Retrospective Study

Analysis of Factors Influencing Medical Treatment Outcomes in Herpes Zoster Patients

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Background: The routine treatment for herpes zoster (HZ) focuses on symptom control, including the use of antiviral medication, anticonvulsants, and painkillers. However, the analgesic properties of these medical treatments have been reported to be less than highly effective in some HZ patients. The factors influencing the efficacy of medical treatments for HZ patients are not yet fully understood, warranting further investigation.

Objectives: This study aims to explore the factors influencing the efficacy of medical treatments in HZ patients and provide insights for clinical management of the condition.

Study Design: A retrospective study.

Setting: This retrospective study included 76 individuals diagnosed with HZ who met specific inclusion criteria and were receiving treatments at Changde Hospital between February 2023 and December 2023.

Methods: The patients were divided into 2 groups. Data on age, gender, family history, comorbidities, prior use of antiviral drugs, rash location, skin lesion severity, HZ stage, visual analog scale (VAS) scores at admission and discharge, and responses to questionnaires were collected and statistically analyzed.

Results: The study revealed no significant differences in gender, family history, comorbidities, prior use of antiviral medication, rash location, or VAS scores between the 2 groups of patients. However, the results demonstrated a significant correlation between the analgesic effects of medical treatments and age, skin lesion severity, disease duration, and plasma adrenocorticotropic hormone (ACTH) and cortisol levels. Depression, anxiety, and sleep quality also influenced the treatment outcomes.

Limitations: The limitations of this study include the relatively small sample size and the lack of long-term follow-up data.

Conclusion: Age, skin lesion severity, disease duration, depression, sleep quality, and levels of anxiety and stress hormones are important factors influencing the efficacy of medical treatments for HZ patients.

Key words: Herpes zoster; postherpetic neuralgia; skin lesion; adrenocorticotropic hormone; cortisol

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The varicella-zoster virus (VZV), which belongs to the human alpha herpes virus family, typically establishes latency in the body after the initial infection. This latent virus can reactivate, leading to the development of herpes zoster (HZ), commonly known as shingles (1,2). In China, the estimated incidence of HZ is approximately 7.7%, with individuals facing a lifetime risk of approximately 30% (3). Various factors can trigger the reactivation of VZV, including conditions such as malignancies, immune deficiencies, transplantations, autoimmune diseases, stress, and immunosuppressive therapies (4). Individuals with compromised immune systems, especially those with reduced cell-mediated immunity, face a higher risk of VZV reactivation.

The onset of HZ is typically marked by initial symptoms like headache, mild fever, and abnormal skin sensations before the characteristic rash appears. This rash tends to be unilateral, following specific nerve pathways, and progresses from maculopapular lesions to vesicles that eventually crust over within one to 2 weeks (5). Standard treatment for HZ focuses primarily on managing symptoms, utilizing topical agents such as lidocaine or capsaicin as well as oral medications like gabapentin, pregabalin, or tricyclic antidepressants (6,7). Immune enhancement and antiviral therapies play crucial roles in managing the condition. Despite these treatment options, some HZ patients, particularly those experiencing postherpetic neuralgia (PHN), may not achieve adequate pain relief with conventional approaches.

Cortisol, a stress hormone produced by the adrenal cortex, is known to increase in individuals experiencing stress and poor sleep quality (8). The secretion of adrenocorticotropic hormone (ACTH), which regulates cortisol levels, is controlled by corticotropin-releasing hormone (CRH), released by the hypothalamus in response to low cortisol levels and stress feedback (9). A study involving HZ patients over the age of 50 identified stress, sleep disturbances, depression, and recent weight loss as risk factors for HZ (10). In a trier social stress test comparing individuals with severe depression to healthy individuals, it was found that cortisol levels were significantly higher in the former group than in the latter (11). Additionally, risk factors for PHN may be associated with age, the side of the body where the skin lesions are present, overall clinical presentation, and the severity of pain during the acute phase of HZ (4).

