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Dermatological Health

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Dermatological Health is a peer-reviewed, open access journal that publishes original research articles and review articles related to the prevention, diagnosis, and treatment of disorders of the skin, hair, and nails. The covered topics include, but are not limited to: clinical, investigative, and population-based studies, healthcare delivery and quality of care research, high quality, cost effective, and innovative treatments, new diagnostic techniques, and other topics related to the prevention, diagnosis, and treatment of disorders of the skin, hair, and nails. Each issue includes continuing medical education articles designed to fill practice and knowledge gaps in the delivery of dermatologic care.

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The P25L Mutation in the *KRT5* Gene in a Chinese Family with Epidermolysis Bullosa Simplex with Mottled Pigmentation: A Case Report and Literature Review

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Abstract: *Background:* Epidermolysis bullosa simplex (EBS) with mottled pigmentation (EBS-MP; OMIM 131960) is a rare subtype of EBS that is characterized by blistering, mottled pigmentation, punctate hyperkeratosis, and dystrophic nails. It is predominantly caused by heterozygous gain-of-function mutations in the keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes. *Objective:* The purpose of this study was to identify the *KRT5* and *KRT14* gene mutations in a Chinese family affected with EBS-MP and analyze the clinical manifestations. *Methods:* Whole-exome sequencing (WES) and Sanger sequencing were performed to explore the mutations of an EBS-MP pedigree that included a 24-year-old man and his parents. *Results:* WES revealed a heterozygous c.74C>T (p.Pro25Leu) mutation in *KRT5* in the proband and his mother, which caused the substitution of proline in codon 25 with leucine (p.P25L). The same mutation was not present in the unaffected father. *Conclusion:* We confirmed the diagnosis of EBS-MP in this family, which was caused by the p.P25L mutation in *KRT5*. The proband presents additional manifestations, clinical heterogeneity of EBS-MP about skin features is acknowledged. Further observations and studies of EBS-MP are required to confirm or exclude the possible connection.

Keywords: Epidermolysis bullosa simplex; *KRT5* gene; Gene mutation

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1. Introduction

Although the study of epidermolysis bullosa simplex (EBS) in recent years is more active, epidermolysis bullosa simplex with mottled pigmentation (EBS-MP) is very rare as a subtype of EBS. EBS-MP is a rare subtype of EBS that is characterized by blistering, mottled pigmentation of the trunk and limbs, punctate hyperkeratosis of the palms and soles, and dystrophic nails ^[1]. Representative histological features of EBS-MP are keratinocyte degeneration and intraepidermal cleavage, while ultrastructural analysis of pigmented

areas shows abundant mature melanosomes within basal cells. EBS-MP is predominantly caused by heterozygous gain-of-function mutations in the keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes, and is inherited in either an autosomal dominant or, more rarely, an autosomal recessive manner^[1,2]. Here, we report a Chinese familial case of EBS-MP caused by the p.P25L mutation in *KRT5*. In this study, we analyzed the clinical manifestations and gene mutations of an EBS-MP family, further enriching the mutation spectrum of the EBS gene and exploring the pathogenesis of EBS-MP, which promotes clinical diagnosis, prenatal screening, and gene therapy in the future.

2. Materials and methods

2.1. Ethics approval

The study was approved by the ethical committee at the First Affiliated Hospital of Anhui Medical University and all participants provided signed written informed consent.

2.2. Patient and clinical characteristics

The proband was a 24-year-old man when he first visited our institution. He showed reticulate hyperpigmentation on the trunk and extremities (**Figure 1a**), which had been noted since he was a few months old. Keratotic warty papules on the palmoplantar area and dorsum of the hand and foot (**Figure 1b**), or slight nail dysplasia were also present (**Figure 1c**). Furthermore, he also showed non-cicatricial alopecia (**Figure 1d**). A total of nine members of the family revealed similar manifestations. The family pedigree indicated an autosomal dominant genodermatosis (**Figure 1e**).

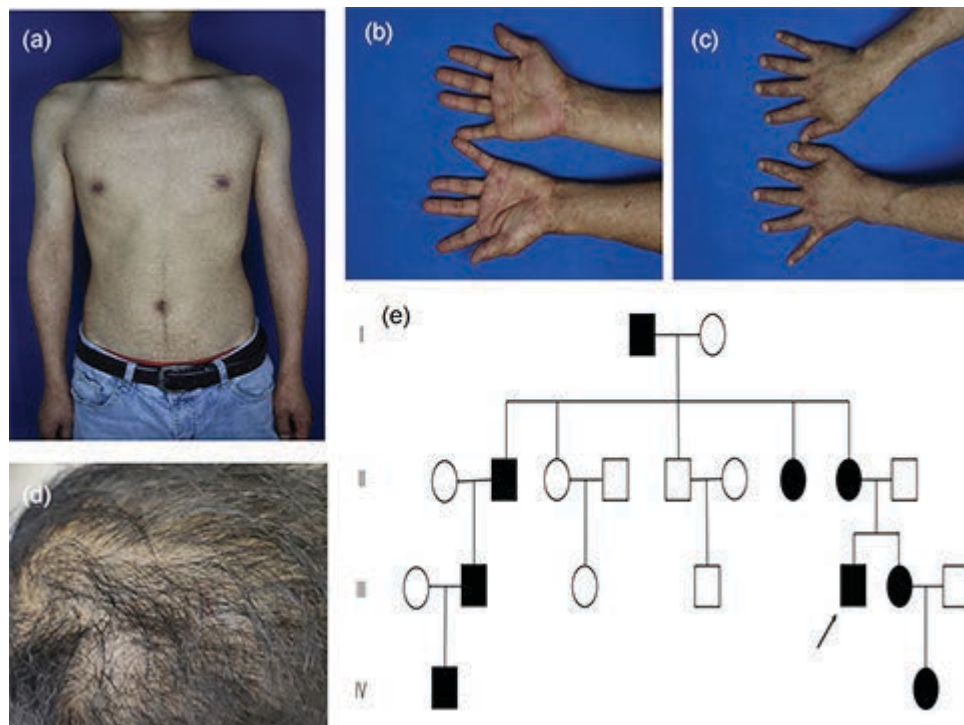


Figure 1. Patient and clinical characteristics

2.3. Gene diagnosis

Genomic DNA was extracted from peripheral blood samples obtained from the proband and his parents. DNA extraction, gene amplification, and sequence analysis were performed in Shulan Health. We performed whole-exome sequencing in the proband and his parents to comprehensively identify all genetic anomalies. Then, the mutation was confirmed by Sanger sequencing in affected members.

