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Correlation analysis between IL-1R/TLRs pathway and superficial dermatomycosis

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Abstract

Objective This study explored the correlation between interleukin-1 receptor/Toll-like receptor (IL-1R/TLRs)-mediated inflammatory signaling pathways and the severity of superficial dermatomycosis.

Methods From May 2020 to August 2022, 76 patients with superficial dermatomycosis (infected group) and 52 patients without infection (non-infected group) were enrolled. The indicators related to IL-1R/TLRs pathway were analyzed, and the diagnostic value of the combined detection of each index for superficial dermatomycosis and disease severity was analyzed. The correlation between each index and the severity of infection was analyzed.

Results IL-1β, TLR4, IL-6, and TNF-α in the infected group were higher than those in the non-infected group ($P < 0.05$). The AUC of IL-1R/TLRs combined detection in the group diagnosed with a superficial dermatomycosis was higher than that of each single detection ($P < 0.05$). IL-1β, TLR4, IL-6, and TNF-α in the severe group were higher than those in the mild group ($P < 0.05$). IL-1β, TLR4, IL-6, and TNF-α were positively correlated with the degree of infection ($P < 0.05$). The AUC of IL-1R/TLRs combined detection was higher than that of each single test ($P < 0.05$). IL-1β ≥ 2.87 ng/L, TLR4 ≥ 3.12 ng/L, IL-6 ≥ 4.58 ng/L, TNF-α ≥ 70.53 ng/L were the influencing factors of severe superficial dermatomycosis ($P < 0.05$).

Conclusion IL-1R/TLRs pathway is related to the severity of superficial dermatomycosis, and the collective identification of each indicator provides diagnostic insight into infection severity.

Keywords Superficial dermatomycosis, Severity, Interleukin-1β, Toll-like receptor 4, Interleukin-6, Tumor necrosis factor-alpha

Introduction

Superficial dermatomycosis is a prevalent infectious skin condition caused by the growth of fungi on various body parts, including the scalp, hair, mucous membranes, hands, feet, toenails, and groin [1]. With an aging population and increased use of immunosuppressants and corticosteroids, along with lifestyle changes and evolving fungal characteristics, the incidence of superficial dermatomycosis has been rising annually. Drug-resistant superficial fungal infections have also emerged in several areas [2]. The mechanisms behind persistent dermatophytosis remain unclear. Studies suggest that fungal infections are closely linked to cellular inflammatory factors activated by the immune system [3, 4]. Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns and trigger both innate and adaptive immune responses [5]. Research indicates that Candida albicans can elevate levels of interleukin (IL)-10, interferon, and other inflammatory factors [6, 7]. However, there is no reported connection between TLR signaling pathways and superficial dermatomycosis. This study investigates

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the correlation between IL-1R/TLRs pathways and the severity of superficial dermatomycosis.

Data and methods

Clinical data

In this study, 76 patients with superficial dermatomycosis (infected group) and 52 patients without infection (non-infected group) from May 2020 to August 2022 were studied (all East Asians).

Inclusion criteria

(i) Patients who met the diagnostic criteria for superficial dermatomycosis in Clinical dermatology in China [8]; (ii) patients who met the clinical manifestations of each of the superficial dermatomycosis (tinea cruris, tinea corporis, and onychomycosis); (iii) patients who were assessed as positive for fungal microscopic examination by a professional clinician, all of which were confirmed cases; (iv) patients with complete clinical data; and (vi) patients who voluntarily signed an informed consent form.

Exclusion criteria

(i) Patients with poorly controlled diabetes; (ii) patients with severe abnormalities of liver and renal function; (iii) patients who have received systemic antifungal drug therapy within the last 3 months, and patients who have had topical application of antifungal drugs within the last 1 month [9]; (iv) patients with combination of infections in other parts of the body; (v) patients with malignant neoplastic disease; (vi) patients with systemic signs of infection; and (vii) patients with psychiatric disorders.

