

# Risk factors associated with the progression from mild keloids to severe keloids

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## Abstract

**Background:** Keloids are benign fibrous growths that are caused by excessive tissue build-up. Severe keloids exert more significant effects on patients' quality of life than do mild keloids. We aimed to identify factors associated with the progression from mild keloids to severe keloids, as distinct from those associated with the formation of keloids.

**Methods:** In this retrospective case-control study, 251 patients diagnosed with keloids at West China Hospital between November 2018 and April 2021 were grouped according to the severity of lesions (mild [ $n = 162$ ] or severe [ $n = 89$ ]). We collected their basic characteristics, living habits, incomes, comorbidities, and keloid characteristics from Electronic Medical Records in the hospital and the patients' interviews. Conditional multivariable regression was performed to identify the independent risk factors for the progression of keloids.

**Results:** Eighty-nine patients (35.5%) were classified as having severe keloids. We found the distribution of severe keloids varied with sex, age, excessive scrubbing of keloids, family income, the comorbidity of rheumatism, disease duration, characteristics of the location, location in sites of high-stretch tension, the severity and frequency of pain, the severity of pruritus, and infection. Multivariable analysis revealed significant associations between severe keloids and infection (odds ratio [OR], 3.55;  $P = 0.005$ ), excessive scrubbing of keloids (OR, 8.65;  $P = 0.001$ ), low or middle family income (OR, 13.44;  $P = 0.021$ ), comorbidity of rheumatism (OR, 18.97;  $P = 0.021$ ), multiple keloids located at multiple sites (OR, 3.18;  $P = 0.033$ ), and disease duration >15 years (OR, 2.98;  $P = 0.046$ ).

**Conclusion:** Doctors should implement more active and thorough measures to minimize the progression of mild keloids in patients who have any of the following risk factors: infection, excessive scrubbing of keloids, low or middle family income, comorbidity of rheumatism, multiple keloids located at multiple sites, and disease duration >15 years.

**Keywords:** Keloid; Disease progression; Risk factors; Multivariate analysis

## Introduction

Keloids are benign fibrous growths that are produced by excessive tissue build-up during the wound-repair process. Keloids occur in 4.5% to 16% of Hispanic and African American individuals.<sup>[1]</sup> Studies have shown that the formation of keloids is triggered by a combination of systemic and local factors, including hormone concentrations,<sup>[2]</sup> local stretch tension,<sup>[3,4]</sup> metabolic factors,<sup>[5]</sup> and inflammation.<sup>[6]</sup> Keloids invade normal skin adjacent to the original wound area and protrude from the surrounding skin.<sup>[7]</sup> However, their clinical manifestations vary widely. Some keloids are small, self-limited, and remain stable for long periods, whereas others behave more aggressively, continuing to grow and spread over time. A previous study found that about 40% of keloids progress to become severe keloids.<sup>[8]</sup> As the intrinsic and

extrinsic causes of keloids with severe characteristics have not yet been comprehensively investigated,<sup>[9,10]</sup> we suspected that such development may be stimulated by various strong and persistent predisposing factors that differ, at least in part, from the factors that are responsible for the initial formation of keloids. Therefore, in the present study, we focused on analyzing possible risk factors for the development of severe keloids.

In practice, many patients opt to ignore mild keloids and to leave them for long periods. When and if they finally seek treatment for such keloids, doctors can choose from a wide variety of options, including freezing, injection, laser, surgery, and radiotherapy. In contrast to smaller growths, severe keloids are often ugly and accompanied by recurrent infections and significant pain or pruritus, all of which can greatly affect patients' quality of life.<sup>[11,12]</sup> Although patients

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with such keloids strongly desire medical intervention, few effective treatment options are available for them. The main available options are surgery and radiotherapy, which often achieve relatively unsatisfactory results.<sup>[13]</sup> Identifying risk factors for progression to severe keloids could enable doctors to encourage patients at high risk to adopt preventive measures or undergo active interventions in the early stages of keloid development. Previously identified risk factors for the formation of keloids include family history,<sup>[14,15]</sup> smoking,<sup>[16]</sup> blood groups,<sup>[4,17]</sup> anatomical site,<sup>[3,4]</sup> skin pigmentation,<sup>[18,19]</sup> type of skin injury,<sup>[4]</sup> and sex,<sup>[20]</sup> but the previous study emphasized the importance of investigating risk factors for severe keloids, not just keloids.<sup>[8]</sup> Moreover, to the best of our knowledge, there have been few studies concerning risk factors for progression to severe keloids in Chinese individuals.

