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RESEARCH

Clarifying sleep characteristics and analyzing risk factors of sleep disorders to promote a predictive, preventive, and personalized medicine in patients with burn scars

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Abstract

Purpose This study assessed sleep quality in patients with burn scars and investigated risk factors of sleep disorders to guide clinical therapy. From the strategy of predictive, preventive, and personalized medicine (PPPM/3PM), we proposed that risk assessment based on clinical indicators could prompt primary prediction, targeted prevention, and personalized interventions to improve the management of sleep disorders present in patients with burn scars.

Methods This retrospective study recruited patients with burn scars and healthy volunteers from the Shanghai Burn Treatment Center between 2017 and 2022. Relevant information and data, including demographic characteristics, scar evaluation, and sleep quality, were obtained through the hospital information system, classical scar scale, and self-report questionnaires. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and monitored using a cardiopulmonary-coupled electrocardiograph. Pain and pruritus were assessed using the visual analog scale (VAS). Scar appearance was assessed using the modified Vancouver scar scale (mVSS).

Results The sample was comprised of 128 hypertrophic scar (HS) patients, with 61.7% males, a mean age of 41.1 ± 11.6 years, and burn area of 46.2 ± 27.9% total body surface area (TBSA). Patients with PSQI ≥ 7 accounted for 76.6%, and the global PSQI score was 9.4 ± 4.1. Objective sleep data showed that initial enter deep sleep time, light sleep time, awakening time, light sleep efficiency, and sleep apnea index were higher but deep sleep time, sleep efficiency, and deep sleep efficiency were lower in HS patients than that in healthy controls. Preliminary univariate analysis showed that age, hyperplasia time of scar, narrow airway, microstomia, VAS for pain and pruritus, and mVSS total (comprised of pigmentation, vascularity, height and pliability) were associated with the PSQI score ($p < 0.1$). Multivariable linear regression showed narrow airway, VAS for pain and pruritus, and mVSS specifically height, were the risk factors for PSQI score ($p < 0.1$).

Conclusions This study model identified that narrow airway, pain, pruritus and scar appearance specifically height may provide excellent predictors for sleep disorders in HS patients. Our results provided a basis for the predictive diagnostics, targeted prevention, and individualized therapy of somnipathy predisposition and progression of HS patients in the setting of PPPM/3PM health care system, which contributed to a paradigm shift from reactive cure to advanced therapy.

Keywords Predictive preventive personalized medicine (PPPM/3PM) · Hypertrophic scar (HS) · Burn · Sleep quality · Sleep disorder · Risk assessment

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Abbreviations

HS	Hypertrophic scar
PPPM/3PM	Predictive, Preventive and Personalized Medicine
BMI	Body mass index
ECM	Extracellular matrix
ECG	Electrocardiogram
REM	Rapid eye movement
mVSS	Modified Vancouver Scar Scale
SD	Standard deviation

IQR	Interquartile range
QoL	Quality of life
TBSA	Total body surface area
VAS	Visual analogue scale
PSQI	Pittsburgh Sleep Quality Index
CI	Confidence interval

Introduction

Hypertrophic scar (HS) is a skin disorder characterized by excessive deposition of collagen fibers resulting from overactivated fibroblasts [1]. According to the related research, HS occurred in 91% of burn patients due to deep injury [2]. In addition to functional problems and esthetic concerns, the burn patients suffering from HS also experience loss of thermoregulation, severe pruritus and neuropathic pain, and sleep disorders, with a consequence of poor quality of life (QoL), incomplete social reintegration, and even mental disturbance including depression, anxiety, and schizophrenia [3–5]. These challenges could compel them to burn out and eventually choose suicide [6].

Healthy sleep is essential for the body to renew and maintain physical and mental health [7]. Poor sleep can severely affect life satisfaction, leading to depression, anger, fatigue, confusion, and even suicide [8]. Moreover, lack of sleep can also weaken immune function and worsen wound healing [9]. Therefore, effectively maintaining normal sleep is important to protect health of patients with burn scars. Sleep disorders in burn patients have become a widespread concern, and steps are being taken to address their sleep deprivation [10, 11]. A study revealed that more than 85% burn patients had trouble sleeping throughout their treatment [12]. Problems such as increased pain, anxiety, and pruritus can lead to insomnia among burn patients [13, 14]. Our clinical team also observed persistent sleep disorders in patients with burn scars [15]. Nevertheless, systematic clinical studies are still lacking to confirm that patients with HS suffer from sleep disorders. Despite its clinical significance, sleep disorders remain underdiagnosed and under-treated in several cases. As the detailed pathogenesis of sleep disorders is so complex and not fully understood, clarifying sleep characteristics of the patients with burn scars seems more imperative.

