

Original Article

Therapeutic effect of alternating red and blue light irradiation combined with collagen in patients with acne vulgaris and the risk factors of short-term recurrence

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Abstract: Objective: To explore the therapeutic effect of alternating red and blue light irradiation combined with collagen in patients with acne vulgaris and the risk factors of short-term recurrence. Method: A retrospective analysis was conducted on 105 patients with acne vulgaris treated in Baoji Hospital of Traditional Chinese Medicine from January 2019 to February 2020. 50 patients received conventional treatment (Pumen red and blue light) were taken as the control group, and the other 55 patients treated with collagen dressing on the basis of control group were taken as the research group. Clinical efficacy, changes of serum interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) before and after treatment, and the occurrence of adverse reactions were compared between the two groups of patients. The scores of inflammatory skin lesions, facial seborrhea scores, stratum corneum water content and transepidermal water loss (TEWL) were compared before and after the treatment. The 1-year review records of patients were queried, and they were divided into a relapse group and a non-relapse group according to the recurrence situation. Logistic regression was used to analyze the risk factors affecting the recurrence of the patients. Results: The clinical efficacy of the patients in research group after treatment was significantly higher than that in the control group ($P < 0.05$). IL-1 β and IL-6 in the serum of patients after treatment were markedly decreased, and such decline in the research group was more evident after treatment ($P < 0.05$). The incidence of adverse reactions, the scores of inflammatory skin lesions, and facial seborrhea and TEWL in the research group after treatment were all lower than those in the control group (all $P < 0.05$), while the water content of the stratum corneum was higher comparatively ($P < 0.05$). 17 patients were confirmed with recurrence within 1 year after treatment. Logistic regression analysis found that age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 were risk factors for recurrence. Conclusion: Alternating red and blue light irradiation combined with collagen can improve the treatment efficacy in patients with acne vulgaris. And indexes like age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 are risk factors affecting the recurrence of patients.

Keywords: Red and blue light, collagen patch, acne vulgaris, short-term recurrence, risk factors

Introduction

Acne vulgaris is a common dermatological disease in adolescence and often lasts into adulthood. Only a small number of patients over 30 have trouble in recovering [1]. The exact mechanism of acne has not been fully confirmed currently, but most studies claimed that excessive keratinization of hair follicle epithelium, excessive secretion of sebaceous glands, and inflammatory reactions increase the incidence of acne [2]. It is believed that the causes of acne

vulgaris include hyperactivation of androgen receptors in sebocytes to stimulate sebum production, abnormal keratinization of pilosebaceous ducts, proliferation of *P. acnes*, inflammation and immune responses [3]. Past survey has shown that acne vulgaris was a common disfiguring skin disease with high incidence [4]. Another one [5] revealed that the incidence of acne in the Chinese population is above 80%, with repetitive course of disease and long duration. Post-inflammatory hyperpigmentation or even permanent scars may be left in severe

Analysis of risk factors for short-term recurrence after acne treatment

cases, causing greater psychological pressure and economic burden to patients, especially to adolescents.

There are great differences in the selection of acne treatment, and the efficacy of some treatment methods is uncertain and lacks support of evidence-based medicine [6]. In recent years, more and more studies have been conducted on the interaction between laser and tissue, including research on bacterial colonization of the epidermis, sebaceous gland function, and porphyrin metabolism. A series of new lasers and light source equipment have emerged for acne treatment [7]; red and blue light irradiation treatment is found to be one of those to repair inflammatory acne and relieve sunburn with good efficacy [8]. Single application of that, however, will cause different degrees of skin burning, dryness, flushing and other adverse symptoms [9]. Collagen has the functions of moisturizing, whitening, anti-wrinkle, freckle removal, etc., which can be extensively applied in beauty products to improve the microcirculation of epidermal cells, promote skin tissue metabolism, and accelerate skin tissue regeneration and repair [10]. However, the factors affecting the short-term efficacy and recurrence after the combined irradiation and collagen treatment are still up for debate.

In this study, we aimed to analyze the therapeutic effect of combined treatment of alternating red and blue light and collagen on patients with acne vulgaris and the risk factors for its short-term recurrence, so as to provide a reference for the clinical treatment of acne vulgaris.

Methods and treatments

Clinical information

A retrospective analysis was conducted on 105 patients with acne vulgaris treated in Baoji Hospital of Traditional Chinese Medicine from January 2019 to February 2020. 50 patients received conventional treatment (Pumen red and blue light) were taken as the control group (CG), and the other 55 patients treated with additional collagen dressing on the basis of CG were taken as the research group (RG). This study was conducted under the approval of the Medical Ethics Committee of Baoji Hospital of Traditional Chinese Medicine (Ethical approval number: BJSZYYY-LWFB-20220905).

Inclusive and exclusion criteria

Inclusion criteria: Patients in line with relevant diagnostic and grading criteria of the “Acne Treatment Guidelines” [11]; patients with no cognitive impairment; patients with good communication skills; patients with complete clinical data.

Exclusion criteria: Patients with recent retinoic acid or antibiotics treatments; patients with light-sensitive skin diseases; patients with severe liver and kidney insufficiency; patients with systemic infection, skin cancer, or mental illness; patients in pregnancy or breastfeeding; patients with allergy to foreign proteins; patients unwilling to cooperate with treatment; patients with intolerance to the treatment method of present study; patients with scar constitution; patients with facial infection.