Methods

Detection of IL-1R/TLRs pathway-related indicators

Fasting venous blood of 3 mL was collected from all subjects at enrollment. The blood sample was placed in a dry test tube and allowed to stand at room temperature until the blood was solidified. The blood was centrifuged at 3000 r/min for 15 min at 4 ℃ (centrifugal radius of 12 cm), frozen and stored in a −80 ℃ refrigerator. The serum was taken out and thawed before testing. All samples were tested within 12 h after collection. IL-1β, TLR4, IL-6, and TNF-α were determined by enzyme-linked immunosorbent assay (ELISA) method. The product numbers are as follows: IL-1β (PI301, Beyotime Inc, Shanghai, China); TLR4 (D711339-0096, Sangon Biotech Inc, Shanghai, China); IL-6 (PI325, Beyotime); TNF-α (PT518, Beyotime).

Severity

Patients in the infected group were divided into the mild group and the severe group according to whether they were combined with invasive fungal infection.

Observation indicators

(1) IL-1R/TLRs pathway-related indicators were observed, and the diagnostic value of the combined detection of each indicator for superficial dermatomycosis was analyzed. (2) IL-1R/TLRs pathway-related indicators in the mild group and the severe group were compared, the diagnostic evaluation value of each indicator on the severity of infection was analyzed, and the correlation between each indicator and the severity of infection was analyzed.

Statistical analysis

All the data were processed by SPSS22.04 software. Count data were expressed as % and compared by χ^2 test. Measurement data were expressed by ($\overline{x} \pm s$) after normal test, and compared by t test. ROC curve analyzed the diagnostic value of IL-1R/TLRs for superficial dermatomycosis. Spearman test analyzed the correlation between each index and the severity of infection. Logistic regression analyzed the effects of each index on severe superficial dermatomycosis. $P<0.05$ meant that the difference was statistically significant.

Results

Clinical data analysis

The total number of patients who participated in our study was 128 and the patients were categorized into infected ($n=76$) and non-infected ($n=52$) groups based on their infection status. Comparison of the clinical data of the two groups of patients showed that there was no statistical significance in the differences between the infected and non-infected groups in the general data of gender, age, history of antimicrobial drugs, marital status, and residence ($P>0.05$, Table 1). In the infection group, there were 19 cases of tinea corporis, 13 cases of tinea pedis, 15 cases of tinea faciei, 17 cases of pityriasis versicolor, and 12 cases of tinea capitis. As for pathogenic fungi, there were 30 cases of dermatophyte, 21 cases of candida, 25 cases of mold.

IL-1R/TLRs-related indicators

Serum IL-1β, TLR4, IL-6, and TNF-α in the infected group were higher than those in the non-infected group (all $P<0.05$, Table 2; Fig. 1).

Analysis of the diagnostic value of IL-1R/TLRs-related indicators

The ROC curve showed that in the diagnosis of superficial dermatomycosis, the diagnostic values of IL-1β, TLR4, IL-6 and TNF-α alone were 0.857, 0.810, 0.758 and 0.740, respectively. And the AUC value of combined

Table 1 Comparison of general data between infected group and non-infected group

Indicators	Infected group ($n=76$)	Non-infected group ($n=52$)	χ^2/t	P
Male	49	35	0.11	0.74
Female	27	17		
Age (years)	49.37 ± 6.15	50.58 ± 6.32		
History of antibacterial drugs	10	5	0.375	0.541
Skin history (cases)	8	4	0.292	0.589
Marital status (cases)			0.52	0.471
Married	51	38		
Unmarried and divorced	25	14		
Residence (cases)				
Rural area	41	30	0.175	0.675
City	35	22		

Table 2 Comparison of IL-1R/TLRs-related indicators between infected and non-infected groups

Indicators	Infected group ($n=76$)	Non-infected group ($n=52$)	P
IL-1β (ng/L)	2.71 ± 0.53	1.96 ± 0.41	<0.001
TLR4 (ng/L)	2.85 ± 0.67	2.13 ± 0.45	<0.001
IL-6 (ng/L)	4.39 ± 0.81	3.74 ± 0.75	<0.001
TNF-α (ng/L)	70.03 ± 13.58	59.67 ± 11.31	<0.001

detection of IL-1R/TLRs-related indicators was 0.972, which was greater than the AUC value of independent detection of each indicator ($P<0.05$, Table 3; Fig. 2).