Recently, a strategy of predictive approach, targeted prevention, and personalized treatment has been emphasized for the management of affective disorders and chronic diseases, such as suicide risk in depression and cardiovascular events [16, 17]. Current HS treatments include massage, pressure dressings, moisturizing cream, silicone sheeting, intralesional steroid injection, laser, and direct excision [18–22]. However, these methods seem to have no clear improvement on QoL of HS patients. Although sedatives and hypnotics could be taken to alleviate insomnia in most cases, the prolonged or excessive intake of sleeping medications could put patients in drug dependence and drug tolerance [23]. Sleeping pills could chronically activate the hypothalamic–pituitary–adrenal system with the increasing risk of death [24]. Currently, researchers, specifically in developing countries, have rarely paid attention to sleep disturbances in patients with burn scars. However, poor sleep seriously affects the effect of clinical treatment and impedes sufferers' rehabilitation [25]. Hence, it is of much importance to identify the potential risk factors of this intractable postburn complication to realize the early prediction and targeted protection, and further explore the appropriate interventions to achieve the individual therapy. Predictive, Preventive and Personalized Medicine (PPPM/3PM), an integrative strategy in health career, has attracted much attention for its new and comprehensive concept aiming to develop predictive diagnostic tools, targeted prevention strategies and personalized medicine for populations [26]. Therefore, early prediction of somnipathy predisposition, timely prevention of somnipathy onset or progression, and individualized cure of somnipathy outcomes could protect patients with burn scars from severe clinical manifestations and obtain a better psychophysiological health.

This study intended to verify that patients with HS suffered from sleep disorders in a systematic statistical way and further investigated the risk factors for sleep disturbance in HS patients. From the perspective of PPPM/3PM, effective identification of risk factors for sleep disorders in patients with burn scars can early screen the high-risk population, timely execute targeted prevention, and guide individualized clinical therapy, to ameliorate the sleep state, improve the QoL, and finally realize the social reintegration.

Methods

Study population

Patients aged 16 years or older with a definitive clinical diagnosis of HS caused by burn injuries were recruited during the study period from July 2017 to September 2022. The cause of burn injuries included flame, thermal fluid, electricity, or chemicals. However, patients with HS due to surgery, acne, or other skin damages (degloving injury, puncture, and knife trauma…) were excluded. And patients with keloid and atrophic scars were also ruled out [27]. What is particularly noteworthy is that all enrolled patients denied any history of psychological/mental illness or use of psychoactive drugs. Past medical records, paper or electronic, would be reviewed if available. Other exclusion criteria were presented as follows: pregnancy or breastfeeding; respiratory or cardiovascular disease; psychological trauma; alcoholomania. Healthy volunteers were matched and included as controls. All the enrollers in this study have not been

infected or contacted with CoViD-19 positive patients, and their lives have not been seriously affected by the CoViD-19 epidemic. Therefore, the negative impact of the CoViD-19 pandemic on health quality and sleep patterns of healthy controls and patient cohort was ignored in this study.

Study design

This single retrospective cohort study using prospective data was conducted with the approval of the ethics committee of Changhai Hospital affiliated to Naval Medical University (CHEC2014-096). Patients' demographics and medical data were obtained from the Changhai hospital medical information system, classical scar scale, and patient questionnaires. The information involved sex, age, body mass index (BMI), burn causes, total body surface area (TBSA), burn depth of scars, wound healing time, hyperplasia time of scar, inhalation injury, narrow airway, and microstomia. In this study, the wound healing time was defined as the period from the lesion to the entire epithelium of the target area. Hyperplasia time was the duration between entire epithelium of the target area and the patients receiving the questionnaires. With no "gold standard" treatment for HS, all patients received conventional clinical treatments such as compression therapy, steroid injection, silicone products, 5-fluorouracil, and fractional laser [28]. The HS patients enrolled was random and the measurements in this study was performed before patients receiving treatment or from one to three months after treatment. Every enroller only accepted once questionnaire survey. Written informed consent was obtained from all subjects. This study was conducted according to the guidelines of the Helsinki Declaration of Human Medical Research Ethics and Good Clinical Practice as defined by the International Committee for Harmonization [29].

Outcomes

Sleep quality

Sleep quality and disturbances were assessed by a questionnaire called Pittsburgh Sleep Quality Index (PSQI) [30]. It has seven domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the past 1 month. Scoring of the answers in each domain is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert scale with the global sum ranging from 0 to 21. All questionnaires were completed by the patient self-report under the guidance of the investigator.