Therefore, in this study, we aimed to investigate the risk factors associated with the development of severe keloids. We incorporated risk factors for keloids as reported in previous studies, as well as factors related to pathogenesis such as comorbidities and certain living habits, and assessed their association with progression to severe keloids. We believe that the predictors we have identified will enable screening for those at high risk of developing severe keloids and encourage clinicians to adopt preventive measures or perform active interventions in that subgroup.

## Methods

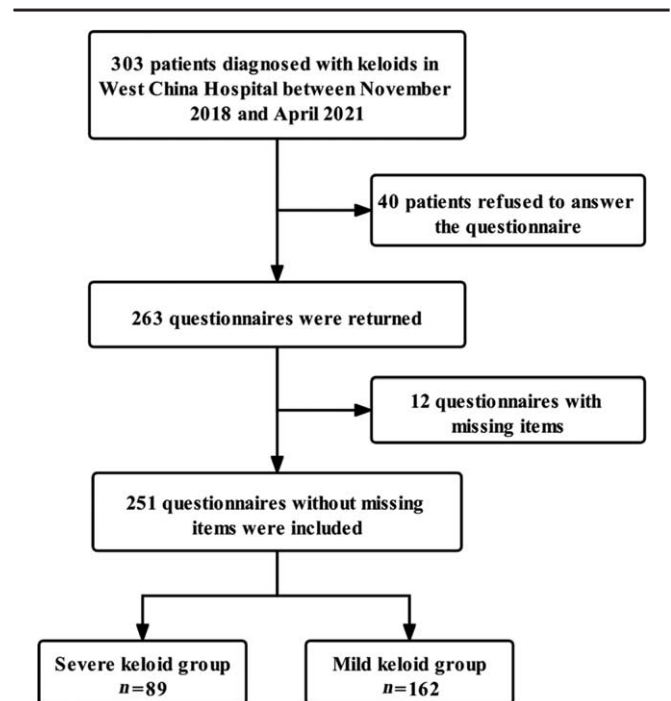
### Ethical statement

The study was conducted in accordance with the *Declaration of Helsinki* (as revised in 2000). It was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2021[336]). The requirement for individual written consent was waived in view of its retrospective nature. Nonetheless, while distributing electronic questionnaires, we informed all patients about the content of this study. Furthermore, participants gave their informed consent electronically by checking the corresponding item in the questionnaire.

### Study cohort and data collection

We included 303 consecutive patients who had been diagnosed with keloids in West China Hospital between November 2018 and April 2021. The diagnoses were made in accordance with the following criteria<sup>[21,22]</sup>: scar invading normal skin adjacent to the original wound area and protruding above the level of the surrounding skin. All patients had been carefully examined by at least two plastic surgeons. Patients with hypertrophic scars were excluded from our study.

Medical records of these patients were obtained from the Electronic Medical Records of our hospital and retrospectively reviewed. Additionally, we collected further data by sending participants a structured questionnaire about their personal characteristics, living conditions, and previous treatment via WeChat in June 2021. These questionnaires were distributed by each patient's supervising physician. Forty patients refused to respond to the questionnaire; thus,



**Figure 1:** Flow of inclusion for patients with severe or mild keloids in the study.

263 (86.8%) completed questionnaires were returned. Finally, data from (215) questionnaires without missing items were included in this study, as shown in Figure 1. Information missing from the incomplete questionnaires included responses to questions related to pre-treatment history and comorbidities. The final study cohort comprised 87 men and 164 women with a mean age of 34.37 years.

The 251 study patients were then divided into two groups according to keloid severity (severe *vs.* mild). Severe keloids were defined as keloids with a total area of  $\geq 40$  cm<sup>2</sup> or a total number of keloids  $\geq 10$  [Figure 2]. Finally, 89 (35.5%) patients were classified into the severe keloid group, and 162 (64.5%) patients were classified into the mild keloid group.

### Design of questionnaire

The questionnaire was based on the Japan scar workshop scar scale (2015)<sup>[23]</sup> and previously reported risk factors for keloids.<sup>[14-20]</sup> The items in the questionnaire were chosen by discussions between five qualified plastic surgeons in our group. Our questionnaire had three major domains of questions: relevant demographic and personal characteristics, comorbidities, and characteristics of keloid lesions.

### Demographic and personal characteristics of the patients

The first domain of the questionnaire covered basic information, including living habits, sex, age, body mass index, race, blood type, food preference, daily exercise, occupation, skin texture, excessive scrubbing of keloids, smoking, alcohol, and family income.