Analysis of IL-1R/TLRs-related indicators patients with different infection degrees

According to the infection severity, the infected patients were further divided into mild group ($n=52$) and severe group ($n=24$). Comparison of serum IL-1R/TLRs-related

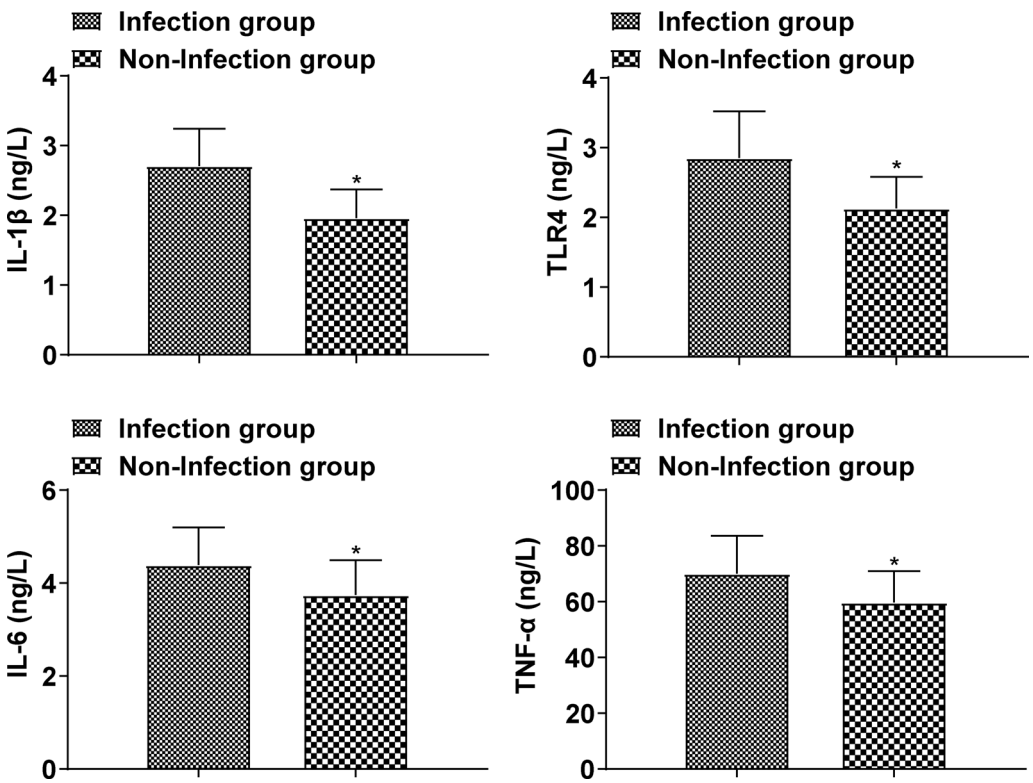

Fig. 1 Comparison of IL-1R/TLRs-related indicators between the infected group and the non-infected group (*$P<0.05$)

Table 3 The diagnostic value of IL-1R/TLRs in superficial dermatomycosis

Indicators	Cut-off value	AUC	SE	95% CI
IL-1β	2.19 ng/L	0.857*	0.033	0.784–0.913
TLR4	2.52 ng/L	0.810*	0.038	0.731–0.874
IL-6	4.07 ng/L	0.758*	0.043	0.674–0.829
TNF-α	63.71 ng/L	0.740*	0.043	0.655–0.814
Combined		0.972	0.011	0.926–0.993

