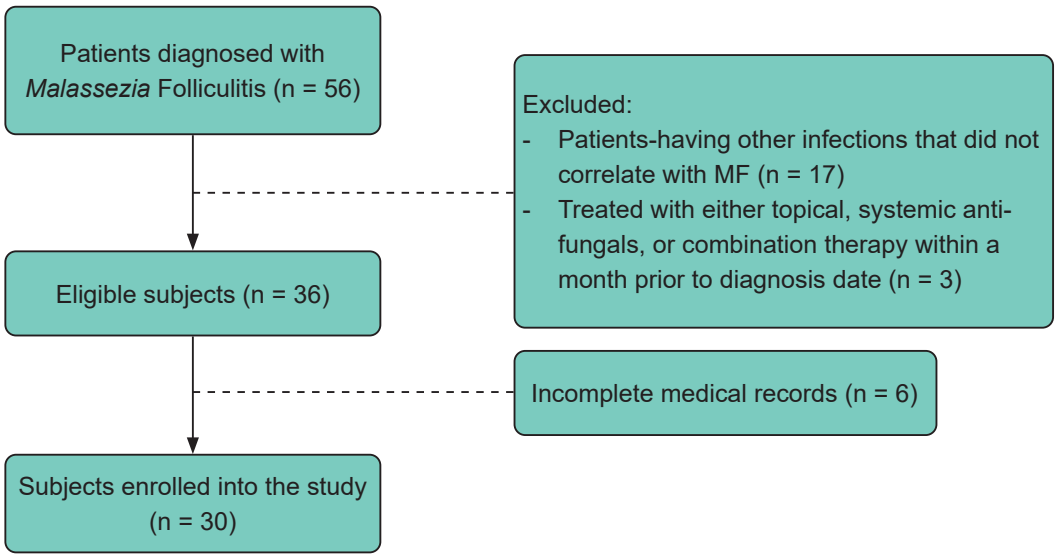

Figure 1. Flow chart of selection of study participants.

Table 1. Baseline characteristics of patients with *Malassezia* folliculitis

	Outcome				*P*-value
	Loss to follow-up		Improvement		
	n	%	n	%	
Gender					
Male	12	44.4%	15	55.6%	0.586
Female	2	66.7%	1	33.3%	
Age					
<18 y/o	4	40.0%	6	60.0%	0.605
18-59 y/o	10	50.0%	10	50.0%	
Itchiness					
No	3	75.0%	1	25.0%	0.222
Yes	11	42.3%	15	57.7%	
History of same complaint					
No	13	44.8%	16	55.2%	0.277
Yes	1	100.0%	0	0.0%	
History of pityriasis versicolor					
No	10	50.0%	10	50.0%	0.605
Yes	4	40.0%	6	60.0%	
Comedones					
No	12	54.5%	10	45.5%	0.151
Yes	2	25.0%	6	75.0%	
Follicular papules-pustules					
No	0	0.0%	0	0.0%	
Yes	14	46.7%	16	53.3%	
Interscapular					
No	2	66.7%	1	33.3%	0.464
Yes	12	44.4%	15	55.6%	
Scapula					
No	11	44.0%	14	56.0%	0.513
Yes	3	60.0%	2	40.0%	
Chest					
No	0	0.0%	5	100.0%	0.022*
Yes	14	56.0%	11	44.0%	