Participants' races were all classified as Chinese Han or Chinese minority. Daily exercise did not include low-intensity



**Figure 2:** Examples for mild keloid (A) and severe keloids (B, C).

activities such as walking. “Standing jobs” denoted jobs that involved standing for at least half of the patient’s working hours, examples including surgeons and porters. The opposite of these jobs included clerks and students. In addition, the skin color of the inner upper arm was assessed in all patients by three of the authors using the Von Luschan chromatic scale (VLCS), the final score being the median of the three scores.<sup>[24,25]</sup> In accordance with the recommendations of the previous study of the skin color of Asian individuals, we allocated skin color to one of the following three categories: light brown (VLCS score < 21), medium brown (VLCS score 21–25), and dark brown (VLCS score > 25).<sup>[24]</sup> We divided family income into four categories: low, middle, middle-high, and high, in accordance with the categories in the China Statistical Yearbook (2020).

### Comorbidities

The second domain of the questionnaire investigated the following comorbidities: acne, hypertension, diabetes, rheumatism, allergic diseases, tumors, bacterial/fungal/ viral skin disease, and other skin diseases, all conditions having been diagnosed by previous specialists. “Rheumatism” covered connective tissue, arthritic, and musculo-skeletal disorders, including systemic lupus erythematosus, osteoarthritis, rheumatoid arthritis, gout, systemic sclerosis, ankylosing spondylitis, and fibromyalgia.<sup>[26]</sup> “Allergic disease” covered all conditions related to allergic hyper-sensitivity,<sup>[27]</sup> the most common being allergic rhinitis, eczema, asthma, and food allergy. Bacterial/fungal/viral skin disease included folliculitis, boils, carbuncles, and nail fungal disease. Skin diseases that could not easily be classified as belonging to one of the abovementioned categories, such as alopecia areata, were classified as “other skin diseases.”

### Characteristics of keloid lesions

The third domain of the questionnaire investigated the keloids’ features, including location, local stretch tension, cause, age of onset, disease duration, family history, location characteristics, presence of pain, pruritus, or infection, and previous treatment.

Distribution was classified into one of the following four categories: single keloid at one site, multiple keloids at

one site, single keloid at multiple sites, and multiple keloids at multiple sites. “Single keloid at multiple sites” denotes a single keloid in a number of different anatomical sites, whereas “multiple keloids at multiple sites” denotes more than one keloid in each of a number of different anatomical sites. The shoulder, back, chest wall, and abdominal midline were classified as sites of high-stretch tension; other sites were classified as low-stretch tension.<sup>[28]</sup> Severe pain or pruritus was defined as unbearable pain or pruritus affecting daily life or sleeping. “Previous treatment” denotes treatment received before patients visited our hospital and inclusion in this study.

### Statistical analysis

We first described the distribution of potential factors related to the development of severe keloids among patients who met and did not meet the outcome (severe keloids). Unpaired *t*-tests or Mann-Whitney tests were used to analyze the continuous variables. Categorical variables were analyzed by using the  $\chi^2$  test or Fisher’s exact test as appropriate.

Variables with a *P* value < 0.05 in the univariable analysis were used as independent variables in logistic regression. We applied a conditional multivariable logistic regression model matched by sex to determine the risk factors for severe keloids. When assessing the risk factors that predict severity, we excluded the degree and frequency of both pain and pruritus from the multivariable regression analysis because these symptoms may be caused by severe keloids rather than being a risk factor for the progression of severe keloids. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *P* values < 0.05 were considered to denote significance.

## Results

### Demographic and personal characteristics

The cohort of this study comprised 251 patients who had been diagnosed with keloids between November 2018 and April 2021 [Table 1]. The severe keloid group comprised 89 (35.5%) patients, the remaining 162 having mild keloids according to the criteria presented above. Univariable analysis was used to compare the characteristics of patients with severe and mild keloids. The results showed that the male sex was significantly associated with severe keloids (*P* = 0.034) and that patients with severe keloids were significantly older than those with mild keloids ( $37.38 \pm 17.29$  vs.  $32.72 \pm 13.21$  years, *P* = 0.018).