However, the factors that influence the efficacy of drug treatments remain uncertain. This current study aims to investigate and identify potential factors affecting responses to HZ drug treatments. To this end, we have collected comprehensive data on HZ patients from our pain medicine department, adhering to standardized exclusion criteria. All patients completed questionnaires to evaluate the intensity of their pain (using the Visual Analog Scale), their levels of depression, and the quality of their sleep. Additionally, we have gathered biochemical analysis data, including serum levels of cortisol and ACTH, to further explore potential factors that may impact the effectiveness of drug treatments.

METHODS

Patients

This study had a retrospective design. Additionally, this study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics committee of Changde Hospital, Xiangya School of Medicine, Central South University (First People's Hospital of Changde, No. 2023-003-02). All patients provided written informed consent. The study included a total of 76 HZ patients aged 50-80 years who met specific inclusion criteria: they were experiencing persistent HZ-related pain with a VAS score of $\geq$ 5, were aged between 50 and 80 years, had no history of psychiatric or neurological disorders, and were receiving treatments at Changde Hospital, Xiangya School of Medicine, Central South University (First People's Hospital of Changde) between February 2023 and December 2023. Exclusion criteria encompassed HZ patients with mental health conditions, severe cardiocerebrovascular or hepatorenal insufficiency, disorders related to the hypothalamic-pituitary-adrenal cortical axis (HPA axis), or infectious diseases such as tuberculosis and AIDS, or who had used hormone medications such as dexamethasone, hydrocortisone, or methylprednisolone within 2 months before admission.

Upon admission, the demographic and clinical data of HZ patients were collected, including gender, age, duration of illness, VAS score for pain assessment, extent of skin lesions, presence of comorbidities, family medical history, and location of rash. Additionally, patients completed questionnaires to evaluate their pain levels, depressive symptoms, and sleep quality. These assessments included the Simple McGill Scale for pain evaluation, the Patient Health Questionnaire-9 (PHQ-9)

for depression screening, the Pittsburgh Sleep Quality Index (PSQI) for sleep assessment, and the State-Trait Anxiety Inventory (STAI) for anxiety assessment. HZ patients were divided into 2 groups based on their response to medical treatments: those whose VAS score decreased to equal or more than 3 were classified into Group A, while those whose VAS scores saw less reduction were classified into Group B.

Plasma Collection and Assay

Venous blood samples were drawn from HZ patients at 6 a.m. using vacuum tubes containing EDTA-K2. Following 5 minutes of centrifugation at 3000 rpm, the plasma was separated and stored at -80°C. The levels of cortisol (CORT) and adrenocorticotropic hormone (ACTH) in the plasma were measured using the chemiluminescence immunoassay method with the IMMULITE® 1000 automatic chemiluminescence instrument (Siemens Healthineers), in accordance with the manufacturer's guidelines. The CORT assay kit was obtained from Beijing North Biotechnology Research Institute, while the ACTH assay kit was supplied by Roche.

Statistical Analysis

The data were presented as mean ± standard division of the mean (mean ± SEM). Statistical analysis included the use of the Chi-square test for categorical data and the unpaired Student's t-test for continuous variables. Data analysis was performed using SPSS 26.0 (IBM Corp.), and GraphPad Prism 8 (GraphPad Software, LLC) was used for creating charts. A significance level of $P < 0.05$ was considered statistically significant.

RESULTS

General Characteristics of Patients

In the present study, 76 HZ patients aged 50-80 years were included based on the inclusion and exclusion criteria outlined in Table 1. The results revealed that 73.68% of HZ patients presented with VAS scores of 7-10 upon admission, 40.79% had comorbidities, 50% had no family history of HZ, 78.9% were over 60 years old, 52.63% had thoracic region involvement, and 72.37% were in the acute stage of the disease (Table 1).