3. Results

3.1. Histopathological changes

Two biopsy specimens were taken from the proband, respectively from the hyperpigmented area and hypopigmented area of the left forearm. Histopathology of skin from the hyperpigmented area of the left forearm showed abundant melanocytes within the basal layer and thickened stratum corneum (**Figure 2a**). Hypopigmented area of the left forearm demonstrates reduction of melanocytes in the basal layer, increased collagen fiber, and no inflammatory cells infiltrated in the dermis (**Figure 2b–2c**).

3.2. Gene detection results

Whole-exome sequencing (WES) revealed a heterozygous C-T transition at nucleotide position 74 in the affected members, resulting in the substitution of leucine for proline residue at position 25 (P25L) in *KRT5*. The mutation was confirmed by Sanger sequencing in two affected members (**Figure 2d**).

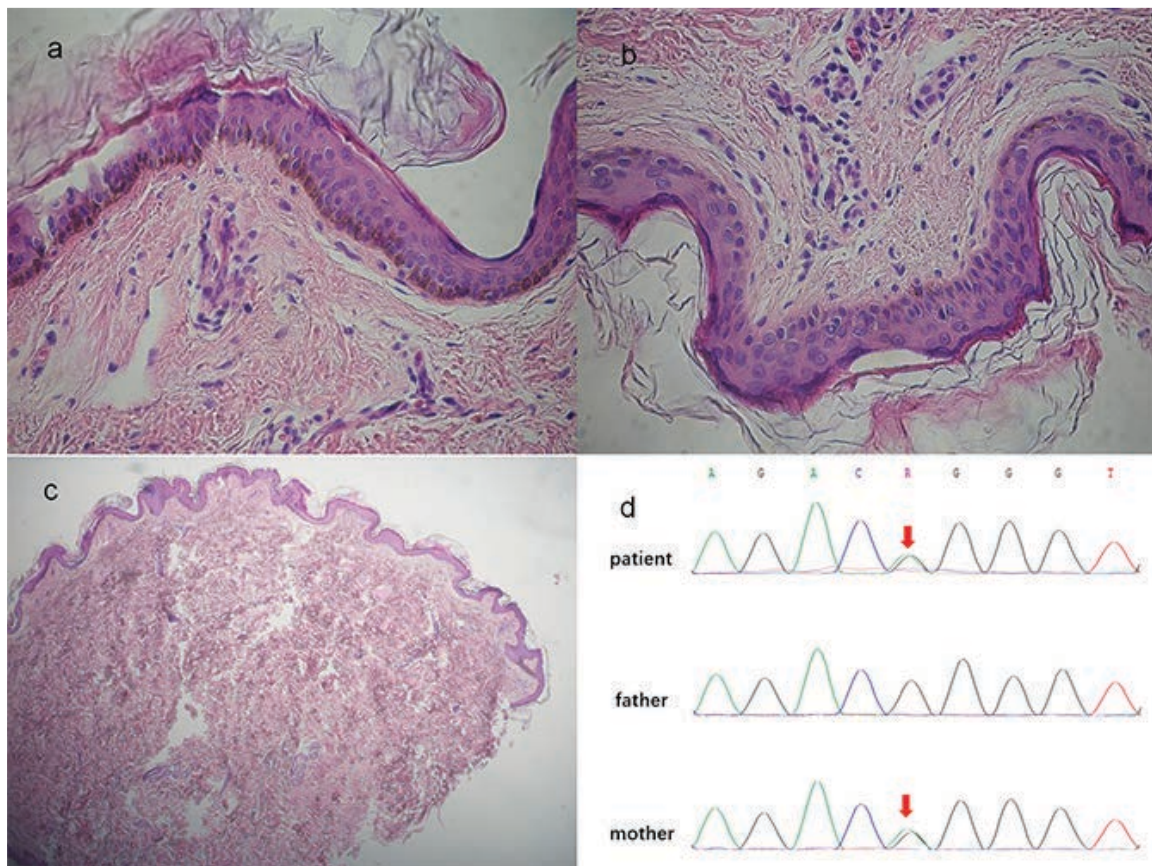


Figure 2. Histopathological changes and gene detection results

4. Discussion

EBS-MP is a rare genodermatosis with a limited number of affected members published from all over the world, first reported by Fischer and Gedde-Dahl in 1979 ^[3]. This study described a heterozygous mutation of the *KRT5* gene (c.74C>T) in a pedigree and analyzed the clinical characteristics and pathogenesis. In this case, the p.P25L mutation of the *KRT5* gene was found by WES. Generally, mutations in *KRT5* or *KRT14* are associated with the EBS-MP. To date, in addition to the p.P25L mutation of *KRT5*, other mutations reported to cause EBS-MP include P.G550AFSX77, and 1649delG mutations in *KRT5*, mutations of P.M119T, p.Ile373_Glu386dup, and P.I373EFSX53 of *KRT14*, with mutations of EXPH5:c.3917C>G, p.Ser1306 (**Table 1**). In all reported cases, the mutation most usually found in EBS-MP is the p.P25L mutation in *KRT5*.