To evaluate objective sleep parameters, an electrocardiogram (ECG) recorder (AECG-100A, Fengsheng Yongkang Software Co, Nanjing, China) was used. Throughout the whole sleep monitoring process, cardiopulmonary coupling software automatically operates and analyzes total time in bed, total sleep time, initial enter deep sleep time, deep and light sleep time, rapid eye movement (REM) sleep time, awakening time, sleep efficiency (total sleep time/total time in bed), and sleep apnea index [31, 32].

All patients with HS did the survey of PSQI questionnaire, while sleep monitoring with ECG recorder was executed according to patients' intention. All healthy volunteers accepted PSQI and sleep monitoring with ECG recorder.

Scar evaluation

Pain and pruritus were evaluated using the visual analog scale (VAS) [33, 34]. Scars' appearance was assessed by the Vancouver Scar Scale (VSS), involving pigmentation, vascularity, height and pliability [35, 36]. Recently, many published studies have used the modified Baryza VSS (mVSS, up to 15 points), which is characterized by high employee compliance and inter-rater reliability. Hence, we selected the mVSS to evaluate scars in the study and higher overall mVSS score indicated more serious scarring [37–41].

For patients with extensive scars, the scar with the greatest impact on the patient's sleep quality was selected for evaluation. The mVSS of each patient was individually assessed by the same two experienced observers, and the average was used as the final score.

Statistical analysis

All statistical analyses were performed in SPSS 26.0. Patient baseline characteristics and outcome were expressed as mean with standard deviation (SD), median with interquartile range (IQR) or count with percentage. Chi-square test was used for count data, and t test was used for independent sampling of normal distribution of continuous variables. Alternatively, a non-parametric test (such as the Mann–Whitney U test) was used whenever the data showed a significant lack of normality. Univariate linear regression analysis was applied to assess the independent effect of patient characteristics (sex, age, BMI, burn causes, burn area, target scar location, burn depth of target scar, wound healing time and hyperplasia time of scar, inhalation injury, narrow airway, and microstomia), VAS for pain and pruritus, and mVSS total and its components on PSQI-rated sleep quality of patients with burn scars. The covariates with a $p < 0.10$ were included in the subsequent multivariable linear regression. The $p < 0.05$ was considered statistically significant.

Results

Sample information

According to the inclusion criteria, the sample in this study was comprised of 128 patients with burn scars. The data of

demographic characteristics were presented in Table 1. A total of 61.7% of patients were of the male sex, the average age was 41.1 ± 11.6 years, the burn area was 46.2 ± 27.9% TBSA, and the common burn cause was fire ($n = 99$, 77.3%). Regarding the target scars, the wound healing time was 62.7 ± 39.2 days, the hyperplasia time was 9.7 ± 8.1 months, and the locations were mainly in the limbs ($n = 64$, 50%). In addition, 42.2% patients suffered from inhalation injury, with 28.1% narrow airway and 26.6% microstomia.

Table 1 Demographic characteristics of the scar patients ($n = 128$)

	Mean ± SD
Age (years)	41.1 ± 11.6
BMI (kg/m^2)	23.2 ± 3.0
Burn area (%TBSA)	46.2 ± 27.9
Wound healing time of target scar (days)	62.7 ± 39.2
Hyperplasia time (months)	9.7 ± 8.1
	Number, Frequency (%)
Males (*n*, %)	79 (61.7)
Burn causes (*n*, %)	
Fire	99 (77.3)
Hot liquid	19 (14.8)
Others	10 (7.8)
TBSA (*n*, %)	
≤ 10%	14 (10.9)
11–30%	34 (26.6)
31–50%	29 (22.7)
> 50%	51 (39.8)
Burn location (*n*, %)	
Face or neck	85 (66.4)
Trunk	102 (79.7)
Limbs	120 (93.8)
Target scar location (*n*, %)	
Face or neck	26 (20.3)
Trunk	38 (29.7)
Limbs	64 (50.0)
Burn depth of target scar (*n*, %)	
Deep II	35 (27.3)
III	93 (72.7)
Hyperplasia time (*n*, %)	
< 6 months	60 (46.9)
6–12 months	26 (20.3)
> 12 months	42 (32.8)
Inhalation injury (*n*, %)	54 (42.2)
Narrow airway (*n*, %)	36 (28.1)
Microstomia (*n*, %)	34 (26.6)

BMI body mass index (kg/m^2), *TBSA* total body surface area, *SD* standard deviation

Sleep quality

In the enrolled 128 patients with burn scars, the PSQI scale showed that nearly three-quarters (76.6%) of patients had sleep disorders (Table 2). Besides, the data in Table 2 presented that the global score of PSQI was 9.4 ± 4.1, comprised of sleep quality (1.5 ± 0.7), sleep latency (1.8 ± 0.9), sleep time (1.2 ± 0.9), sleep efficiency (1.3 ± 1.0), sleep disturbances (1.7 ± 0.7), sleep medications (0.3 ± 0.8), and daytime dysfunction (1.7 ± 0.8).