Furthermore, the PHQ-9 scale was utilized to evaluate the levels of depression in patients. Based on the ranges of the PHQ-9 scores, the degree of depression was categorized as follows: no depression (0-4), mild depression (5-9), moderate depression (10-

Table 1. *Clinical characteristics of HZ patients.*

Characteristics	Groups	Patients
Age	50-59 years	16 (21.1%)
	60-69 years	33(43.4%)
	70-80 years	27 (35.5%)
	Average age	66.34
Gender	Male	29 (38.2%)
	Female	47 (61.8%)
Degree of skin lesion	Mild	24 (31.58%)
	Moderate	27(35.53%)
	Severe	25 (32.89%)
Comorbidities	Yes	31 (40.79%)
	No	45 (50.21%)
Took antiviral drugs before admission?	Yes	46 (60.53%)
	No	30 (39.47%)
Family history	Yes	38 (50%)
	No	38 (50%)
VAS scores on admission	5-6 points	20(26.32%)
	7-10 points	56 (73.68%)
Location	V1-3	15 (19.74%)
	C1-8	14 (18.42%)
	T1-12	40 (52.63%)
	L1-5	6 (7.89%)
	S1-5	2 (2.63%)
	L+S C+T	8 (10.53%) 53 (69.74%)
Stage of HZ	AHZ SHZ PHN	55 (72.37%) 11(14.47%) 10 (13.16%)

AHZ: acute herpes zoster, SHZ: subacute herpes zoster, PHN: postherpetic neuralgia.

14), and severe depression (20-27). The results indicated that 40.79% of HZ patients had no depression, as depicted in Table 2. Additionally, the PSQI scale was employed to assess the sleep quality experienced by HZ patients. Sleep quality was classified as very good (0-5), good (6-10), average (11-15), and very poor (16-21). Statistical analysis revealed that 56.58% of HZ patients experienced sleep disturbances, as detailed in Table 2.

The Analgesic Effect of Medical Treatments Is Correlated with Various Factors, Including Age, Degree of Skin Lesions, and Course of the Disease

Upon admission, all HZ patients in the study received medical treatments, which included antiviral drugs (acyclovir, valaciclovir), anticonvulsant drugs

Table 2. *PHQ-9 and PSQI scores of HZ patients.*

	Groups	Number of patients (n)
PHQ-9 score	0-4	31 (40.79%)
	5-9	27 (35.52%)
	10-14	8 (10.53%)
	15-19	8 (10.53%)
	20-27	2 (2.63%)
PSQI score	0-5	19 (25.00%)
	6-10	14 (18.42%)
	11-15	36 (47.37%)
	16-21	7 (9.21%)

PHQ-9: Patient Health Questionnaire-9 for depression screening, PSQI: Pittsburgh Sleep Quality Index for sleep assessment.

(pregabalin, gabapentin), and painkillers (tramadol, Tylox [oxycodone and acetaminophen]). Based on the analgesic effect of the medical treatments, the patients were divided into 2 groups: Group A (VAS decreased by 3 or more) and Group B (VAS decreased by less than 3). Patients in Group B, who experienced less significant pain relief than those in Group A, might have received additional interventional treatments such as nerve blocks, pulsed radiofrequency, and spinal cord electrical stimulation.

This study included 38 patients in each group, and the distributions of various factors such as age, gender, degree of skin lesion, comorbidities, antiviral treatment history, family history, VAS score on admission, location, and stages of HZ were compared between the 2 groups (Table 3). The analysis revealed several significant findings:

1) Age: Patients in Group B were significantly older than were those in Group A, with a higher proportion of patients over 60 years old in Group B (Fig. 1A).

2) Degree of skin lesions: Group B had a higher percentage of patients with moderate and severe stages of skin lesions than did Group A.

3) Course of the disease: Patients in Group A were predominantly in the acute stage of the disease, while almost half of the patients in Group B were in the stages of subacute herpes zoster (SHZ) and postherpetic neuralgia (PHN) (Table 3).

These results indicate significant differences in age, degree of skin lesions, and disease course between Group A and Group B, highlighting the importance of considering these factors in the management and treatment of herpetic neuralgia.