Table 1. Clinical and genetic features of reported cases in the literature

Reference	<i>n</i>	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Fisher and Gedde-Dahl ^[3]	11(F)	at birth, upon trauma	mosaic pattern, mainly the extremities, faded with age	knees; palms	+	photosensitivity	Unknown
Verbov et al. ^[4]	6(F)	in infancy	predominantly extremities	palmar	+	scalp hair thinning	Unknown
Boos et al. ^[5]	2(F1) 7(F2)	after birth, hands and feet	particularly on the limbs	palms and soles	+	no	Unknown
Bruckner-Tuderman et al. ^[6]	1(S)	since birth, extremities	trunk, axillae, face and extremities.	-	+	mild photosensitivity	Unknown
Coleman et al. ^[7]	2(F)	since 4 months of age; in infancy	upper thighs; most of her skin	at 5 years of age, palms and soles	+	nonpruritic raised red scaly lesions, skin atrophy	Unknown
Combemale et al. ^[8]	1(S)	since birth, after minor trauma	over the limbs	weight-bearing areas	+	no	Unknown
Uttam et al. ^[9]	2(F1) 11(F2)	at birth	trunk and extremities	no	+	erosions within the oral cavity	KRT5-c.74C>T p.P25L
Irvine et al. ^[10]	1(S)	acral	limbs	soles	-	no	KRT5-c.74C>T p.P25L
Moog et al. ^[11]	3(F) 1(S)	after minor trauma; since infancy; confined to the feet	folds of the trunk, neck, arms, and legs; faded with age	-	+	photosensitivity	KRT5-c.74C>T p.P25L
Irvine et al. ^[12]	3(F1) 27(F2)	lifelong, exacerbation in the summer	trunk and limbs	punctate or focal palmoplantar	-	no	KRT5-c.74C>T p.P25L
Hamada et al. ^[13]	2(F)	after minor trauma, palms and soles	trunk and extremities	punctuate palmoplantar	-	no	KRT5-c.74C>T p.P25L
Westerhof et al. ^[14]	5(F)	after birth	over the body	palms and soles	+	itch	Unknown

Reference	n	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Yasukawa et al. ^[15]	2(F)	since 1 month of age, palms and soles; most of his body	axillae, the wrists, and the dorsa of the hand	axillae, the wrists, and the dorsa of the hand	-	no	KRT5-c.74C>T p.P25L
Hamada et al. ^[16]	1(S)	trunk, extremities, and palmoplantar skin	at the age of 9 months	-	-	no	KRT5-c.74C>T p.P25L
Horiguchi et al. ^[17]	6(F)	extremities and the abdomen exacerbation, in the summer season	trunk and extremities	-	+	no	KRT5-1649delG
Harel et al. ^[18]	1(S)	after birth	limbs and trunk, during early childhood	over the palms and soles	-	no	KRT14-c.356T>C p. M119T
Andres et al. ^[19]	1(F)	since infancy, after minor trauma	since birth	upper extremities and bilateral palmar	+	multiple erosions	Unknown
Tang et al. ^[20]	6(F)	since infancy	lower abdomen and limbs	no	+	no	KRT5-c.1649delG
Arin et al. ^[21]	Unknown	unknown	unknown	unknown	unknown	unknown	KRT14-c.1117_1158dup K14-p.Ile373_Glu386dup
Gray et al. ^[22]	1(S)	at four days of age, on the buttocks and perirectal skin, at sites of trauma, in hot and humid conditions	neck, back, and extremities, around age 2	palmoplantar	+	no	KRT14-p.I373Efs X53
García et al. ^[1]	6(F1) 4(F2)	plantar, in childhood	in early childhood	plantar, at a later age	+	no	KRT5-c.74C>T p.P25L
Browning et al. ^[23]	1(s)	since infancy	limbs and trunk	axillae, dorsal forearms	-	-	KRT5-c.74C>T p.P25L
Echeverría-García et al. ^[24]	3(F1) 3(F2)	f1:since birth, face and frictional areas f2:since birth	f1:axillae and groin f2: arms and legs	f1:palmoplantar f2:palms and soles	-	no	KRT5-c.74C>T p.P25L
Bchetnia et al. ^[25]	1(S)	since birth, extremities	limbs and trunk (2–5 mm)	soles	+	no	KRT5-c.74C>T p.P25L
Geller et al. ^[26]	1(S)	since birth	axilla, lower abdomen, and inguinal folds	-	-	no	KRT5-1649delG
Gerkowicz et al. ^[27]	1(S)	since childhood	extremities	punctate palmar	+	diffuse partial woolly hair	Unknown
Bergant et al. ^[28]	1(S)	since birth	whole body surface	-	-	no	KRT5-c.74C>T p.P25L

Reference	<i>n</i>	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Turcan et al. [2]	1(S)	since 1 year old	trunk, axillae, and proximal extremities	-	-	no	EXPH5-c.3917C>G, p.Ser1306
Nagai et al. [29]	1(F)	+	trunk and extremities	volar edges	-	alopecia (in 4 cases)	KRT5-c.74C>T p.P25L
Okamura et al. [30]	2(F)	since birth, traumatized areas	trunk and extremities	palms and soles	+	1:alopecia 2:no	KRT5-c.74C>T p.P25L
Ferreira et al. [31]	1(S)	since birth, traumatized areas	+	-	+	photosensitivity	Unknown