Moreover, more patients with severe than mild keloids excessively scrubbed their keloids in their daily lives (53.9% [48/89] vs. 32.1% [52/162]; *P* = 0.001). Family income also differed significantly between the two groups, a higher proportion of those with mild keloids than those with severe keloids having high family incomes (13.6% [22/162] vs. 1.1% [1/89]; *P* = 0.002). Most patients with keloids (59.0% [148/251]) had medium brown skin colors

**Table 1: Demographic and personal characteristics of the patients with keloids.**

Characteristics	Overall	Mild	Severe	P value
No. of patients	251	162	89	
Sex				0.034
Male	87 (34.7)	48 (29.6)	39 (43.8)	
Female	164 (65.3)	114 (70.4)	50 (56.2)	
Age (years)	34.37 ± 14.92	32.72 ± 13.21	37.38 ± 17.29	0.018
Body mass index (kg/m <sup>2</sup> )	23.20 ± 10.62	23.48 ± 12.93	22.69 ± 3.74	0.570
Race				1.000
Chinese Han	240 (95.6)	155 (95.7)	85 (95.5)	
Chinese minority	11 (4.4)	7 (4.3)	4 (4.5)	
Skin color				0.204
Light brown (VLCS score <21)	85 (33.9)	61 (37.7)	24 (27.0)	
Medium brown (VLCS score 21–25)	148 (59.0)	91 (56.2)	57 (64.0)	
Dark brown (VLCS score > 25)	18 (7.2)	10 (6.2)	8 (9.0)	
Blood Type				0.396
A type	81 (32.3)	50 (30.9)	31 (34.8)	
B type	54 (21.5)	33 (20.4)	21 (23.6)	
AB type	37 (14.7)	22 (13.6)	15 (16.9)	
O type	79 (31.5)	57 (35.2)	22 (24.7)	
Food preference of sweet	97 (38.6)	62 (38.3)	35 (39.3)	0.977
Food preference of spicy	117 (46.6)	80 (49.4)	37 (41.6)	0.292
Food preference of salty	89 (35.5)	55 (34.0)	34 (38.2)	0.592
Daily exercise with certain strength	123 (49.0)	75 (46.3)	48 (53.9)	0.305
Standing jobs	82 (32.7)	49 (30.2)	33 (37.1)	0.335
Skin texture				0.600
Dry skin	35 (13.9)	25 (15.4)	10 (11.2)	
Normal skin	119 (47.4)	74 (45.7)	45 (50.6)	
Oily skin	97 (38.6)	63 (38.9)	34 (38.2)	0.001
Excessive scrubbing of keloids	100 (39.8)	52 (32.1)	48 (53.9)	
Smoking	40 (15.9)	27 (16.7)	13 (14.6)	0.805
Alcohol	147 (58.6)	100 (61.7)	47 (52.8)	0.216
Family income				0.002
Low family income	33 (13.1)	15 (9.3)	18 (20.2)	
Middle family income	101 (40.2)	64 (39.5)	37 (41.6)	
Middle-High family income	94 (37.5)	61 (37.7)	33 (37.1)	
High family income	23 (9.2)	22 (13.6)	1 (1.1)	

Data were presented as *n* (%) or mean ± SD. VLCS: Von Luschan chromatic scale. SD: Standard deviation.

according to the VLCS, followed by light brown (33.9% [85/251]) and dark brown (7.2% [18/251]), with no significant differences between the two groups ( $P = 0.204$ ). In addition, most patients had one or more food preferences, spicy foods being the most common preference (46.6% [117/251]), followed by sweet foods (38.6% [97/251]) and salty foods (35.5% [89/251]). Furthermore, there were trends toward more patients in the severe keloid than in the mild keloid group who exercised with certain strength (53.9% [48/89] *vs.* 46.3% [75/162];  $P = 0.305$ ) and had jobs that required prolonged standing (37.1% [33/89] *vs.* 30.2% [49/162];  $P = 0.335$ ); these differences were not significant. Other assessed factors, such as alcohol, smoking, and blood type, did not differ significantly between the two groups [Table 1].

### Comorbidities

The most common comorbidities of keloids were acne (29.1% [73/251]), allergic diseases (14.7% [37/251]), and

bacterial/fungal/viral skin diseases (11.2% [28/251]) [Table 2 and Supplementary Figure 1, <http://links.lww.com/CM9/B8>]. It is worth noting that rheumatism was present significantly more frequently in patients with severe keloids than in those with mild keloids (6.7% [6/89] *vs.* 0.6% [1/162];  $P = 0.016$ ).