Compared with combined, *$P<0.05$

Table 4 Comparison of IL-1R/TLRs-related indicators between mild and severe groups

Indicators	Severe group ($n=24$)	Mild group ($n=52$)	*P*
IL-1β (ng/L)	3.02 ± 0.54	2.57 ± 0.51	<0.001
TLR4 (ng/L)	3.16 ± 0.49	2.71 ± 0.42	<0.001
IL-6 (ng/L)	4.83 ± 0.67	4.19 ± 0.75	<0.001
TNF-α (ng/L)	75.19 ± 9.13	67.65 ± 8.92	0.004

indicators between the two groups showed that the levels of IL-1β, TLR4, IL-6 and TNF-α in the severe group were higher than those in the mild group, and the difference was statistically significant ($P<0.05$, Table 4; Fig. 3).

Correlation analysis between IL-1R/TLRs and infection degree

The correlation of IL-1β, TLR4, IL-6 and TNF-α with infection degree was analyzed by Spearman's correlation analysis, which showed that the levels of IL-1β ($r=0.557$), TLR4 ($r=0.521$), IL-6 ($r=0.537$) and TNF-α ($r=0.415$) were positively correlated with the degree of infection ($P<0.05$, Table 5).

Evaluation value of IL-1R/TLRs-related indicators on the severity of infection

The value of IL-1R/TLRs-related indicators in assessing the severity of infection was further analyzed by ROC curves, which also showed that the AUC of the combined IL-1R/TLRs-related indicators (0.966) was greater than that of the independent testing of each of the indicators