F: familial cases; S: sporadic cases

Clinical manifestations of EBS-MP vary with age: the skin fragility and blisters significantly reduced with age, mottled pigmentation gradually appeared on the limbs and trunk, punctate hyperkeratosis of the palms and soles often at a later age, and nail dystrophy. Review of previous cases: blisters and bullae caused by mechanical trauma mainly occurred in the extremities, usually begin at birth or during infancy, and generally tend to disappear in adults, but can reappear in some cases. Some authors found blisters worsened in summer, but this situation is not consistently recorded (**Table 1**). Keratin 5 and 14 form the primary keratin pair of epidermal keratinocytes. Keratin molecules carrying K5-25L result in tonofilament clumping ^[29], this is important for K5 and K14 to form a heterodimer and assemble into intermediate filaments, suggesting that this mutation in *KRT5* results in abnormal formation of intermediate filaments, leading to abnormal perinuclear aggregation of keratin intermediate filaments. This leaves keratinocytes vulnerable and prone to rupture. Minor skin trauma, such as rubbing or scraping, can cause these cells to break down and form fluid-filled blisters and bullae.

Mottled pigmentation generally does not precede the appearance of blisters, and the area of abnormal skin pigmentation is independent of the area of blisters. In reported cases, pigmentation was described as reticulate hyperpigmentation, which in some cases may be accompanied by hypopigmented plaques (**Table 1**). The keratin head domain is known to be involved in melanosome transport ^[9]. This mutation in *KRT5* results in abnormality of melanosome transport, which may be responsible for the failure to transfer mature melanosomes to the neighboring keratinocytes and the large accumulation of mature melanosomes in basal cells, which accordingly explains the causes of abnormal pigmentation and hypopigmentation in patients.

Hyperkeratosis tends to occur in the palms and soles, and a small proportion of cases occur in the limbs. And it is more generalized in older patients than in youth. Abnormalities of desmosome-associated molecules such as desmoplakin and desmoglein have been proven to cause palmoplantar keratoderma (**Table 1**). The P25L mutation is located in the amino-terminal head domain of keratin 5, which contains the keratin-desmoplakin I binding sites ^[15]. It has been postulated that palmoplantar hyperkeratotic lesions in EBS-MP are the consequence of disruption of binding between the keratin filaments of the keratinocytes and the desmosomal proteins.

The proband presented with decreasing skin fragility with age, slowly progressive reticular hyperpigmentation over the body, focal keratinization on the palms, and marked thinning of hair. Patients of EBS-MP (included in this case) generally no longer appear tribological blisters and bullae after adulthood.

Therefore, the diagnosis of EBS-MP is difficult and needs to be differentiated from a variety of genetic diseases. The main differential diagnosis is other types of EBS, principally the herpetiformis type of Dowling-Meara (EBS-DM; OMIM 131760), Dowling-Degos disease (DDD; OMIM 179850), and Kindler syndrome (KS; OMIM 173650). Most diseases can be identified by a history of increased skin fragility in EBS-MP and genetic testing. It is noteworthy that we noticed non-cicatricial alopecia in the proband. In all reported cases, we found many cases of EBS-MP with non-cicatricial alopecia^[4,27,29,30]. Therefore, we suspect that non-cicatricial alopecia is a common feature of EBS-MP that has not been noticed. Further observation is needed to confirm whether hair abnormality is a characteristic manifestation of EBS-MP.

Due to the rarity and phenotypic heterogeneity of EBS-MP, it is unknown whether the patient's other concomitant symptoms are caused by the *KRT5/KRT14* mutation. Further accumulation of cases of EBS-MP can provide more accurate diagnostic criteria for genetic disorders of the *KRT5/KRT14*, provide valuable insights into clinical diagnosis, and assist in genetic counselling for this disease. The prognosis of EBS-MP is better with decreasing occurrence of blisters in adults, but there is no effective means of treatment for EBS-MP at present. DNA-based prenatal testing has been developed, and the disease can only be detected early by prenatal screening and prenatal diagnosis.

5. Conclusion

In this study, we identified a heterozygous c.74C>T (p.P25L) mutation in *KRT5* in a Chinese family with EBS-MP. The proband presented with reticulate hyperpigmentation, palmoplantar keratotic papules, nail dysplasia, and non-cicatricial alopecia, expanding the phenotypic spectrum of this disorder. Notably, non-cicatricial alopecia—observed in our case and multiple reported cases—may represent an underrecognized feature of EBS-MP warranting further study. Currently, no curative therapy exists for EBS-MP; management remains supportive. Genetic counseling and DNA-based prenatal diagnosis are essential for affected families. Continued accumulation of clinical and genetic data will refine diagnostic criteria and guide future targeted therapies.

Disclosure statement

The authors declare no conflict of interest.

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Association Between Scar Formation and Stigma in Survivors of Deep Burns to Sensitive Areas

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Abstract: Survivors of burns to sensitive areas can develop scars of different degrees and are highly likely to experience stigma. However, current evidence on the association between scar formation and stigma in survivors of burns to these sensitive areas is limited and inconsistent. The objective was to determine whether scar formation is independently associated with stigma in survivors of burns to sensitive areas. 109 survivors of deep burns to sensitive areas were selected via convenience sampling to fill out a questionnaire. The degree of stigma was evaluated with the Social Influence Scale (SIS). R software version 4.3.0 was used to perform *t*-tests and logistic regression analyses. After adjusting for age, sex, education level, occupation, marital status, means of medical payment, proportion of medical insurance reimbursement, total score of disability acceptance, and perceived social support score, scar formation was associated only with the degree of social marginalization (odds ratio = 1.199, 95% confidence interval: 1.002–1.436). Scar formation increases the degree of stigma among survivors of deep burns to sensitive areas. If scar formation cannot be prevented, active rehabilitation treatments should be adopted in the early stages of scar formation to reduce the degree of resulting stigma.