### Characteristics of keloid lesions

In addition to the patient's baseline characteristics, we also analyzed the risk factors related to the characteristics of keloids. We found no significant differences in the cause, age of onset, or family history between patients with mild *vs.* severe keloids [Table 3]. The commonest causes of the development of keloids were trauma (24.7% [62/251]) and surgery (24.7% [62/251]), followed by acne (21.9% [55/251]). The overall average age of onset was  $22.04 \pm 12.18$  years. The proportion of patients with a positive family history did

**Table 2: Comparison of comorbidities between patients with mild and severe keloids.**

Comorbidities	Overall	Mild	Severe	P value
No. of patients	251	162	89	
Acne	73 (29.1)	43 (26.5)	30 (33.7)	0.294
Allergic diseases	37 (14.7)	27 (16.7)	10 (11.2)	0.330
Bacterial/fungal/viral skin disease	28 (11.2)	21 (13.0)	7 (7.9)	0.309
Hypertension	15 (6.0)	7 (4.3)	8 (9.0)	0.225
Other skin diseases	12 (4.8)	7 (4.3)	5 (5.6)	0.880
Tumor	13 (5.2)	7 (4.3)	6 (6.7)	0.596
Diabetes	9 (3.6)	5 (3.1)	4 (4.5)	0.827
Rheumatism	7 (2.8)	1 (0.6)	6 (6.7)	0.016

Data were presented as *n* (%).

**Table 3: The comparison of the characteristics of keloid lesions between patients with mild and severe keloids.**

Characteristics	Overall	Mild	Severe	P value
No. of patients	251	162	89	
Cause				0.389
Acne	55 (21.9)	31 (19.1)	24 (27.0)	
Surgery	62 (24.7)	40 (24.7)	22 (24.7)	
Trauma	62 (24.7)	43 (26.5)	19 (21.3)	
Others	32 (12.7)	24 (14.8)	8 (9.0)	
No obvious reason	40 (15.9)	24 (14.8)	16 (18.0)	
Onset age (years)	22.04 ± 12.18	22.25 ± 11.40	21.66 ± 13.53	0.714
Disease duration (years)	12.33 ± 9.68	10.46 ± 7.58	15.72 ± 11.97	<0.001
Family history	73 (29.1)	42 (25.9)	31 (34.8)	0.180
Characteristics of location				0.005
Single keloid at one site	99 (39.4)	77 (47.5)	22 (24.7)	
Multiple keloids at one site	40 (15.9)	22 (13.6)	18 (20.2)	
Single keloid at multiple sites	43 (17.1)	25 (15.4)	18 (20.2)	
Multiple keloids at multiple sites	69 (27.5)	38 (23.5)	31 (34.8)	
Located at sites with high stretch tension				0.014
None	58 (23.1)	46 (28.4)	12 (13.5)	
One specific location	160 (63.7)	99 (61.1)	61 (68.5)	
More than one specific location	33 (13.1)	17 (10.5)	16 (18.0)	
Pain degree				0.001
None	69 (27.5)	51 (31.5)	18 (20.2)	
Mild	130 (51.8)	89 (54.9)	41 (46.1)	
Severe	52 (20.7)	22 (13.6)	30 (33.7)	
Pain frequency				0.049
None	69 (27.5)	51 (31.5)	18 (20.2)	
Intermittent	139 (55.4)	89 (54.9)	50 (56.2)	
Always exist	43 (17.1)	22 (13.6)	21 (23.6)	
Pruritus degree				0.019
None	26 (10.4)	18 (11.1)	8 (9.0)	
Mild	161 (64.1)	112 (69.1)	49 (55.1)	
Severe	64 (25.5)	32 (19.8)	32 (36.0)	
Pruritus frequency				0.180
None	26 (10.4)	18 (11.1)	8 (9.0)	
Intermittent	150 (59.8)	102 (63.0)	48 (53.9)	
Always exist	75 (29.9)	42 (25.9)	33 (37.1)	
Infection	107 (42.6)	54 (33.3)	53 (59.6)	<0.001

Data were presented as *n* (%) or mean ± SD. SD: Standard deviation.

not differ significantly between those with severe *vs.* mild keloids (34.8% [31/89] *vs.* 25.9% [42/162];  $P=0.180$ ). However, patients in the severe keloid group had a significantly longer disease duration than did those in the mild keloid group ( $15.72 \pm 11.97$  years *vs.*  $10.46 \pm 7.58$  years;  $P < 0.001$ ). In addition, more patients with severe than with mild keloids had multiple keloids located at multiple sites (34.8% [31/89] *vs.* 23.5% [38/162];  $P = 0.005$ ; Supplementary Figure 2A, <http://links.lww.com/CM9/B8>) and keloids located at sites with high-stretch tension (86.5% [77/89] *vs.* 71.6% [116/162];  $P = 0.014$ ; Supplementary Figure 2B, <http://links.lww.com/CM9/B8>).