Table 1. Continued

	Outcome				*P*-value
	Loss to follow-up		Improvement		
	n	%	n	%	
Upper arm					
No	7	41.2%	10	58.8%	0.491
Yes	7	53.8%	6	46.2%	
Face					
No	12	48.0%	13	52.0%	0.743
Yes	2	40.0%	3	60.0%	
Others					
No	8	47.1%	9	52.9%	0.961
Yes	6	46.2%	7	53.8%	
Spore grade					
0	7	53.8%	6	46.2%	0.634
1	2	28.6%	5	71.4%	
2	4	57.1%	3	42.9%	
3	1	33.3%	2	66.7%	
Systemic treatment					
None	8	80.0%	2	20.0%	0.015*
Ketoconazole	1	12.5%	7	87.5%	
Itraconazole	5	41.7%	7	58.3%	
Topical treatment					
None	4	33.3%	8	66.7%	0.823
Selenium sulfide lotion	5	55.6%	4	44.4%	
Selenium sulfide shampoo	1	50.0%	1	50.0%	
Ketoconazole shampoo	3	60.0%	2	40.0%	
Acne feldin lotion	1	50.0%	1	50.0%	
Treatment					
Isolated topical therapy	8	80.0%	2	20.0%	0.033*
Isolated systemic therapy	4	33.3%	8	66.7%	
Combination therapy	2	25.0%	6	75.0%	
Comorbidities					
No data	10	52.6%	9	47.4%	0.278
Moderate acne vulgaris	0	0.0%	2	100.0%	
Severe acne vulgaris	0	0.0%	1	100.0%	
Bacterial folliculitis	0	0.0%	1	100.0%	
Keratosis pilaris	1	100.0%	0	0.0%	
HIV	1	100.0%	0	0.0%	
Myasthenia gravis	1	100.0%	0	0.0%	
Leprosy	0	0.0%	2	100.0%	
Pulmonary tuberculosis	1	100.0%	0	0.0%	
Pemphigus foliaceus	0	0.0%	1	100.0%	

*Statistically significant
Abbreviations: y/o, years old.

Figures 2 and 3. All patients were examined, and spore load samples were taken from each patient's follicular papulopustular lesions. Medication was given for once a week, and even though follow-up should be performed every week, only less than 60% of patients came as scheduled. The duration of treatment ranged from 1 to 5 weeks.

In the univariate prognostic factor analysis, clinical parameters of predilection for chest area, systemic therapy, and or combination therapy had a significant association with the treatment outcome. Based on the global analysis, those variables were analyzed further using multivariate analysis. In the bivariate prognostic factor analysis, a predilection for the chest area, systemic therapy, and/or combination therapy positively affected the outcome. The incidence of MF in males tended to be higher than females (90% vs. 10%), but there

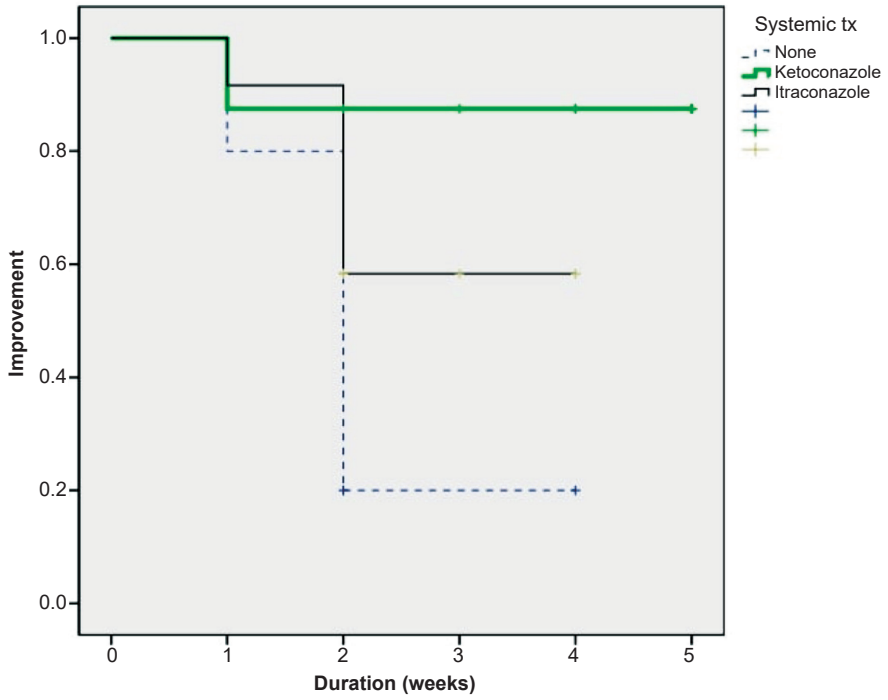

Figure 2. Estimation of improvement based on systemic therapy.