In order to objectively verify the sleep disorders in patients with burn scars, 28 patients with burn scars and 18 healthy volunteers were processed with sleep monitoring by ECG recorder. The two groups were comparable in baseline characteristics including sex, age, and BMI (Table 3). The objective sleep parameters collected by ECG recorder were exhibited in Table 4. Patients with burn scars had significantly higher total time in bed than healthy volunteers (9.1 ± 1.7 vs. 7.7 ± 1.1, $p = 0.002$). Meanwhile, they scored markedly lower in deep sleep time (2.2 ± 1.2 vs. 3.5 ± 0.9, $p < 0.001$), sleep efficiency (84.6 ± 8.4 vs. 90.6 ± 5.6, $p = 0.011$), and deep sleep efficiency (25.1 ± 13.8 vs. 45.8 ± 11.4, $p < 0.001$) (Table 4). Moreover, scar patients had significant higher initial enter deep sleep time (1.3, 0.6–3.7 vs. 0.2, 0.1–1.0, $p = 0.001$), light sleep time (3.7 ± 1.5 vs. 2.0 ± 0.7, $p < 0.001$), awakening time (1.4, 0.7–1.9 vs. 0.6, 0.3–0.9, $p = 0.002$), light sleep efficiency (41.4 ± 16.8 vs. 26.0 ± 7.7, $p < 0.001$), and sleep apnea index (11.6, 5.8–20.6 vs. 4.1, 0.4–7.0, $p = 0.003$). Sleep monitoring showed that 78.6% of patients with burn scars had sleep apnea, with only 50.0% in healthy volunteers ($p < 0.001$) (Table 4).

Table 2 Pittsburgh Sleep Quality Index (PSQI) of the scar patients ($n = 128$)

	Mean ± SD
Global score	9.4 ± 4.1
Sleep quality	1.5 ± 0.7
Sleep latency	1.8 ± 0.9
Sleep time	1.2 ± 0.9
Sleep efficiency	1.3 ± 1.0
Sleep disturbances	1.7 ± 0.7
Sleep medications	0.3 ± 0.8
Daytime dysfunction	1.7 ± 0.8
Number, Frequency (%)	
Sleep disorder (global score ≥ 7)	98 (76.6)
No-sleep disorder (global score < 7)	30 (23.4)

SD standard deviation, *PSQI* Pittsburgh Sleep Quality Index

Table 3 Demographic characteristics of the study population

Variables	Healthy volunteers ($n=18$)	Scar patients ($n=28$)	p
Males (n)	6	17	> 0.05
Age (years, mean ± SD)	35.5 ± 8.5	37.7 ± 11.3	> 0.05
BMI (kg/m^2, mean ± SD)	21.9 ± 3.1	23.1 ± 3.1	> 0.05
Burn area (%TBSA, mean ± SD)	–	44.4 ± 26.4	–
Inhalation injury (n)	–	23	–
Narrow airway(n)	–	13	–
Microstomia (n)	–	14	–
Wound healing time of target scar (days, mean ± SD)		57.9 ± 33.7	–
Hyperplasia time (months, mean ± SD)		9.3 ± 8.4	–

Analysis for male compared with healthy volunteers were performed with chi-square test. Other data were performed with independent sample t test. Data are presented as mean ± SD

p value compared with healthy volunteers; BMI body mass index (kg/m^2), TBSA total body surface area, SD standard deviation