Keywords: Burn survivors; Burns to sensitive areas; Stigma; Scar formation; Cross-sectional study

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1. Introduction

Burns are sudden traumas that occur frequently in daily life, and are the fourth-most common threats to life and health after traffic accidents, falls, and violent encounters ^[1]. Deep burn accidents (that is, accidents that produce burns of degree II and above) often involve exposed or functionally sensitive areas, such as the head, face, neck, hands, perineum, and joints, and result in different degrees of scarring and tissue contracture after wound healing ^[2], in turn potentially leading to changes to the victim's appearance, dysfunction, and, potentially, a profound impact on the patient's social interactions. The occurrence of stigma, the complex

psychological experience of belittling or denial by society due to the presence of physical defects, is closely related to different sociocultural concepts, the psychological characteristics of the individual, and in the case of burn victims, the physical attributes of scars. Epidemiological surveys have shown that each year, approximately 11 million individuals worldwide experience burns, among whom approximately 180,000 people die, and the incidence of burns continues to increase at a rate of 450,000 people per year^[3]. Therefore, the association between scar formation and stigma in survivors of deep burns to sensitive areas has become an important topic in the fields of burn rehabilitation and psychosocial medicine.

Due to advancements in medical technology, multiple types of treatments have been developed for burn survivors. However, they are basically limited to two main categories: surgical treatment and rehabilitation (conservative) treatment, while scar management is limited to improving physiological status and an inability to completely eliminate burn scars and the associated psychological burden^[4]. To address this problem, existing intervention strategies emphasize the use of the “biopsychosocial model,” which combines early scar management (such as via pressure therapy and laser treatment) and functional reconstructive surgery; cognitive behavioral therapy, which can help reconstruct self-cognition and relieve loneliness and anxiety; and, at the social level, anti-stigmatization campaigns and family education, which can be used to reduce prejudice. Relevant studies have shown that there is a significant positive association between the visibility of scars and the degree of stigma^[5]; additionally, chronic pain or pruritus may further worsen mental status through neuroendocrine mechanisms. In the long term, unrelieved stigma may evolve into post-traumatic stress disorder (PTSD), occupational limitations, or marital problems, with effects that can last for decades^[6]. Therefore, effective mitigation of adverse psychological states such as stigma in the early stages of scar formation is important for improving the outcomes of burn survivors. However, few studies have investigated the association between scar formation and stigma, and the strength of this association among survivors of deep burns to sensitive areas remains unexplored. Therefore, this study investigated the associations between scar formation and stigma in survivors of deep burns to sensitive areas.

2. Methods

2.1. Data source

This was a cross-sectional study conducted at a burn treatment center in a first-tier city in China. Convenience sampling was used to recruit 109 survivors of deep burns to sensitive areas as participants. Demographic characteristics, socioeconomic status, health status, and health-related behavior data were collected during hospitalization. The study subjects were patients who were hospitalized in the Department of Plastic and Burns in a tertiary hospital in Shenzhen from 2020 to 2021. The investigation timeframe of this project was August 2020 to April 2021. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) deep (degree II) burns occupying $>10\%$ of the total body surface area (TBSA) or degree III burns occupying $>5\%$ of the TBSA^[7,8]; (3) burns located in sensitive areas (including the head, face, neck, hands, feet, perineum, or joints); (4) burns past the shock stage and the acute infection stage and in the recovery stage; (5) habitation in their own home for ≥ 1 month^[9]; and (6) clarity of consciousness and ability to fully cooperate in participating in this study. The exclusion criteria were as follows: (1) cognitive impairment or a history of mental illness; (2) other serious diseases (such as heart failure and stroke); and (3) scars in specific areas due to causes other than burns and that resulted in functional disorders. Among 113 individuals initially recruited, 109 subjects were included as the sample for the final analyses. This study was approved by the Ethics

Review Committee of the Burn Center, and all survey subjects provided prior oral informed consent.

2.2. Scar formation

Data on the occurrence of scarring were obtained during hospitalization through a disease data questionnaire. Scars growth peaks from 30 to 180 days after the burn injury ^[2]. Scar hyperplasia after wound healing involves an entire process including exercise, physical therapy, and plastic surgery; however, the decision to perform plastic surgery, which can range from the treatment of hypertrophic scars, scar resection alone, and breaking up scar adhesions to Z-plasty, depends on the nature and extent of scar hyperplasia and whether it affects body function or physical appearance. Burn survivors who experience scar formation and require plastic surgery were evaluated in this study.

2.3. Determination of stigma

The degree of stigma was evaluated with the reliable, validated, and widely used Social Influence Scale (SIS). This scale consists of 24 self-reported items in four domains: social exclusion (6 items; score range 1–4), economic discrimination (6 items; score range 1–4), internalized stigma (6 items; score range 1–4), and social marginalization (6 items; score range 1–4). By adding the scores of these 24 items, an overall stigma score (score range 24–96) is obtained, in which a higher score indicates a greater degree of stigma.