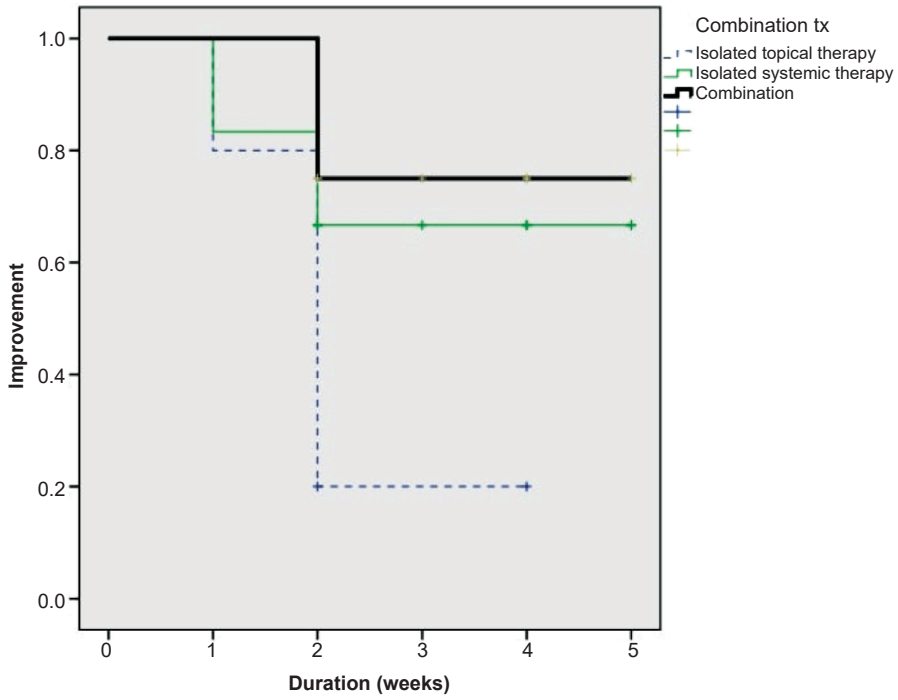

Figure 3. Estimation of improvement based on the type of treatment.

was no significant correlation between male gender and the clinical outcome following MF treatment.

The clinical appearance of MF in all subjects was perifollicular papules and pustules, especially located in the upper body area. Patients treated with oral antifungal therapy, such as ketoconazole

(87.5%) or itraconazole (58.3%), showed good results compared to those without systemic treatment. Patients treated with combination of topical and systemic treatment showed greater improvement (75%) than with systemic treatment only (66%). It needs to be noted that, in our study, only 10% of patients had a 3+ grade for spore load from direct microscopy examination with KOH solution and Parker ink, while the rest of the patients varied between the 1+ and 2+ grades.

Hazard ratios of factors affecting the clinical outcome are depicted in Table 2. Factors associated with good prognosis rate were a predilection for the chest area, systemic therapy with ketoconazole or itraconazole, and combination therapy. In contrast, female gender, comedones, a predilection for sites other than the chest area, and isolated topical treatment were not significantly associated with the clinical outcome. The presence of comedones might be due to concomitant acne vulgaris.

We used the Kaplan-Meier survival curve to determine factors influencing the rate of recovery and the log-rank test to find out whether there were differences between the survival curves. It was concluded from the Kaplan-Meier curve (Figures 2 and 3) that the type of treatment was one of the dominant factors that affected the treatment outcome and resulted in clinical improvement. The survival and recovery curves of combination therapy were above the curves of isolated topical therapy.