Accompanying symptoms of pain, pruritus, and infection were analyzed [Table 3]. Significantly more patients with severe than with mild keloids had severe pain (33.7% [30/89] *vs.* 13.6% [22/162];  $P = 0.001$ ), constant pain (23.6% [21/89] *vs.* 13.6% [22/162];  $P = 0.049$ ), and severe pruritus (36.0% [32/89] *vs.* 19.8% [32/162];  $P = 0.019$ ). This correlation also held true for infection (59.6% [53/89] *vs.* 33.3% [54/162];  $P < 0.001$ ). There was a tendency for more patients with severe than with mild keloids to have constant pruritus (37.1% [33/89] *vs.* 25.9% [42/162];  $P = 0.180$ ); however, this difference was not significant.

The most common treatments for keloids were surgery (45.0% [113/251]), triamcinolone acetonide (TAC) injection (37.8% [95/251]), and silicone sheeting (33.5% [84/251]) [Table 4]. The prescribed treatment modalities

were similar in the two groups except for radiotherapy, which tended to be administered more often in patients with severe keloids (39.3% [35/89] of patients with severe keloids *vs.* 27.8% [45/162] of patients with mild keloids;  $P = 0.082$ ); however, this difference was not significant.

**Multivariable regression analysis**

Conditional multivariable logistic regression analysis was performed to examine factors independently associated with severity [Table 5]. After screening according to previously set criteria, eight risk factors were included in multivariable regression analysis, six of which were found to be independently associated with severe keloids. The final logistic regression model included excessive scrubbing of keloids (odds ratio [OR], 8.65;  $P = 0.001$ ), low or middle family incomes (OR, 13.44;  $P = 0.021$ ), comorbidity of rheumatism (OR, 18.97;  $P = 0.021$ ), disease duration of over 15 years (OR, 2.98;  $P = 0.046$ ), infection (OR, 3.55;  $P = 0.005$ ), and multiple keloids located at multiple sites (OR, 3.18;  $P = 0.033$ ). Other variables, including location in sites of high-stretch tension, were not significantly associated with an increased risk of developing severe keloids.

**Discussion**

The incidence of keloids in Chinese individuals is 0.15%.<sup>[29]</sup> The clinical manifestations of keloids differ greatly, with

**Table 4: The comparison of previous treatment characteristics between patient with mild and severe keloids.**

Characteristics	Overall	Mild	Severe	P value
No. of patients	251	162	89	
Prophase treatment				
Surgery	113 (45.0)	67 (41.4)	46 (51.7)	0.150
TAC Injection	95 (37.8)	63 (38.9)	32 (36.0)	0.747
Silicone sheeting	84 (33.5)	50 (30.9)	34 (38.2)	0.299
Radiotherapy	80 (31.9)	45 (27.8)	35 (39.3)	0.082
Laser	22 (8.8)	13 (8.0)	9 (10.1)	0.744
Oral medicine	20 (8.0)	12 (7.4)	8 (9.0)	0.842

Data were presented as *n* (%). TAC: triamcinolone acetonide.

**Table 5: Multivariate regression analysis of factors associated with severe keloids.**

Variables	Severe keloid			P value
	OR	95% Confidence interval		
Excessive scrubbing of keloids	8.65	2.39	31.31	0.001
Low or middle family income	13.44	1.48	122.26	0.021
Comorbidity of rheumatism	18.97	1.55	232.30	0.021
Disease duration more than 15 years	2.98	1.02	8.74	0.046
Infection	3.55	1.46	8.66	0.005
Multiple keloids located at multiple sites	3.18	1.10	9.23	0.033
Older than 30 years	1.39	0.57	3.40	0.469
Located at sites with high stretch tension	0.28	0.06	1.21	0.088

OR: Odds ratio.

some patients reporting extremely severe symptoms. In the present study, our definition of severe keloids was based on the number and surface area of the keloids, as recommended previously by others.<sup>[8]</sup> We have found that, of the many objective indicators currently used to evaluate keloids, their number and size are the factors that most markedly impact patients' quality of life, appearance, and motor function. Because our institution is the largest general hospital in southwest China, more severe cases are often referred to us. When planning the present study, we aimed for a definition of severe keloids that would achieve the selection of patients with the most typical symptoms of advanced keloids for analysis. With this aim in mind, we defined severe keloids as those with a total surface area of  $\geq 40$  cm<sup>2</sup> or totaling 10 or more. Even with such strict criteria, 89 of the 251 patients in our study cohort were classified as having severe keloids. We believe that these patients are representative of those with severe keloids.