Table 4 Sleep parameters of the study population

Sleep parameters	Healthy volunteers ($n=18$)	Scar patients ($n=28$)	p
Total time in bed (hour)	7.7 ± 1.1	9.1 ± 1.7	0.002
Total sleep time (hour)	7.0 ± 0.9	7.6 ± 1.4	> 0.05
Initial enter deep sleep time (hour)	0.2, 0.1–1.0	1.3, 0.6–3.7	0.001
Deep sleep time (hour)	3.5 ± 0.9	2.2 ± 1.2	< 0.001
Light sleep time (hour)	2.0 ± 0.7	3.7 ± 1.5	< 0.001
REM sleep time (hour)	1.4 ± 0.5	1.7 ± 0.8	> 0.05
Awakening time (hour)	0.6, 0.3–0.9	1.4, 0.7–1.9	0.002
Sleep efficiency (%)	90.6 ± 5.6	84.6 ± 8.4	0.011
Deep sleep efficiency (%)	45.8 ± 11.4	25.1 ± 13.8	< 0.001
Light sleep efficiency (%)	26.0 ± 7.7	41.4 ± 16.8	< 0.001
Sleep apnea index (events per hour)	4.1, 0.4–7.0	11.6, 5.8–20.6	0.003
Number, Frequency (%)			< 0.001
Sleep apnea (apnea index ≥ 5)	9 (50)	22 (78.6)	
No-sleep apnea (apnea index < 5)	9 (50)	6 (21.4)	

Analysis for initial enter deep sleep time, awakening time and apnea index compared with healthy volunteers were performed with Mann–Whitney U test. Other data were performed with independent sample t test. Data are presented as median, IQR or mean ± SD

p value compared with healthy volunteers; *IQR* inter quartile range, *SD* standard deviation, *PSQI* Pittsburgh Sleep Quality Index

Scar evaluation

In terms of scar overall condition, we applied VAS to assess pain and pruritus of scars and mVSS to evaluate scar appearance (Table 5 and Table 6). As shown in Table 5, the scar VAS scores of pain and pruritus were 3.5 ± 1.8 and 4.6 ± 1.9, respectively. The mVSS total was 9.7 ± 2.9, consisted with pigmentation (2.4 ± 0.8), vascularity (2.1 ± 0.8), height (2.6 ± 1.2), and pliability (2.6 ± 1.0). As shown in Table 6, more than half of scars had hyperpigmentation (57.0%), 79% of scars appeared red and purple, 52.3% measured > 2 mm, and 72.7% were primarily characterized as yielding and firm.

Table 5 Scar overall condition by the VAS and mVSS of the scar patients ($n=128$)

	Mean ± SD
VAS score of pain	3.5 ± 1.8
VAS score of itch	4.6 ± 1.9
mVSS total	9.7 ± 2.9
Pigmentation	2.4 ± 0.8
Vascularity	2.1 ± 0.8
Height	2.6 ± 1.2
Pliability	2.6 ± 1.0

SD standard deviation, *VAS* visual analogue scale, *mVSS* modified Vancouver Scar Scale

Table 6 Distribution of mVSS component scores ($n = 128$)

Total group				
	Pigmentation (%)	Vascularity (%)	Height (%)	Pliability (%)
0	1 (0.8)	4 (3.1)	1 (0.8)	1 (0.8)
1	20 (15.6)	23 (18.0)	32 (25.0)	9 (7.0)
2	34 (26.6)	61 (47.7)	28 (21.9)	59 (46.1)
3	73 (57.0)	40 (31.3)	21 (16.4)	34 (26.6)
4			46 (35.9)	19 (14.8)
5				6 (4.7)

mVSS modified Vancouver Scar Scale

Risk factors for sleep disorders of HS patients

As shown in Table 7, univariate analysis showed that age, hyperplasia time of scar, narrow airway, microstomia, VAS for pain and itch, and mVSS total (comprised of pigmentation, vascularity, height and pliability) were significantly associated with the PSQI score.

We further did multivariate linear regression analysis and the results in Table 8 including covariates with a $p < 0.10$ through preliminary analysis showed that narrow airway, VAS for pain and pruritus, and height were positively correlated with the PSQI total score ($p < 0.1$). Moreover, the identical analysis, integrating pigmentation, vascularity, height, and pliability as one covariate mVSS total, indicated that the PSQI total score increased as VAS for pain and pruritus ($p < 0.05$), narrow airway ($p < 0.1$), and mVSS total aggravated ($p < 0.1$) (Table 8).

Discussion

Sleep disorders are a common and lasting problem in the whole healing process after burn injuries and could impose heavy social and personal burdens on burn sufferers [42]. Many investigations have indicated that people suffering from burn, one of the most traumatic injuries with high morbidity and mortality, have been almost ended with HS, experiencing limited function, unaesthetic appearance,

Table 7 Univariate analysis of risk factors for sleep disorder of hypertrophic scarring