DISCUSSION

The diagnosis and treatment of MF can be intriguing, and physicians sometimes misdiagnose MF and treat it as a simple bacterial folliculitis or prescribe anti-acne medications instead of antifungal medications [2,20]. To avoid misdiagnosis, our policy is to use specific criteria for diagnosis based on clinical symptoms, grading of spore load from direct microscopic examination, and response to antifungal therapy.

In terms of age, it is known that MF usually occurs in the young to middle age group [21]. In line with previous studies by Song *et al.* and Suzuki *et al.*, which stated that MF occurred more commonly in males rather than females with 83.3% and 79.5% rates, respectively [2,18], our study also clearly indicated that MF tended to happen more in the male population (90%). This contradicts the study performed by Abdul-Razek in Saudi Arabia, which showed a lower rate of MF in males (35.4%) [1].

MF, caused by an opportunistic pathogen, is often associated with systemic diseases, especially human immunodeficiency virus (HIV) infection [5]. However, in this study, we found only 11 patients with comorbidities, and only one of them had HIV. The other comorbidities were acne vulgaris, bacterial folliculitis, keratosis pilaris, myasthenia gravis, leprosy, tuberculosis, and pemphigus foliaceous. Furthermore, the comorbidities did not significantly correlate with the treatment outcome.

Itchiness on a specific lesion might be the main subjective complaint of MF patients [22]. Our study also showed the presence of itchiness in most of the patients (86%). This is in line with studies performed by Thayikkanu *et al.* and Potter *et al.*, which mention that pruritus is the hallmark of MF [10,11].

Table 2. Hazard ratios of factors affecting clinical outcome of *Malassezia* folliculitis treatment

Variable	Outcome				*P*-value	RR (CI95%)
	Improvement		Loss to follow-up			
	n	%	n	%		
Chest						
Yes	11	44.0%	14	56.0%	0.022*	0.44 (0.28-0.68)
No	5	100.0%	0	0.0%		
Systemic treatment						
Ketoconazole	7	87.5%	1	12.5%	0.029*	4.37 (1.23-15.53)
Itraconazole	7	58.3%	5	41.7%		2.91 (0.77-11.01)
None	2	20.0%	8	80.0%		Ref
Treatment type						
Combination	6	75.0%	2	25.0%	0.045*	3.75 (1.01-13.79)
Isolated systemic therapy	8	66.7%	4	33.3%		3.33 (0.91-12.26)
Isolated topical therapy	2	20.0%	8	80.0%		Ref

*Statistically significant compared to other categories.
Abbreviations: RR, relative risk.

Malassezia spp. are the only yeasts likely responsible and correlated with MF and pityriasis versicolor (PV) [21]. In accordance with the etiopathogenesis of the disease, previous history of PV was included as a potential prognostic factor for MF, but only 30% of patients had a history of PV in our study. As for recurrences, even though MF treatment generally yields satisfying results, the recurrence rate is often high [23]. Recurrence is very common in MF and almost always happens after the completion of treatment [24]. Despite the fact that *Malassezia* spp. play a role in MF, we found that a history of a similar disease (pityriasis versicolor) had no association with MF.

On clinical examination, dome-shaped or follicular erythematous papules and/or pustules ranging from 2 to 3 mm in size are generally found in MF, spreading spread over the chest, back, and upper arms. Skin environment factors such as occlusion and sweating might contribute to the distribution of lesions [25,26]. An important clinical finding to differentiate MF from acne is the presence of few to no comedones [22]. In this study, the presence of follicular papules and pustules on the back, and certain areas, especially the chest, was protective and was considered a good prognostic factor for MF clinical outcome. Such findings can be a clue to differentiate MF from acne vulgaris since both have similar clinical findings but are different entities. The clinical presentation of one of the patients is shown in Figure 4.