Thus far, numerous studies have aimed to identify the risk factors for the formation of keloids.<sup>[16,30-32]</sup> The purpose of these studies was to minimize the formation of keloids by identifying factors associated with the formation of these lesions during the process of wound repair. However, for patients who have already developed keloids, considering that the occurrence and progression of the disease are two different stages in the disease process, these factors can be used as a reference, but they are not completely applicable. The main purpose of the present study was therefore to fill this gap.

Tirgan<sup>[33,34]</sup> reported a few risk factors in patients with severe keloids on the neck and earlobe. However, we designed a more comprehensive survey of risk factors including diverse perspectives, namely patients' baseline characteristics, living habits, income level, comorbidities, and characteristics of their keloids, and recruited a fairly large sample to obtain a more rigorous and reliable results.<sup>[8]</sup> To the best of our knowledge, this is the first study in China to comprehensively analyze the risk factors for severe keloids, which progress in a different way than do "normal" keloids.

In this study, we found that male sex, age, excessive scrubbing of keloids, family income, the comorbidity of rheumatism, disease duration, characteristics of the location, location at high-stretch tension sites, degree and frequency of pain, the severity of pruritus, and infection are associated with the development of severe keloids. Further analysis revealed excessive scrubbing of keloids, infection, low or middle family income, the comorbidity of rheumatism, multiple keloids located at multiple sites, and disease duration of over 15 years to be independent risk factors for severe keloids. We, therefore, recommend that physicians more actively and methodically implement interventions, such as surgery followed by radiotherapy, in patients with keloids who have one or more of the above risk factors.

In addition, we believe that keloids should be treated thoroughly and that affected patients should be followed up for life. Currently, therapy is suspended in some facilities after several laser treatments or TAC injection treatments, regardless of the degree of relief achieved. Such short-term treatment is not enough to stop the

progression of keloids. Additionally, physicians should educate their patients on the importance of thorough, rather than short-term, treatment for keloids.

We found that excessive scrubbing of keloids is an independent risk factor for progression to severe keloids. The mechanical stimulation produced by such scrubbing may stimulate the progression of the relevant keloid.<sup>[32]</sup> Affected individuals may engage in excessive scrubbing in the hope of making large keloids less unsightly. Although a causal relationship between scar scrubbing and keloid severity has not definitely been established, we still recommend that patients avoid excessive scrubbing of keloids. Nonetheless, it should be emphasized that, to minimize infection, keloids should be cleaned thoroughly daily while avoiding excessive scrubbing. Mechanical stimulation seems to be a risk factor for both formation of keloids and their progression to severe keloids. Other reported risk factors for the formation of keloids, such as family history,<sup>[14,15]</sup> blood type,<sup>[4,17]</sup> and smoking,<sup>[16]</sup> are not associated with progression to severe keloids according to the findings of the present study. Our findings indicate that the formation of keloids and their progression, at least in part, are different processes with different risk factors. For example, family history only contributes to the formation of keloids, whereas the progression of keloids depends on more individual factors, such as scrubbing and other forms of mechanical stimulation of keloids. In other words, keloid patients whose only risk factor is a positive family history may not require overly aggressive treatment.

Common comorbidities of keloids include acne, allergic diseases, and other skin diseases. In fact, acne, one of the leading causes of keloids, ranked first in the comorbidity-related survey.<sup>[6]</sup> In our study, the multivariable analysis identified rheumatism as the comorbidity most strongly associated with severe keloids (OR, 18.97;  $P = 0.021$ ). Although a previous study has reported that keloids share certain characteristics with autoimmune diseases, including detection of IgA, IgM, C3, and C1q deposits in keloid tissue,<sup>[35]</sup> our research is the first to provide clinical evidence of an association between these two conditions. This association may be attributable to activation of an inflammatory response, leading to the type of tissue injury and organ fibrosis found in autoimmune diseases; keloids are fibrotic skin diseases characterized by immune cell infiltration.<sup>[36]</sup> Another possible mechanism revolves around the fact that the development of rheumatism may be triggered by certain infectious agents or antigens produced by microorganisms and severe keloids are commonly accompanied by infection.<sup>[36]</sup> We postulate that hormones may also be involved in the association between rheumatism and keloids: the pathological mechanisms underlying the development of some rheumatic diseases are closely associated with imbalances in estrogen and progesterone.<sup>[37,38]</sup> Of interest, hormone imbalance can contribute to the occurrence of keloids.<sup>[39]</sup>

In our study, multivariable regression analysis identified family income as an independent risk factor for keloid severity. Patients with high family incomes were more likely to have mild keloids than were those with lower

incomes. Given that keloids are not covered by general medical insurance in China, we speculate that economic considerations, at least in part, determine patients' ability to visit a doctor and comply with recommended treatment.