	PSQI total		
	Coefficient	*p* value	95% CI
Sex	–0.269	0.719	–1.746, 1.208
Age	0.067	0.033	0.005, 0.128
BMI	–0.108	0.373	–0.346, 0.131
Burn causes			
Fire	0.975	0.477	–1.727, 3.677
Hot water	0.921	0.568	–2.260, 4.102
Others	–	–	–
Burn area (TBSA%)	0.016	0.233	–0.010, 0.041
Target scar location			
Face or neck	0.755	0.430	–1.130, 2.640
Trunk	1.010	0.231	–0.650, 2.670
Limbs	–	–	–
Burn depth of target scar (III° vs. Deep II°)	0.970	0.233	–0.632, 2.573
Wound healing time of target scar	0.010	0.290	–0.008, 0.028
Hyperplasia time of scar	–0.082	0.067	–0.169, 0.006
Inhalation injury	0.445	0.545	–1.007, 1.898
Narrow airway	2.432	0.002	0.894, 3.971
Microstomia	1.631	0.046	0.030, 3.231
VAS for pain	1.216	< 0.001	0.873, 1.559
VAS for itch	1.228	< 0.001	0.925, 1.531
Pigmentation	1.175	0.011	0.270, 2.079
Vascularity	1.907	< 0.001	1.053, 2.762
Height	1.577	< 0.001	1.061, 2.093
Pliability	0.773	0.032	0.069, 1.478
mVSS total	0.612	< 0.001	0.386, 0.838

PSQI Pittsburgh sleep quality index, *CI* confidence interval, BMI body mass index (kg/m^2), *TBSA* total body surface area, *VAS* visual analogue scale, *mVSS* modified Vancouver Scar Scale

Table 8 Multivariate analysis of risk factors for sleep disorder of hypertrophic scarring

	PSQI total		
	Coefficient	*p* value	95% CI
Age	0.042	0.104	–0.009, 0.092
Hyperplasia time	–0.041	0.273	–0.115, 0.033
Narrow airway	1.282	0.086	–0.186, 2.749
Microstomia	–0.352	0.638	–1.832, 1.128
VAS for pain	0.411	0.055	–0.009, 0.831
VAS for itch	0.726	< 0.001	0.346, 1.107
Pigmentation	–0.096	0.834	–1.002, 0.810
Vascularity	0.229	0.636	–0.726, 1.185
Height	0.833	0.005	0.259, 1.407
Pliability	–0.345	0.310	–1.014, 0.324
Age	0.040	0.112	–0.009, 0.090
Hyperplasia time	–0.042	0.239	–0.113, 0.028
Narrow airway	1.411	0.062	–0.075, 2.898
Microstomia	–0.322	0.673	–1.825, 1.182
VAS for pain	0.428	0.044	0.011, 0.846
VAS for itch	0.781	< 0.001	0.402, 1.160
mVSS total	0.208	0.068	–0.015, 0.431

PSQI Pittsburgh sleep quality index, *CI* confidence interval, *VAS* visual analogue scale, *mVSS* modified Vancouver Scar Scale

severe pain, and mental stress [2, 4, 6]. All of these could affect patients' sleep quality and mental functioning [43, 44]. A recent study showed that mental functioning was closely associated with sleep quality and low mental functioning could disturb patients' sleep [45]. Moreover, sleep disturbances could promote people in weariness, bewilderment, anxiety, and even depression, which form a positive feedback aggravation on sleep disturbances, ultimately driving HS patients far away from complete psychological and physiological recovery [46–48]. Therefore, executing risk assessment and solving sleep problems to further predict mental functioning prevent and treat mental illness in patients with HS are of high clinical importance [49]. Our study has applied a systematic statistical way to demonstrate that patients with burn scars did suffer from sleep disorders and the following data model clarified that age, hyperplasia time of scar, microstomia, narrow airway, pain, pruritus, and scar appearance were the significant risk factors for sleep disorders.

From the standpoint of PPPM/3PM, effective identification of reliable biomarkers is of much significance to intervene diseases. Of note, what we can do first is to evaluate these biomarkers to harvest valuable predictive information of disease onset or prognosis. Once high-risk groups are early predicted, timely protective measures including pharmacological or non-pharmacological interventions could be taken to slow down the disease progression. Furthermore, specific risk factors could also guide subsequent individualized treatment. In this study, we have identified reliable risk factors of sleep disorders through analyzing the characteristics of sleep patterns in HS patients. The results of the research could supply a scientific basis for early screenings of groups at high risk, achieve early prediction and primary prevention of sleep disorders, and provide an individualized therapy, which prompt the paradigm shift from reactive medicine to the advanced strategy by practicing PPPM/3PM concepts.