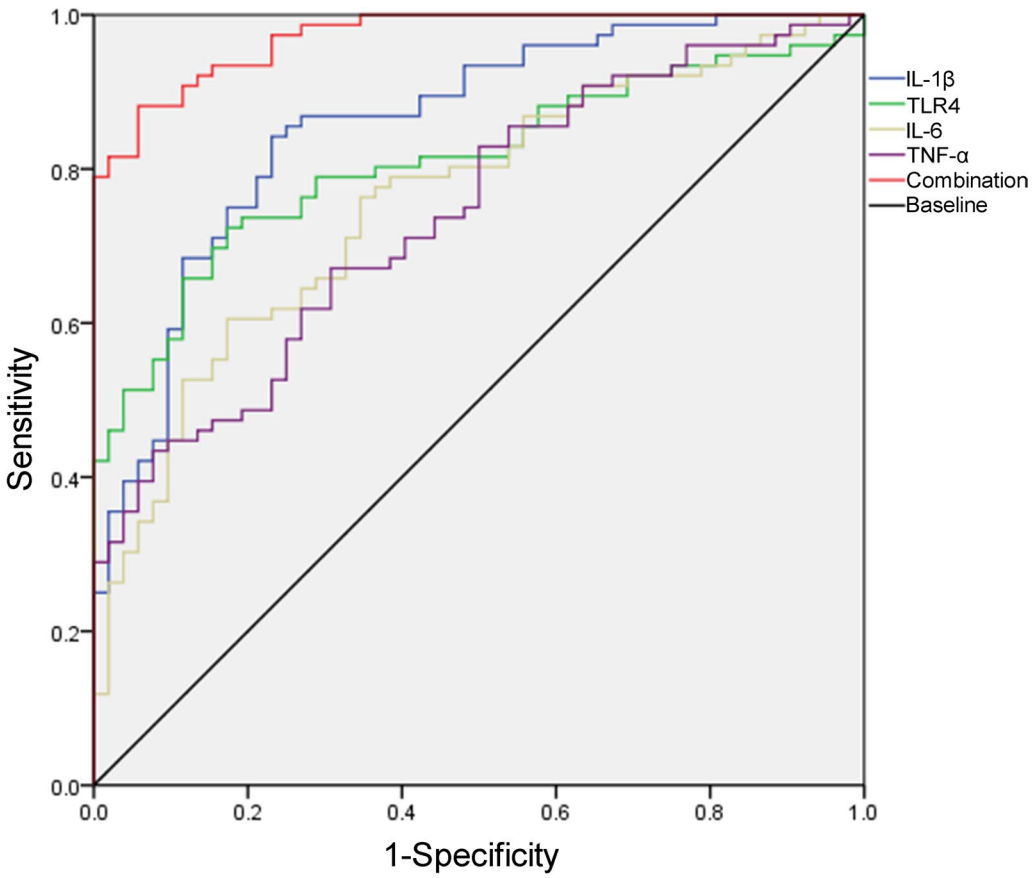

Fig. 2 ROC curve of IL-1R/TLRs-related indicators in the diagnosis of superficial dermatomycosis

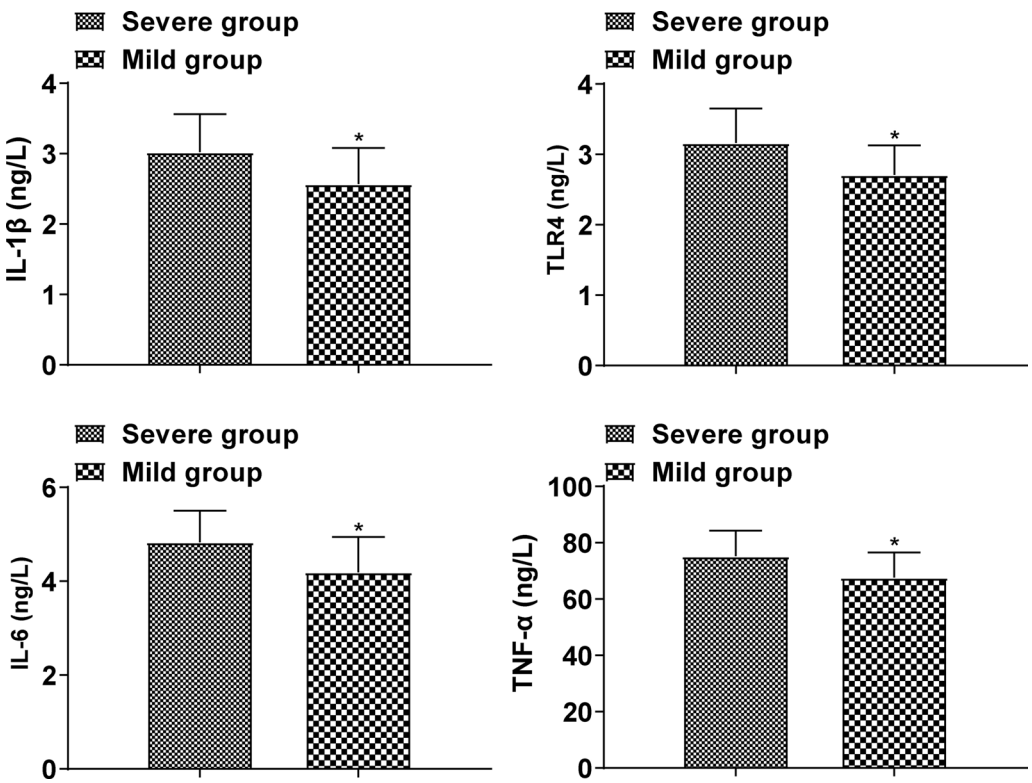

Fig. 3 Comparison of IL-1R/TLRs-related indicators between mild group and severe group (*$P < 0.05$)

Table 5 Correlation analysis between IL-1R/TLRs and infection degree

Indicators	*r*	*P*
IL-1β	0.557	<0.001
TLR4	0.521	<0.001
IL-6	0.537	<0.001
TNF-α	0.415	<0.001