2.4. Covariates

Several covariates, including age (in years), sex, education level, occupation, marital status, means of medical payment, proportion of medical insurance reimbursement, monthly family income per capita, score of the ability to perform daily activities, total score of disability acceptance, and perceived social support scale (PSSS) score, were evaluated at baseline. Educational level was recorded as the highest level of education completed by the participant, which was divided into elementary school and below, middle school, high school, technical secondary school, junior college, and college (bachelor's degree or above). Occupational status included retired, student, homemaker, worker, farmer, and other. Marital status included married, single, divorced, and widowed. The means of medical payment refers to the main payment method used by the participant for treatment and includes self-pay, medical insurance, commercial insurance, and private payment by the participant's employer. The proportion of medical insurance reimbursement refers to the medical insurance reimbursement status of the participant for the treatment and was classified into $\geq 90\%$, 60–85%, $< 60\%$, none, and other. The monthly family income per capita is an important indicator for assessing the financial status of the participant's family and was divided into $\leq 1,000$, 1,000–1,999, 2,000–4,999, 5,000–10,000, and $> 10,000$. The ability to perform daily activities is an important basis for assessing the participant's self-care capability and was scored with the Barthel index (BI); this value ranges from 0 to 100 points, with higher scores indicating stronger independence. Disability acceptance refers to the degree of acceptance of an individual after experiencing an injury event, including his or her perceptions and beliefs about his or her disability status changes, and was assessed with the Acceptance of Disability Scale-Revised (ADS-R); the score ranges from 32 to 128 points, with higher scores indicating higher levels of disability acceptance. Perceived social support is a type of social support that reflects the true subjective feeling of the individual with respect to social support. This factor was evaluated with the PSSS; the total score of this scale, ranging from 12 to 84 points, reflects the total level of real social support perceived by the individual ^[10], which was subsequently divided into low levels of support (12–28 points), moderate levels of support (29–56

points), and high levels of support (57–84 points).

2.5. Statistical analysis

Binary logistic regression analysis was performed to analyze the association between scar formation and stigma in survivors of burns to specific areas. In this study, three independent regression models were constructed, each with the level of stigma at the time of the investigation as the dependent variable and the presence or absence of scar formation at sensitive areas as an independent variable. Model 1 was not adjusted (i.e., the original model). Starting from Model 1 as a basis, Model 2 was adjusted for age, sex, education level, occupation, and marital status (adjusted model). Model 3 was based on Model 2 and further adjusted for means of medical payment, proportion of medical insurance reimbursement, monthly family income per capita, total burn area, score of the ability to perform daily activities, total score of disability acceptance, and PSSS score.

All analyses were performed in SPSS version 23.0 (IBM SPSS Statistics for Windows; IBM Corporation). Measurement data that conformed to a normal distribution are expressed as mean $\pm$ standard deviation (SD), and intergroup comparisons were performed with the two-sample independent *t*-test. Count data are expressed as frequencies (percentages), and intergroup comparisons were performed with the χ^2 test or Fisher's exact probability test. $P < 0.05$ was considered to indicate statistical significance. The significance level was $\alpha = 0.05$ (two-sided).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population are summarized in **Table 1**. A total of 109 survey respondents were included in this study. Among them, 60 were men; 18% had a primary school education or less; and the mean age was 40.85 ± 13.57 years. A total of 45.1% of burn survivors developed scars after a burn injury and underwent surgery. Compared with burn survivors who did not experience scar formation, most burn survivors who experienced scarring were married or had previously been, and most burn areas were between 10% and 30% of the total body surface area. The overall degree of stigma of the population in this study was moderate (58.38 ± 7.10). Among the four dimensions of the degree of stigma, the difference in the social marginalization score between burn survivors with or without scarring was the most obvious (**Table 1**).

Table 1. Basic characteristics of survivors of burns to sensitive areas with and without scarring

Baseline characteristics	Total, <i>n</i> (%) (<i>n</i> = 109)	With scars, <i>n</i> (%) (<i>n</i> = 49)	Without scars, <i>n</i> (%) (<i>n</i> = 60)	<i>P</i> value
Age (years)	40.85 $\pm$ 13.57	41.1 $\pm$ 11.98	40.62 $\pm$ 14.83	0.841
Sex				0.707
Male	60 (55.05)	26 (43.33)	34 (56.67)	
Female	49 (44.95)	23 (46.94)	26 (53.06)	
Education level				0.059
Primary school or below	18 (16.51)	3 (6.12)	15 (25)	
Middle school	28 (25.69)	12 (24.49)	16 (26.67)	
High school	13 (11.93)	9 (18.37)	4 (6.67)	
Technical secondary school	15 (13.76)	6 (12.24)	9 (15)	

Baseline characteristics	Total, <i>n</i> (%) (<i>n</i> = 109)	With scars, <i>n</i> (%) (<i>n</i> = 49)	Without scars, <i>n</i> (%) (<i>n</i> = 60)	<i>P</i> value
Junior college	17 (15.6)	10 (20.41)	7 (11.67)	0.026
College (bachelor's degree or above)	18 (16.51)	9 (18.37)	9 (15)	
Marital status				
Married	31 (28.44)	13 (26.53)	18 (30)	
Single	40 (36.7)	12 (24.49)	28 (46.67)	
Divorced	19 (17.43)	11 (22.45)	8 (13.33)	0.858
Widowed	19 (17.43)	13 (26.53)	6 (10)	
Occupational status				
Retired	36 (33.03)	15 (30.61)	21 (35)	
Student	22 (20.18)	12 (24.49)	10 (16.67)	
Homemaker	24 (22.02)	9 (18.37)	15 (25)	0.114
Worker	9 (8.26)	5 (10.2)	4 (6.67)	
Farmer	7 (6.42)	3 (6.12)	4 (6.67)	
Other	11 (10.09)	5 (10.2)	6 (10)	
Primary means of medical payment				
Self-pay	10 (9.17)	2 (4.08)	8 (13.33)	0.824
Medical insurance	68 (62.39)	29 (59.18)	39 (65)	
Commercial insurance	18 (16.51)	9 (18.37)	9 (15)	
Private payment by the employer	13 (11.93)	9 (18.37)	4 (6.67)	
Proportion of medical insurance reimbursement				
≥ 90%	50 (45.87)	23 (46.94)	27 (45)	0.628
60–85%	28 (25.69)	13 (26.53)	15 (25)	
< 60%	9 (8.26)	4 (8.16)	5 (8.33)	
None	13 (11.93)	4 (8.16)	9 (15)	
Other	9 (8.26)	5 (10.2)	4 (6.67)	
Monthly family income per capita (yuan)				0.044
≤ 1,000	16 (14.68)	9 (18.37)	7 (11.67)	
1,000–1,999	30 (27.52)	13 (26.53)	17 (28.33)	
2,000–4,999	32 (29.36)	12 (24.49)	20 (33.33)	
5,000–10,000	23 (21.1)	10 (20.41)	13 (21.67)	
> 10,000	8 (7.34)	5 (10.2)	3 (5)	0.338
Total burn area				
< 10%	8 (7.34)	1 (2.04)	7 (11.67)	
10–30%	46 (42.2)	27 (55.1)	19 (31.67)	
30–50%	41 (37.61)	15 (30.61)	26 (43.33)	
> 50%	14 (12.84)	6 (12.24)	8 (13.33)	0.536
Total score for perceived social support scale	53.29 ± 9.12	54.22 ± 7.73	52.53 ± 10.11	
Total score for disability acceptance	81.53 ± 6.51	81.10 ± 6.86	81.88 ± 6.25	