Depression and Sleep Conditions Can Significantly Impact the Outcomes of Medical Treatments in HZ Patients

On admission and at discharge, there was no statistical difference in the VAS scores between HZ patients in the 2 groups ($P > 0.05$, Fig. 1B, Table 4). However, the post-treatment VAS scores were significantly higher in Group B ($P < 0.05$, Fig. 1B, Table 4). The Simple McGill Scale was utilized to evaluate the sensory and emotional conditions of each patient, with the Pain Rating Index (PRI) score and Present Pain Intensity (PPI) score as key components. The PRI score is the sum of the emotion item score and sensory item score, the latter including descriptions of various degrees of pain such as stabbing pain, tingling pain, burning pain, and tenderness. The emotion item score comprises weakness, boredom, fear, and guilt scores. In this study, our results indicated no statistical differences in PRI scores and PPI scores between the Group A and B patients ($P > 0.05$, Fig. 2A and B, Table 4).

Furthermore, we assessed depression, sleep conditions, and anxiety in HZ patients by comparing key parameters of the PHQ-9, PSQI, and STAI, respectively. The findings revealed that the PHQ-9, PSQI, and STAI scores of HZ patients in Group B were significantly higher than those in Group A. This result suggests that depression, anxiety and sleep conditions may influence the outcomes of medical treatments in HZ patients ($P < 0.05$, Figs. 2 C, 2D, 2E, and 2F, Table 4).

Patients Who Experienced Poor Outcomes from Medical Treatment Exhibited Elevated Levels of Stress Hormones

Cortisol (CORT), a well-known stress hormone associated with pain, sleep disturbances, and depressive symptoms, plays a crucial role in modulating these physiological responses (12). Furthermore, adrenocorticotropic hormone (ACTH), a hormone that stimulates the synthesis and release of cortisol, is known to be upregulated during periods of heightened stress and depression (13). To investigate this relationship further, we conducted an analysis of the plasma CORT and ACTH levels in the HZ patients categorized into Groups A and B. The results revealed a significantly greater elevation in both CORT ($P < 0.05$, Fig. 3A) and ACTH ($P < 0.01$, Fig. 3B) concentrations among Group B patients than in those within Group A. These findings highlight the potential role of stress hormones in the pathophysiology of Group B and suggest a possible mechanism by which stress may exacerbate symptoms

Table 3. *Clinical characteristics of Group A and B.*

Characteristics	Group A	Group B	*P*-value
Age			
50-59 years	11 (28.95%)	5 (13.16%)	
60-69 years	16 (42.10%)	17 (44.74%)	0.025
70-80 years	11 (28.95%)	16 (42.10%)	
Average age	64.34	68.32	
Gender			
Male	12 (31.58%)	17 (44.74%)	0.238
Female	26 (68.42%)	21 (55.26%)	
Skin lesion			
Mild	20 (52.63%)	4 (10.52%)	
Moderate	10 (26.32%)	17 (44.74%)	0.000
Severe	8 (21.05%)	17 (44.74%)	
Took antiviral drugs before admission?			
Yes	24 (63.16%)	22 (57.89%)	0.723
No	14 (36.84%)	16 (42.11%)	
VAS scores on admission			
5-6 points	11 (28.95%)	9 (23.68%)	0.988
7-10 points	27 (71.05%)	29 (76.32%)	
Location			
V1-3	2(5.26%)	12 (31.58%)	
C1-8	8 (21.05%)	7 (18.42%)	
T1-12	23 (60.53%)	17 (44.74%)	
L1-5	4 (10.53%)	2 (5.26%)	0.014
S1-5	2 (5.26%)	0 (0%)	
C+T	30 (81.58%)	23 (63.16%)	
L+S	5(13.15%)	2 (5.26%)	
Stage of HZ			
AHZ	35 (92.11%)	20 (52.64%)	
SHZ	2 (5.26%)	9 (23.68%)	0.001
PHN	1 (2.63%)	9 (23.68%)	

AHZ: acute herpes zoster, SHZ: subacute herpes zoster, PHN: postherpetic neuralgia.

in these patients. Further research into the interplay between stress hormones and patients in Group B could offer valuable insights into the underlying mechanisms and help in the development of targeted therapeutic interventions.