PSQI, developed in 1989 by Dr. Buysse at the University of Pittsburgh, is the most widely and reliable scale to evaluate the sleep quality of patients with sleep disorders and mental disorders [30]. Table 2 showed that from PSQI analysis, nearly three-quarters (76.6%) of patients did have sleep disorders, which was much higher than that of general population (8.6–30%) [45, 50, 51]. They had high PSQI total scores, and defects in sleep quality, sleep latency, sleep efficiency, sleep disturbances, and daytime dysfunction (Table 2). This suggested that sleep disorders were common in patients with burn scars, and the changes in sleep patterns could also increase the severity of the patients' condition. At present, many studies used subjective scales to evaluate sleep quality, extremely lacking objective data. The method of questionnaire survey is largely limited by personal bias and low reliability [52, 53]. In the study, we employed ECG recorder to objectively monitor sleep parameters with the purpose to accurately reflex the patient's sleep quality[15, 54, 55]. The results showed that the deep sleep time and the deep sleep efficiency of patients with burn scars were significantly lower, suggesting that their memory and rest were not good, which would affect their study and work as well as health and well-being (Table 4).

In a normal sleep cycle, early deep sleep is crucial to maintain a satisfying sleep quality. Frequent cortical arousals may lead to sleep fragmentation and even sleep deprivation, and most sleep disturbances are found to be related to nocturnal awakenings and insomnia [56–58]. Study indicated that REM comprised 20 to 25% of the total sleep period [59]. Depression have been reported to be associated with the disruption of REM sleep, thereby causing sleep disorders [60]. In our study, HS patients took more time to fall asleep, which would have serious effects on sleep quality. Moreover, awakening time was significantly longer in patients with burn scars, thus reducing awakening time and increasing sleeping time are of much importance for improving sleep of scar patients. When the apnea index is ≥ 5/h, sleep-disordered breathing is considered present [61]. In our study, most scar patients (78.6%) had apnea index ≥ 5 (Table 4). This phenomenon may be associated with the application of garment pressure therapy for HS [62, 63]. Therefore, the potential side effect of sleep-disordered breathing or obstructive sleep apnea should be considered

before pressure therapy, specifically on the susceptible patients with high BMI, facial and neck scars.

From the perspective of PPPM/3PM, clarification of cost-effective and reliable risk factors is crucial for disease prevention. Therefore, it is imperative to explore the predictors for the sleep quality and solving sleep problems to further improve mental functioning to promote a predictive, preventive, and individual therapy in burn scar patients. In the current study, we hypothesized that patients' demographic characteristics and scar evaluation might be instrumental to predict the risk factors of sleep disorder for personalized supervision of patients with burn scars by prevention tailored to predicted risks. Several published studies reported the epidemiology and risk factors for hypertrophic burn scarring. Major risk factors for HS formation included sex, age, genetic predisposition [extracellular matrix (ECM) molecules, hTERT, MC1R, single-nucleotide polymorphism (p53)], immunological responses of the patient, injury type, wound size and depth, anatomical site, and mechanical tension of the wound [2, 36, 64–71]. However, only a few investigated HS-related sleep disorders [15]. Early trauma has negative effects on sleep during later life, contributing to the long-term deterioration of physiological and psychological health [72]. Sleep disorder complicates the healing process and makes the burn patients more distressed [73, 74]. Physiological pain resulted from tissue damage and dressing change, psychic anxiety caused by changes in appearance, and uncertainty of treatment outcome, can lead to sleep disorders in patients with acute burns and in the initial stages of their treatments [75–78]. The improvement of sleep quality is of great significance for the early wound repair. Excellent wound repair can also reduce scar hyperplasia and improve patients' sleep quality, which is very important for patients' rehabilitation.

This study analyzed the demographic information, medical data, scar characteristics, and sleep quality of HS patients. The results demonstrated that narrow airway, pain, pruritus, and scar appearance may provide excellent predictors for sleep disorders in HS patients (Table 8). Narrow airway was an independent risk factor affecting sleep quality. Along with microstomia, it could affect the patient's breathing comfort and deteriorate sleep quality (Table 7 and Table 8). Therefore, solving airway obstruction is particularly critical for sleep improvement. The mVSS total, which cannot be ignored, was a potent risk factor for sleep disorders in scar patients (Table 7 and Table 8). According to our findings, therapeutic modalities (including triamcinolone, 5-fluorouracil, corticosteroids, and lasers) targeting scar appearance, specifically height, may largely improve sleep quality of HS patients.