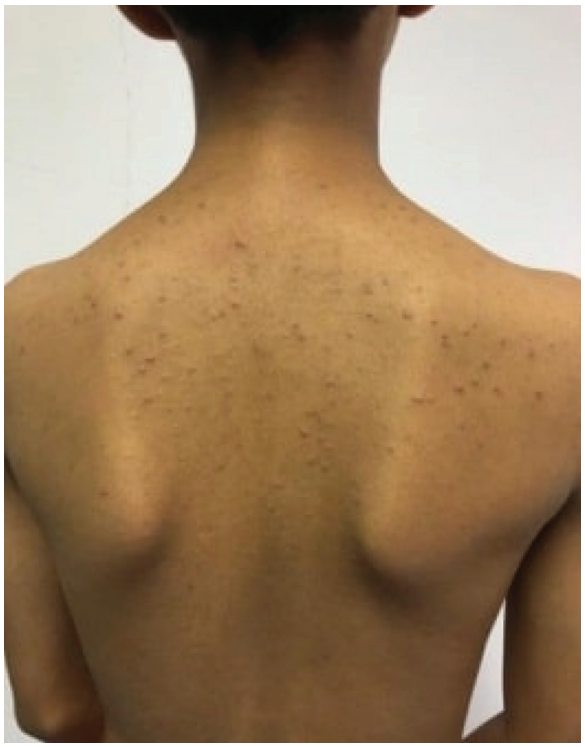

Figure 4. One of the patients diagnosed with MF at the DV Outpatient Clinic of Dr. Cipto Mangunkusumo Hospital Jakarta showed follicular erythematous papules and pustules varied in size ranging from 2 to 3 mm in the back region. The patient also complained of itching and had a history of the same complaint.

In our study, no patient with a clinical diagnosis of MF had a 4+ spore load, which Jacinto-Jamora suggested as a leading factor for diagnosing MF [14]. Another study claimed the diagnosis of MF by direct examination using acidic methylene blue staining. The diagnoses were made when ten or more yeast organisms were observed per follicle [18]. In our study, the spore load had no association with MF outcome.

In our study, there were five patients with facial lesions (16.7%), where the main concern for the diagnosis of MF is its similarity with seborrheic dermatitis (SD) lesions. On the face, SD presents with erythematous plaques and scales with a predilection for the glabella, eyebrows, nose, and paranasal folds, while MF presents as papules and pustules on hair follicles [16]. Hence, the diagnosis was established through clinical assessment and the presence of spores in direct microscopic examination.

Treatment of MF can be challenging due to its high recurrence rate. In 2015, Hald *et al.* summarized the management of skin diseases associated with *Malassezia* spp., concluding systemic antifungal therapy to be more effective and recommending combination therapy with topical antifungal modalities [19]. Systemic therapy, including oral itraconazole 400 mg or oral fluconazole 200 mg, both given once monthly, could be used as maintenance therapy [24]. Our study showed that single systemic antifungal therapy, with either ketoconazole or itraconazole, was enough and had a protective rate regarding MF outcome. However, ketoconazole is no longer used as systemic therapy as evidence show that treatment with oral itraconazole or fluconazole is effective for MF [19]. Topical agents such as selenium sulfide 2.5% lotion once weekly, ketoconazole 2% cream once weekly, and ketoconazole 2% shampoo 2-3 times weekly are sometimes given continuously to reduce the possibility of recurrence [19].

This study has several limitations. Some incomplete medical records had to be excluded, and some data were not documented, such as past medication history. Moreover, we tried to explore whether comorbidities or any risk factors might interfere with the therapeutic outcome, but less than 75% of our data clearly stated this variable, resulting in the smaller number of the study sample, which affected the statistical calculations and results.

CONCLUSION

Studies on prognostic factors following MF treatment are still limited. Therefore, we consider our study a pilot study. Based on our study, factors including a predilection for the chest area, isolated systemic antifungal therapy, and combination therapy played significant roles in achieving good treatment outcomes.

Conflict of interest: None declared.

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