Table 6 Analysis of the value of IL-1R/TLRs-related indicators in evaluating the severity of infection

Indicators	Cut-off value	AUC	SE	95% CI
IL-1β	2.87 ng/L	0.846*	0.046	0.745–0.919
TLR4	3.12 ng/L	0.824*	0.052	0.719–0.902
IL-6	4.58 ng/L	0.833*	0.046	0.730–0.909
TNF-α	70.53 ng/L	0.758*	0.061	0.646–0.849
Combined		0.966	0.017	0.897–0.994

Compared with combined, *$P < 0.05$

(IL-1β 0.846, TLR4 0.824, IL-6 0.833, and TNF-α 0.758) ($P < 0.05$, Table 6; Fig. 4).

Logistic regression analysis of the influence of IL-1R/TLRs on severe superficial dermatomycosis

The effect of IL-1R/TLR on severe superficial dermatomycosis was further analyzed by logistic regression, assigning a value of 0 for mild infection and 1 for severe infection. The results of the analysis showed that IL-1β ≥ 2.87 ng/L, TLR4 ≥ 3.12 ng/L, IL-6 ≥ 4.58 ng/L, and TNF-α ≥ 70.53 ng/L were influencing factors of severe superficial dermatomycosis ($P < 0.05$, Table 7).

Discussion

Fungi are widely distributed in nature and some of them are harmful to humans. Clinically, most pathogenic fungal infections can be categorized into invasive fungal infection and superficial fungal infections. The skin, being the largest organ in the human body, serves to protect the body, regulate sweating, and sense temperature changes and pressure [10]. However, fungi can easily inhabit the skin and its appendages, leading to superficial fungal diseases. The precursor of fungal infection is fungal colonization, and the inability of fungal cultures commonly used in the clinic to differentiate between fungal infection and colonization has inconvenienced the choice of treatment options for this disease [11–13]. Invading fungi and other pathogens are recognized by the immune