DISCUSSION

This study aimed to investigate the factors influencing the efficacy of medical treatments on HZ patients. Our findings suggest that various factors, including age, degree of skin lesions, disease duration, depression, anxiety, and sleep conditions influence the
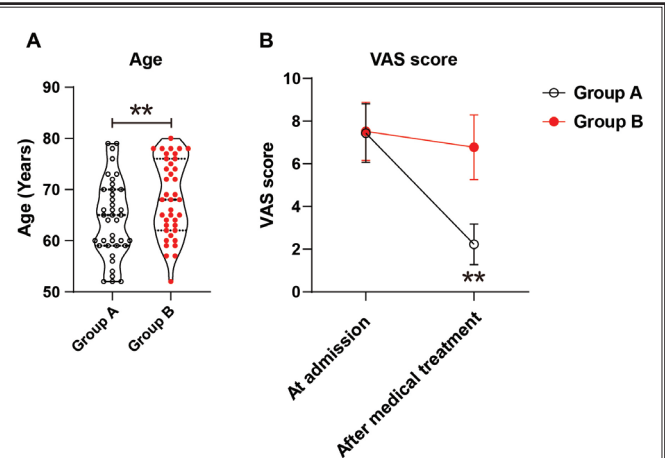

Fig. 1. *The age and VAS score of herpes zoster (HZ) patients in Group A and Group B.*
*(A) The age of HZ patients between Group A and Group B. (B) The VAS score of HZ patients on admission and after medical treatment between the 2 groups. The data are presented as mean ± SEM, and statistical significance is indicated by **P < 0.01. The statistical analysis was conducted using an unpaired Student's t-test.*

Table 4. *Differences between answers to questionnaire items between Groups A and B.*

	A (Mean ± SEM)	B (Mean ± SEM)	*P*-value
VAS scores on admission	7.44 ± 1.38	7.52 ± 1.37	0.806
VAS scores before other treatments		6.78 ± 1.52	
VAS score at discharge	2.23 ± 0.95	2.50 ± 1.29	0.323
PRI scores	15 ± 7.69	16.63 ± 6.69	0.327
Score of sensory items	11.63 ± 5.32	12.89 ± 5.03	0.425
Score of emotion items	3.36 ± 3.58	4.00 ± 3.27	0.292
PPI scores	2.97 ± 0.88	3.21 ± 0.74	0.210
PHQ-9 score	5.63 ± 5.11	8.00 ± 6.03	0.076
PSQI score	8.92 ± 5.00	11.32 ± 4.24	0.027
Score of state anxiety	39.37 ± 10.20	46.39 ± 11.34	0.006
Score of trait anxiety	31.66 ± 6.25	37.97 ± 9.50	0.001