Moreover, some participants reported persistent symptoms of scar pain and pruritus (Table 5), which could severely disturb the patients' sleep [15, 79]. Meanwhile, disturbed sleep could reduce the pain tolerance in patients [80]. Studies have shown that medicine intervention of pain and pruritus could promote sleep initiation, and improve sleep quality [15, 81, 82]. Our previous study also showed that the scar patients' sleep quality was correlated with pain and pruritus, and fractional laser treatment can alleviate their pain and pruritus and realize sleep improvement [15]. In this study, multivariate linear regression analysis showed that scar pain and itch were the significant risk factors for sleep quality (Table 8), indicating that the more scar pain and itch, the worse the sleep of scar patients. This suggested that the proper use of painkillers and antipruritic medications could have positive effects on patients' sleep.

Patients with high risks of sleep disorders should adapt non-pharmaceutical or pharmaceutical interventions to alleviate the progression, which effectively contribute to the paradigm shift from reactive medicine to the advanced approach by utilizing PPPM/3PM concepts [83]. This suggests that we can improve sleep by laser therapy and medication. Taking a reasonable dosage of sleeping pills could help in many cases. Medication should be based on the simplest approach to minimize and alleviate symptoms. It can be used as an adjunct to insomnia, cognitive behavioral therapy or experimentation [57, 59]. Changes in burn patients' sleep involve psychological and physiological factors and hence, the solution is a combination of physical and mental rehabilitation. Moreover, studies have shown that the non-reimbursable rehabilitation costs and the high cost of continuous medical care lead to a significant economic burden to patients with burn scars [84]. Anxiety caused by economic stress could also affect patients' sleep quality. In the near future of clinical treatment, predictive diagnosis and timely prevention could be much cost-effective in the management of sleep disorders in HS patients. Moreover, we could target pain, pruritus, narrow airway, or scar appearance based on individuality to comprehensively prevent and treat sleep disorders of HS patients.

Limitations

However, our study has the following limitations. First, this was a single-center retrospective study and the sample size was small, with only 128 patients enrolled. Second, this study identified the predictors for sleep disorders in HS patients, but did not determine their practical values mainly in the predictive diagnostics, targeted prevention, and individualized therapy. Therefore, a prospective multi-center and large-sample investigation in the near future should be processed to determine the predictors that can predispose a HS patient to develop sleep disorders and further evaluate their practical values, aiming to promote a predictive, preventive, and personalized medicine in patients with burn scars.

Conclusions and expert recommendations structured

This is the first study to comprehensively assess sleep characteristics of HS patients and systematically identified that narrow airway, pain, pruritus, and scar appearance may be excellent predictors for sleep disorders in HS patients, which could provide a basis for early prediction of sleep disorders in HS patients and effective identification of somnipathy progression (Predictive). Apart from the early predictive approach, comprehensive analyses of risk factors in HS patients could guide the primary targeted prevention for the progression of sleep disorders and more severe consequences. The HS patients in risks of narrow airway, age, hyperplasia time of scar, microstomia, pruritus, pain, or scar appearance (the primary targeted prevention: narrow airway, age, hyperplasia time of scar, and microstomia; the secondary targeted prevention: pruritus, pain, and scar appearance especially height) should attract more attention of the health care providers (Preventive). Furthermore, new preventive and therapeutic strategies are strongly recommended for comprehensive secondary care considering the primary predictive approach. An aggressive pain and pruritus treatment of cost-effective protection needs to be tailored to the personalized patient profile. In the light of the risk identification results including age, hyperplasia time of scar, microstomia, narrow airway, pruritus, pain, and scar appearance, primary prevention or secondary personalized therapy for sleep disorders in high-risk groups is of great importance to control the disease progression and realize the risk reduction (Personalized medicine).

Overall, patients with burn scars did experience sleep disorders and further studies should be implemented to determine the practical values of assessing these significant predictors for sleep disorders, involving the predictive diagnostics, targeted prevention, and individualized therapy. This paradigm shift from reactive cure to advanced therapy fully confirms the application of PPPM/3PM. According to this study, HS patients with risks of age, hyperplasia time of scar, microstomia, narrowed airways, pruritus, pain, and scar appearance could early recognize sleep health issues and timely require individualized supports from rehabilitation exercise, psychotherapy, physical cure, and even pharmaceutical intervention, finally achieving high-QoL and complete social reintegration.

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Author contribution Yongjun Zheng, Kaiyang Lv, and Shichu Xiao designed this study. All authors managed the study with regard to surgery, patient care and data collection. Data analysis was performed by Huazhen Liu, Futing Shu, and Chao Ji. The first draft of the manuscript was written by Huazhen Liu, Futing Shu, and all authors commented on previous versions of the manuscript. Huazhen Liu, Futing Shu, and Chao Ji revised this manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The research protocol was approved by the Changhai hospital local ethics committee (CHEC2014086) and with the 1964 Helsinki declaration.

Consent to participate All study participants provided written informed consent to the study.

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