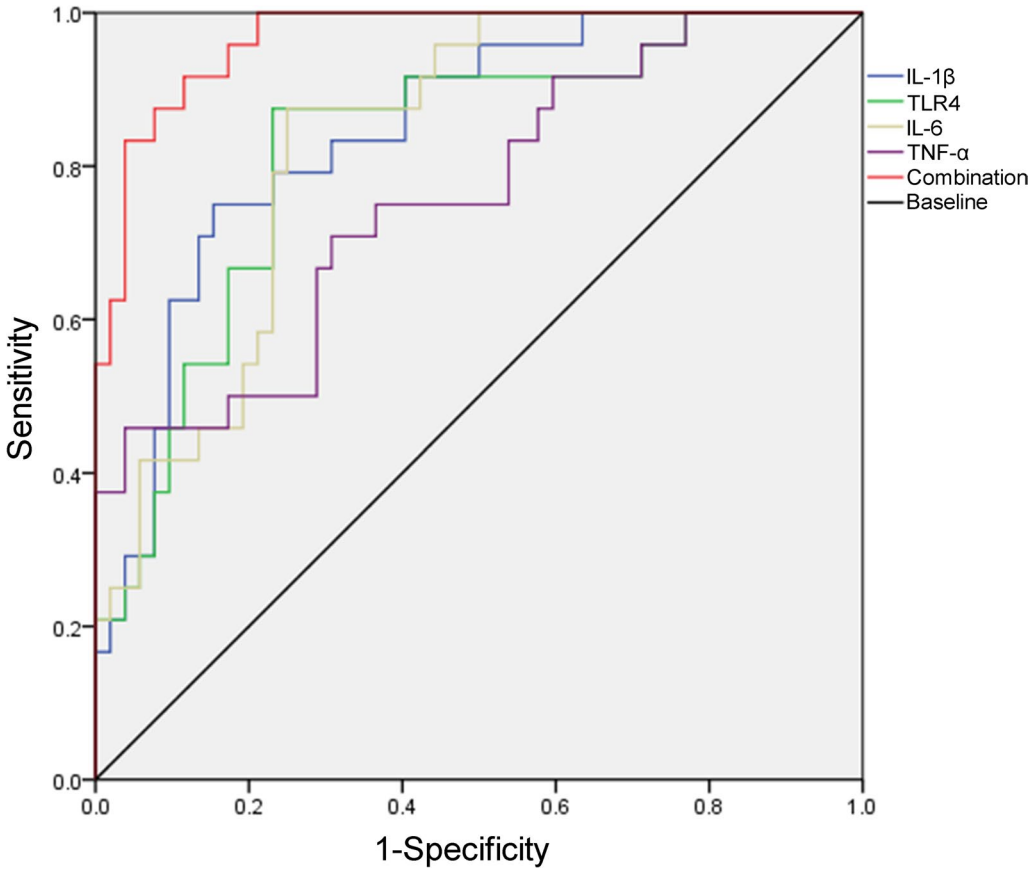

Fig. 4 ROC curve of IL-1R/TLRs-related indicators evaluating the severity of infection

Table 7 Logistic regression analysis of the effect of IL-1R/TLRs on severe superficial dermatomycosis

Indicators	*β*	SE	Wald χ^2	OR	95% CI	*P*
IL-1β	2.498	0.942	7.032	12.158	1.919–77.040	0.008
TLR4	2.855	1.208	5.586	17.374	1.628–185.430	0.019
IL-6	2.26	0.784	8.31	9.583	2.061–44.551	0.004
TNF-α	0.107	0.071	2.271	1.113	0.968–1.279	0.133
Constant	−3.433	0.877	15.323	0.032	0.006–0.180	0

Assignment: IL-1β (≥2.87 ng/L was 1, <2.87 ng/L was 0); TLR4 (≥3.12 ng/L was 1, <3.12 ng/L was 0); IL-6 (≥4.58 ng/L was 1, <4.58 ng/L was 0); TNF α (≥70.53 ng/L was 1, <70.53 ng/L was 0)

system and stimulate an immune response in the host [14]. Clinical data show that fungi can activate phagocytic cells in the body after infection, secrete inflammatory factors, and activate type I immune response [15]. In the TLRs signaling pathway, MyD88 is a key molecule mediating the innate immune response signaling pathway and a signal transduction protein in vivo. Previous studies have shown that the IL-1R/TLRS-mediated inflammatory pathway plays an important role in the secretion of inflammatory cytokines and inflammatory processes [16–18]. TLR4 activation by upstream pathogens further activates its downstream signaling molecular pathways and promotes the release of IL-1β and TNF-α through synergistic effects or by converging with activated downstream TLRs pathways, thus enhancing immune responses, promoting T helper cell-like transformation, and decreasing immune escape from pathogens [19]. This study found that IL-1β, TLR4, IL-6, and TNF-α in the infected group were higher than those in the non-infected group, suggesting that the IL-1R/TLRs pathway may be involved in the process of fungal infection, whereas phagocytosis can secrete a variety of cytokines

after fungal infection, which is mainly related to the activation of phagocytes. In addition, TLRs enhance body immunity by binding to invading pathogens and stimulating downstream signaling pathways, as evidenced by overexpression of various inflammatory factors [20–22]. Furthermore, the research revealed that in the diagnosis of superficial dermatomycosis, the AUC value for the IL-1R/TLRs-associated indicators, when combined, was greater than that of each separate indicator, highlighting the diagnostic value of each marker and predicting its future use in clinical diagnosis.