Baseline characteristics	Total, <i>n</i> (%) (<i>n</i> = 109)	With scars, <i>n</i> (%) (<i>n</i> = 49)	Without scars, <i>n</i> (%) (<i>n</i> = 60)	<i>P</i> value
Total score for basic activities of daily living	61.97 ± 13.86	63.37 ± 13.28	60.83 ± 14.33	0.345
Total stigma score	58.38 ± 7.10	57.70 ± 7.27	57.70 ± 7.27	0.273
Economic discrimination	14.28 ± 2.61	14.25 ± 2.59	14.25 ± 2.59	0.880
Social exclusion	15.22 ± 2.45	15.27 ± 2.39	15.27 ± 2.39	0.828
Internalized stigma	14.55 ± 3.05	14.55 ± 3.05	14.55 ± 3.05	0.999
Social marginalization	14.32 ± 3.00	13.63 ± 2.86	13.63 ± 2.86	0.008

3.2. Multivariable analysis of scar formation and stigma

The results of multivariable logistic regression analysis revealed that, after adjusting for age, sex, education level, occupation, marital status, means of medical payment, proportion of medical insurance reimbursement, monthly family income per capita, total burn area, score of the ability to perform daily activities, total score of disability acceptance, and PSSS score, scar formation was associated with the degree of social marginalization [odds ratio (OR) = 1.199, 95% confidence interval (CI): 1.002–1.436] but not with the degree of economic discrimination (OR = 0.804, 95% CI: 0.623–1.039), social exclusion (OR = 0.994, 95% CI: 0.784–1.259), internalized stigma (OR = 1.039, 95% CI: 0.858–1.259), or the total stigma score (OR = 1.002, 95% CI: 0.935–1.072). The associations between scar formation and the degrees of the dimensions of stigma remained consistent among the three models (**Table 2**).

Table 2. Logistic regression analysis of the association between the degrees of the dimensions of stigma and scar formation

Dimension of stigma	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Economic discrimination	0.973 (0.827–1.145)	0.739	0.889 (0.714–1.108)	0.297	0.804 (0.623–1.039)	0.095
Social exclusion	0.980 (0.827–1.162)	0.819	0.976 (0.794–1.198)	0.813	0.994 (0.784–1.259)	0.958
Internalized stigma	0.980 (0.854–1.125)	0.777	1.046 (0.872–1.256)	0.628	1.039 (0.858–1.259)	0.695
Social marginalization	1.209 (1.050–1.392)	0.008	1.189 (1.003–1.409)	0.046	1.199 (1.002–1.436)	0.048
Total sigma score	1.031 (0.976–1.089)	0.272	1.018 (0.954–1.086)	0.588	1.002 (0.935–1.072)	0.965

Notes:

Model 1 is the raw model and is not adjusted.

Model 2 is based on Model 1 and has been adjusted for age, sex, education level, occupation, and marital status.

Model 3 is based on Model 2 and has been adjusted for the means of medical payment, proportion of medical insurance reimbursement, monthly family income per capita, total burn area, score of the ability to perform daily activities, total score of disability acceptance, and PSSS score.

4. Discussion

This prospective study on representative samples of survivors of burns to sensitive areas was the first to find that scar formation was independently associated with the degree of the social marginalization dimension of stigma. Even after adjusting for sociodemographic factors, total burn area, score of the ability to perform daily activities, total score of disability acceptance, and PSSS score, the degree of social marginalization as a form of stigma among those with scarring increased by approximately 1.2 times compared with that of

patients without scarring. In addition, in this study, the prevalence of scar formation was quite high, as nearly half of the burn survivors (45.1%) reported scar formation and received relevant surgical treatment.

4.1. Comparison with other studies

Few studies have reported on the association between scar formation and stigma in survivors of burns to sensitive areas, and existing evidence is insufficient and contradictory. To our knowledge, only a few prospective studies have evaluated the relationship between scar formation and stigma. In this study, the overall degree of stigma among survivors of deep burns to sensitive areas was moderate, which is similar to the results of the survey administered by Yu *et al.* ^[11] to 221 patients with deep burns to exposed locations; but higher than that reported by Li *et al.* ^[12] among 200 burn patients, which may be related to the fact that nearly half of the subjects in this study experienced scar formation after a burn injury and received surgical treatment. Many studies in China and abroad ^[13–19] have shown that the greater the degree of physical dysfunction or mental impairment imposed by scarring, the greater the degree of stigma is among the study subjects; this is consistent with the findings of Goffman *et al.* ^[20], who found that patients presenting with disease characteristics or physical defects tended to report experiencing a greater degree of stigma. However, these studies evaluated only the overall degree of stigma among burn survivors; they did not analyze the four dimensions of stigma separately or perform independent association analysis on scar formation as a specific symptom of burns to clarify its particular role in the formation of stigma. A German systematic review on hand burns ^[21] revealed that even minor burns may have a major impact on hand function, either due to the wound itself or to scar contraction; such impaired hand function can lead to social isolation and loss of occupational ability. A cross-sectional Vietnamese study showed ^[22] that social isolation can reduce patients' health condition and compliance with disease treatment, which is consistent with the results of this study. The core connotation of the social marginalization dimension of stigma is that patients are excluded from mainstream social interactions due to their disease, thus suffering discrimination, alienation, or devaluation of social roles, resulting in the deprivation of their sense of belonging and participation in society. This dimension emphasizes how burn patients who experience scarring are pushed to the margins of society by the destruction of the individual's social identity, and is therefore worth considering by medical personnel.