Several studies have noted an association between high-tension sites and the formation of keloids.<sup>[18,30]</sup> Our findings suggest that high tension contributes to both the onset of keloids and their progression. This means that physicians need to be especially alert to the possibility of further progression when keloids occur in high-tension areas. More aggressive treatments should be considered, including surgery followed by radiotherapy.

According to univariable analysis, the symptoms of keloids, including pain, pruritus, and infection, differ significantly between patients with mild and severe keloids. We excluded pain and pruritus from the final multivariable analysis because they are subjective and may be a result of severe keloids rather than be risk factors for their development; however, pain and pruritus are common in keloid patients.<sup>[12,40]</sup> Previous studies have reported that, after treatment with silicone gel sheets or cryosurgery, pathological examination shows fewer mast cells infiltrating the keloids, which is consistent with relief of pain and pruritus.<sup>[41,42]</sup> The persistent inflammation induced by mast cells, macrophages, or lymphocytes that contributes to the progression of keloids is strongly associated with pain and pruritus — the more severe the inflammatory reaction, the more pronounced these symptoms.<sup>[6,43]</sup> A high proportion of severe keloids become infected, such infection being another cited contributor to these patients' poor quality of life. Infection may also be a predictor of the development of severe keloids.

Consumption of spicy food can reportedly exacerbate pruritus of keloids.<sup>[16]</sup> In the present study, we found no significant relationship between the consumption of spicy foods and keloid severity. We, therefore, concluded that the exacerbation of pruritus associated with spicy foods may be temporary and that such food is not a risk factor for progression to severe keloids. However, given the previously reported correlation between consumption of spicy food and pruritus, we do not recommend regular consumption of spicy food by patients with keloids. Hypertension has also been reported to be a factor in the development of severe keloids.<sup>[8]</sup> However, in our study, the proportion of patients with hypertension did not differ significantly between patients with severe keloids and those with mild keloids. This discrepancy may be attributable to differences in study cohorts.

The relationship between the formation of keloids and exercise has been widely discussed.<sup>[18,44]</sup> In the present study, we found no significant association between the development of severe keloids and exercise or specific types of physical work. A possible explanation for this apparent discrepancy is that there may be a far more significant correlation between exercise and the formation of keloids than between exercise and progression to severe keloids. One research group suggested that the local

tension generated during exercise causes the formation of keloids.<sup>[16]</sup> However, the dense fibrous tissue of developed keloids may restrict the movement of nearby muscles, thus preventing exacerbation of the condition. Thus, less aggressive treatment options, such as injection or silicone sheeting therapy, should be considered for keloids that are clearly associated with excessive exercise during wound repair.

One limitation of this study is that it was conducted retrospectively; thus, there may have been some recall bias. Therefore, a prospective, large-scale study on this topic is needed to further investigate our findings. Meanwhile, this study had several strengths. To the best of our knowledge, it is the first study to comprehensively assess risk factors for severe keloids in China. Many studies have assessed the risk factors for keloids in general, but few have specifically investigated the risk factors for severe keloids. We hope that our findings will encourage other researchers to investigate the progression to severe keloids. Furthermore, the results of this study could help the physicians with the clinical management of patients with keloids and assist the doctors in the early detection of patients who have a high risk of developing severe keloids.

## Conclusions

In this study, we analyzed 41 potential personal or keloid-related predictors in 251 keloid patients and identified six factors that are independently and significantly associated with the occurrence of severe keloids. These factors are low or middle family income, excessive scrubbing of keloids, infection, the comorbidity of rheumatism, multiple keloids located at multiple sites, and disease duration of over 15 years. Our results highlight the need for physicians to pay attention to the risk factors that may lead to the progression of mild keloids and encourage them to implement more active and thorough measures, such as surgery followed by radiotherapy, in patients with these risk factors.

## Conflicts of interest

None.

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