In superficial dermatomycosis, many fungal infections are persistent and likely to cause cross-infection and spread, potentially leading to systemic infection if not promptly treated [23]. Superficial dermatomycosis can progress to deeper invasion, leading to disseminated cutaneous mycosis and invasive dermatitis [24, 25]. A systematic retrospective study of cases of deep dermatomycosis worldwide from 2000 to 2020 showed that nearly half of the patients had chronic superficial fungal skin infections at the same anatomical site before the onset of invasive infections [26]. TLRs are widely distributed in epithelial cells, lymphocytes, dendritic cells, endothelial cells, macrophages, and immune organs mostly related to hosting defense function. It has been confirmed that many immune cells and their secreted cytokines are related to skin fungal infection [27]. To prevent overactivation of inflammation-related pathways or the emergence of an immunosuppressive microenvironment, several signaling molecules act as inhibitory molecules of the TLRs pathway to reduce immune responses by downregulating the expression of TLRs, interfering with the recognition of TLRs and ligands, and inhibiting the signal transduction of TLRs. It is suggested that TLR4 in patients shows a downward trend with the progression of the disease [28]. The study showed that levels of IL-1R/TLRs-related indicators were positively correlated with the degree of infection, indicating that IL-1R/TLRs-mediated inflammation still played a dominant role in the progression of the disease. Also, it was recognized that an abnormal increase of each index in peripheral blood affected the progression of the disease. In addition, this study found that the AUC of the combined detection of IL-1R/TLRs-related indicators to assess the severity of infection was greater than that of the separate detection of each indicator, indicating that the combined detection of each indicator has an evaluation value for the severity of infection. With the deepening of the research on IL-1R/TLRs-mediated inflammatory signaling pathway, its clinical significance and application value in superficial dermatomycosis will be further expanded. The correlation analysis between IL-1R/TLRs-mediated inflammatory signaling pathway and the severity of superficial dermatomycosis is of great significance in clinical practice. It not only helps to reveal the mechanism of infection, evaluate the degree of infection and guide treatment decisions, but also provides new ideas and methods for the development of diagnostic tools, drug development and personalized treatment. In addition, in recent years, the growing problem of fungal drug resistance has posed a great challenge to the treatment of superficial dermatomycosis. The IL-1R/TLRs-mediated inflammatory signaling pathway plays a key role in the immune response to fungal infections, and studying the correlation between this pathway and the severity of superficial dermatomycosis may provide important clues to understand the mechanism of drug resistance and develop new antifungal strategies.

Limitation

Our study has several limitations. The study had a relatively small patient sample size and was conducted at a single center, which could introduce selective bias. A single-source sample may not accurately capture the general correlation between the IL-1R/TLRs pathway and superficial dermatophytosis in diverse groups. In addition, the diversity of fungal pathogens of superficial dermatophytosis and the differences in pathologic manifestations, genetic background, and environmental exposures among patients have implications for the study of the correlation between IL-1R/TLRs and superficial dermatophytosis. Meanwhile, the immune response itself is a complex process involving multiple cellular, molecular and signaling pathways, and these complex immune response mechanisms increase the difficulty of analyzing the correlation between IL-1R/TLRs pathways and superficial dermatophytosis. In future studies, further optimization of the experimental design, collection of more comprehensive clinical data, and in-depth study of the mechanism of immunomodulatory therapy are needed to further improve the accuracy and reliability of this study.

Conclusion

In summary, IL-1R/TLRs-related indicators are associated with the severity of superficial dermatomycosis. The combined detection of multiple indicators has greater values in the diagnosis of superficial fungal skin diseases. These findings can interpret the causes of resistant dermatophytes and give a clue for treatment in future.

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Author contributions
DongMei Tang designed the research study. XiaoXuan Cao and BeiBei Yuan performed the research. HongXing Zou and MingDe Huang provided help and advice. WeiFeng Shen analyzed the data. DongMei Tang wrote the

manuscript. WeiFeng Shen reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was approved by the Ethics Committee of The First Hospital of Jiaxing, Affiliated Hospital of Jiaxing University and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Competing interests
The authors declare no competing interests.

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