4.2. Potential mechanism

The mechanism underlying the relationship between scar formation and stigma remains unclear. Relevant studies have shown that there is a significant positive correlation between the visibility of the scar and the degree of stigma ^[5]. Scar visibility not only has a visual impact on the individual's appearance but also can reflect loss of function, especially for scars caused by deep burns and scalds reaching below the papillary dermis. After wound healing, the scars and tissue contract, and malformations and some functional abnormalities can occur. In severe cases, amputation and multiple skin grafting surgeries are needed, and chronic pain or itching may further worsen the mental state of the individual through neuroendocrine mechanisms ^[7]. In the long term, unrelieved stigma may develop into PTSD, occupational limitations, or marital problems, with the effects lasting decades ^[4–6]. Therefore, effective mitigation of adverse psychological states such as stigma in the early stage of scar formation is extremely important for improving the outcomes of burn survivors. However, due to a lack of evidence, further studies are needed to explore the potential mechanisms of the associations observed in this study.

4.3. Clinical significance

The results of this study emphasize the importance of risk screening and management of scar formation in burn survivors in daily clinical practice. Scar formation was found to be independently associated with an approximately 1.2-fold increase in the degree of social marginalization stigma. Compared with common risk factors for stigma among burn survivors^[4-6], screening for scar formation is simpler, more effective, and less expensive, and as a predictor of stigma, scar formation is more intuitive, simpler, and more advantageous to assess. Therefore, screening for scar formation can help identify burn survivors at high risk of experiencing stigma, thus providing a potential opportunity for early intervention in clinical practice.

4.4. Strengths and limitations

The strengths of this study include the large sample size and the regional representativeness of the data, as the individuals were recruited from a burn treatment center in a first-tier city in China. In addition, a validated SIS was used to comprehensively evaluate the current state of the patients' experiences with stigma in terms of four dimensions—social exclusion, economic discrimination, internalized stigma, and social marginalization—and provided a new perspective on the relationship between scar formation and each of these dimensions. Moreover, few studies have investigated these dimensions separately, especially the dimension of social marginalization, and studies on burns to sensitive areas are relatively scarce. Furthermore, the models developed in this study were comprehensively adjusted for potential confounding factors, such as sociodemographic factors, total burn area, score of the ability to perform daily activities, total score of disability acceptance, and PSSS score. Finally, in this study, scar formation was defined by whether or not revision plastic surgery was performed, thus differentiating scar formation from no scar formation in an objective, scientific, and rigorous manner.

This study also has several limitations. First, in analyzing the degree of stigma, only survivors of burns to sensitive areas were included, and other patients at high risk of stigma due to scarring from traumatic injuries or diseases were not considered. Therefore, the study results may not be generalizable to individuals whose scar formation and stigma experiences are related to other diseases. Second, given that the types of scars that form after an individual is burned can differ, some potential confounding factors still could not be ruled out despite the use of models adjusted for certain baseline data. However, a recent study^[23] reported that the incidence of scars reached 91% among burn survivors, while another indicated that survivors of burns to the head, face, neck, hands, perineum, joints, and other sensitive areas had difficulties handling the deformities and changes in appearance that emerged after the wound healing process and showed feelings of sadness, loss and disappointment^[24]. Therefore, the potential confounding factors for the formation of different types of scar may have been controlled to some extent in this study. Third, although many adjustments were made in this study for possible confounding factors, because of the cross-sectional nature of the study, we could not confirm a causal relationship or track the progression of the disease or the dynamic changes in the exposure factors. Finally, owing to the relatively limited sample size in this study, the patient data could not be subjected to subgroup analysis according to the location and severity of the burns. Therefore, subsequent studies should include sufficient samples for further subgroup analysis to confirm our findings.

5. Conclusion

Scar formation is very common among survivors of burns to sensitive areas. In this study, the association between stigma and scar formation was investigated in 109 survivors of deep burns to sensitive areas, and the results revealed that scar formation was independently associated with a 1.2-fold increase in the degree of stigma in the dimension of social marginalization. Screening for scar formation may serve as a simple and cost-effective tool for identifying individuals at high risk of social marginalization as a form of stigma.

Disclosure statement

The authors declare no conflict of interest.

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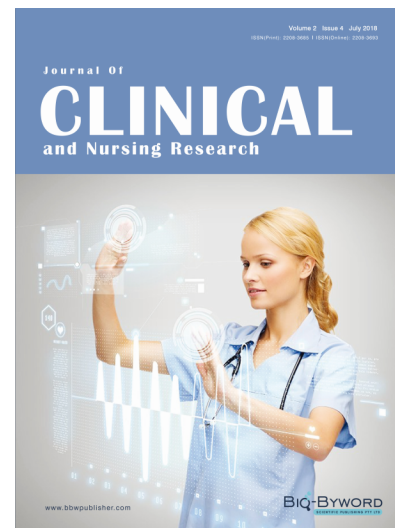
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