VAS: Visual Analog Scale, PRI: Pain Rating Index, PPI: Present Pain Intensity, PHQ-9: Patient Health Questionnaire-9, PSQI: Pittsburgh Sleep Quality Index.
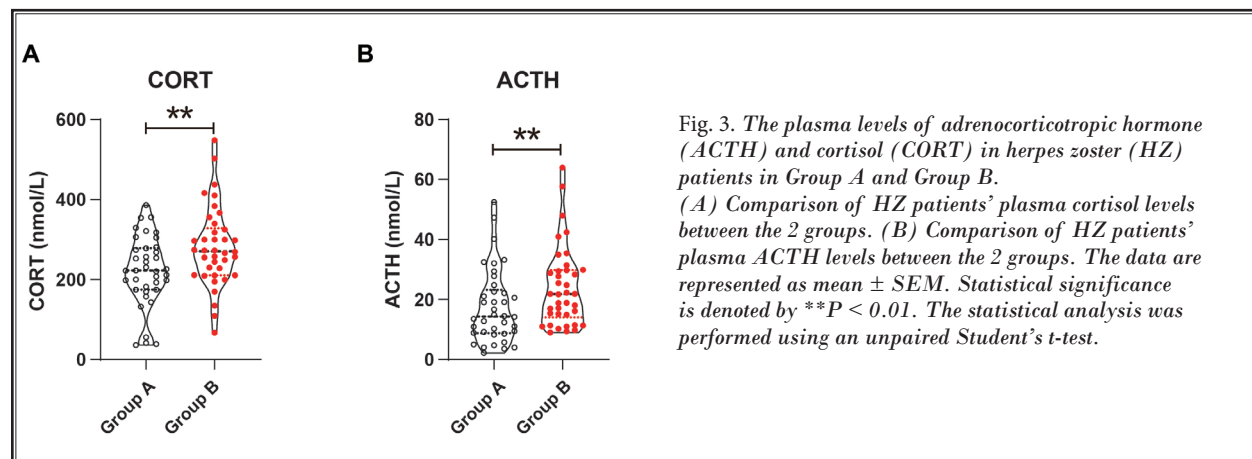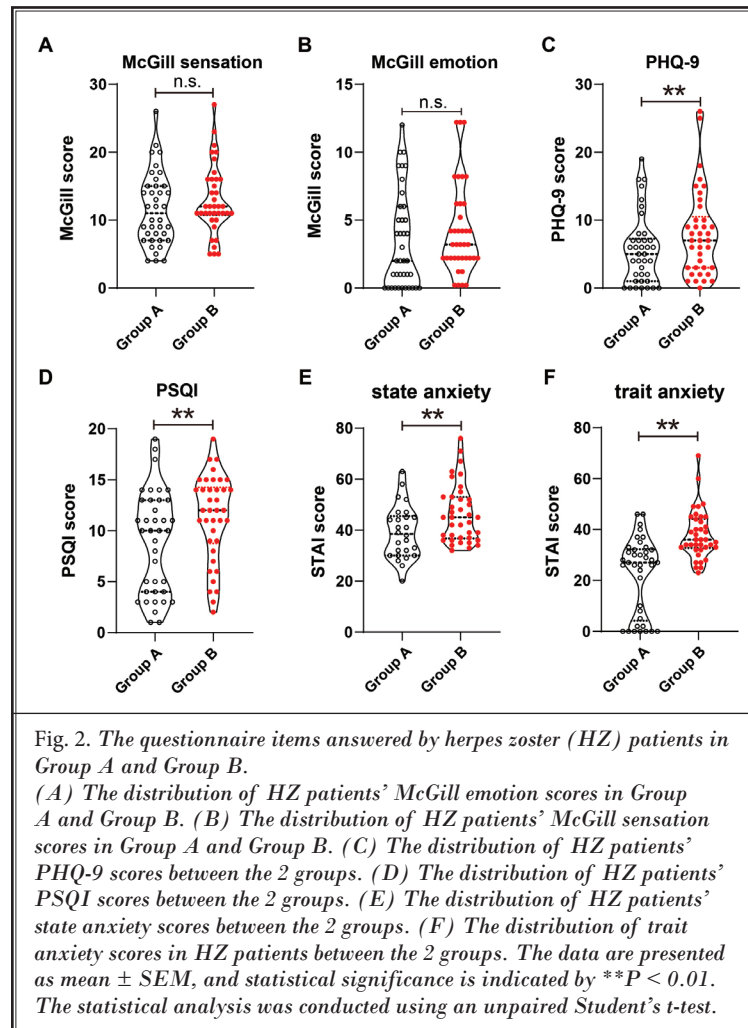
analgesic effect of the medical treatments that HZ patients receive.

Fig. 2. *The questionnaire items answered by herpes zoster (HZ) patients in Group A and Group B.*
*(A) The distribution of HZ patients' McGill emotion scores in Group A and Group B. (B) The distribution of HZ patients' McGill sensation scores in Group A and Group B. (C) The distribution of HZ patients' PHQ-9 scores between the 2 groups. (D) The distribution of HZ patients' PSQI scores between the 2 groups. (E) The distribution of HZ patients' state anxiety scores between the 2 groups. (F) The distribution of trait anxiety scores in HZ patients between the 2 groups. The data are presented as mean ± SEM, and statistical significance is indicated by **P < 0.01. The statistical analysis was conducted using an unpaired Student's t-test.*

It is widely recognized that the incidence of HZ rises with age (14), and certain autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus can increase the risk of HZ (15). Our results demonstrated that age and comorbidities were major risk factors for HZ, findings consistent with previous studies. Interestingly, we found that 50% of HZ patients had no family history of the condition, which aligned with earlier reports suggesting a weak correlation between family history and HZ progression (16,17).

Our analysis revealed several key factors that appeared to have a more significant impact on the poor treatment outcomes observed in Group B patients. Among those factors, age emerged as particularly influential, with patients over 60 years old showing a markedly reduced response to medical treatments. This age-related effect could be attributed to decreased immune function and slower healing processes in older individuals, as suggested by previous studies (14,18).

The severity of skin lesions also played a crucial role, with moderate to severe lesions correlating strongly with poorer outcomes. This finding suggests that the extent of viral replication and tissue damage may be a critical determinant of treatment efficacy. Furthermore, the duration of the disease showed a significant impact, with patients in the subacute and PHN stages responding less favorably to treat-

Fig. 3. *The plasma levels of adrenocorticotropic hormone (ACTH) and cortisol (CORT) in herpes zoster (HZ) patients in Group A and Group B.*
*(A) Comparison of HZ patients' plasma cortisol levels between the 2 groups. (B) Comparison of HZ patients' plasma ACTH levels between the 2 groups. The data are represented as mean ± SEM. Statistical significance is denoted by **P < 0.01. The statistical analysis was performed using an unpaired Student's t-test.*

ment compared to those in the acute phase. This result highlights the importance of early intervention in HZ management, as supported by earlier research (19).

From a statistical perspective, our analysis indicated that elevated levels of stress hormones (cortisol and ACTH) were the most reliable predictors of poor pain control outcomes. The significantly higher levels of these hormones in Group B patients ($P < 0.01$ for ACTH, $P < 0.05$ for cortisol) suggest a strong association between stress physiology and treatment resistance. This finding is consistent with previous studies that have reported higher cortisol levels in individuals with sleep disorders and severe depression (20,21).

Additionally, the presence of depression and sleep disturbances, as indicated by Group B's higher PHQ-9 and PSQI, were also statistically significant predictors of poor treatment outcomes. This association underscores the importance of addressing psychological factors and sleep quality in the management of HZ, a concept supported by earlier research on the relationship between psychological well-being and HZ outcomes (10,11).

In terms of relative impact, our data suggest the following hierarchy of factors influencing poor outcomes, from most to least impactful: elevated stress hormone levels, advanced age (> 60 years), severe skin lesions, longer disease duration (subacute and PHN stages), and presence of depression and sleep disturbances. These findings provide valuable insights for clinicians in identifying patients at higher risk of poor treatment outcomes and may guide more personalized and comprehensive treatment approaches for HZ patients.

Notably, 40.79% of HZ patients in our study had no depression, while 56.38% experienced sleep disorders. The emotional items of the PHQ-9 score, PSQI score, and STAI score of patients who experienced poor outcomes from medical treatments were higher than those of patients who had seen good outcomes. These results imply that the efficacy of medical treatments might be mainly related to the poor psychological condition and the quality of sleep, further emphasizing the need for a holistic approach to HZ management.

Limitations

Limitations of this study include the relatively small sample size and the lack of long-term follow-up data. Additionally, the study did not investigate the potential impact of other factors, such as immune status, medication adherence, and lifestyle habits, on the efficacy of medical treatments in HZ patients. Future studies with larger sample sizes and longer follow-up periods are needed to further explore the factors influencing HZ patients' treatment outcomes.

CONCLUSION

In conclusion, our findings suggest that age, degree of skin lesions, disease duration, depression, anxiety, and sleep conditions significantly influence the analgesic effect of medical treatments received by HZ patients. Emotional well-being and sleep quality may play critical roles in the effectiveness of medical interventions. Clinically, it is essential to consider these factors when devising treatment strategies for HZ patients, potentially leading to more personalized and effective management approaches.

Author Contributions

Wenqin Sun, Quan Zhou, Huajing Guo, Daobo Pan, Xuefeng Wu and Hao Wang were responsible for the concept and design of the study; Wen Sun, Zhejia Hu, Lei Peng, and Xuefeng Wu were involved with experimental and analytical aspects of the manuscript; Wenqin Sun, Zhejia Hu and Quan Zhou performed data interpretation, presentation, and the writing of the manuscript. Wenqin Sun and Hao Wang obtained funding.

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