Instruments and medicines

Common red and blue light: Product model: Carnation-88C, blue light intensity specification: ≥ 100 mW/cm² (light outlet center), wavelength specification: 460 nm \pm 10 nm, energy level: 3; Red light intensity specification: ≥ 100 mW/cm² (light output mouth center), wavelength specification: 640 nm \pm 10 nm, energy level: level 5, irradiation distance: 15-20 cm (Serial number: C88C18C00207; Manufacturer: Shenzhen Pumen Technology Co., Ltd.). Collagen dressing (Guangzhou Chuanger Biological Co., Ltd., 20172640686)

Severity classification of patients

Grade 1: mild acne, mainly manifested as sporadic or multiple blackheads and pimples, which may be accompanied by scattered inflammatory papules; Grade 2: moderate acne, mainly on the basis of first-degree acne with increased number of inflammatory skin lesions and small superficial pustules, of which the inflammation is merely distributed on the face; Grade 3: severe acne, mainly second-degree acne plus deep pustules, principally distributed on the face, neck and chest and back.

Treatment plan

Patients in CG were treated with conventional treatment specifically as follows: before treatment, the skin of patient was thoroughly

Analysis of risk factors for short-term recurrence after acne treatment

cleaned, photographed and archived, with eyes protected with goggles during treatment. Then, alternating red and blue light was conducted, with the treatment unit placed above patient's face and light positioning distance kept at 1-4 cm. Blue light was applied first, then red light. For mild cases, only blue light was used. The treatment was continued for 8 weeks.

Patients in RG were treated with collagen dressings on the basis of CG treatment. Moderate and severe cases were treated with blue-red light irradiation combined with collagen dressings. During the first week of alternating red and blue light therapy, the wound surface was managed once a day, and from the 2nd to the 8th week, it was applied at intervals; mild patients were applied with single blue light combined with collagen dressing.

Inflammatory lesion score

Before each treatment, the patient's front and side were photographed with a high-definition camera, and the acne on the cheek, forehead, and nasal area was carefully observed by the same two dermatologists, and the pustules, erythema, cysts and inflammatory lesions such as papules were scored. Lesion pain, color change, type and number of skin lesions were scored 3 points each, with a total score of 12 points. Higher scores indicate more severe inflammatory skin lesions [12].

Facial seborrhea score

After facial cleaning, the patient was required to wait for 30 minutes in a test room (25°C, 50% humidity). The SebumeterSM815 skin oil measuring instrument provided by German CK Company was used to measure the degree of facial oil spillage, with a total score of 10. The more severe the facial seborrhea, the higher the score [13].

Stratum corneum hydration

CM825 skin physiology detector (Courage + Khazaka Electronic GmbH, Germany) was used to detect the left and right cheeks three times by means of continuous contact measurement, and the average value was taken to express the facial skin moisture content in percentage.

Transepidermal water loss (TEWL)

The skin physiology detector (1.5.3) was utilized for water loss detection. The probe was placed on the highest part of the cheekbones, TEWL value within 10 s was then read and the average value was calculated.

Serological index detection

Serum interleukin-1 β and interleukin-6 levels were detected by Enzyme linked immunosorbent assay (Elisa). The kit was from Shanghai Biyuntian Biotechnology Co., Ltd.

Observation indicators

Main outcome measures: The clinical efficacy in the two groups of patients was compared and categorized as follows: recovery (with skin lesions reduction $\geq 90\%$), markedly effective (with skin lesions reduction $\geq 60\%$), effective (with skin lesions reduction $\geq 20\%$), and ineffective (with skin lesions reduction $< 20\%$). Total effective rate = (markedly effective + effective)/total number of cases $\times 100\%$. Inflammatory skin lesion scores, facial seborrhea scores, stratum corneum water content and TEWL were compared before and after treatment. The 1-year review records of the patients were queried, and they were grouped into relapse group and non-relapse group, and logistic regression was applied to analyze the risk factors affecting patients' recurrence.

Secondary observation indicators: Clinical data of the two groups of patients were compared, including changes of IL-1 β and IL-6 before and after treatment, and the occurrence of adverse reactions.

Statistical analysis

All data collected were statistically calculated using SPSS 20.0, and visualized using Graph Pad Prism 8. Enumeration data were analyzed by the chi-square test. Measurement data were expressed as mean \pm standard deviation. Among them, inter-group comparison and intra-group comparison were analyzed by Student t-test and paired t-test, respectively. Kaplan-Meier (K-M) was taken to analyze the recurrence of patients, logistic regression was used to analyze the risk factors of recurrence in

Analysis of risk factors for short-term recurrence after acne treatment

Table 1. Baseline information

Indicators	Control group (n = 50)	Research group (n = 55)	χ^2	P
Age			0.948	0.330
≥ 20 years old	30	38		
< 20 years old	20	17		
Gender			0.349	0.554
Male	21	20		
Female	29	35		
Course of disease			0.292	0.588
≥ 2 years	33	39		
< 2 years	17	16		
Acne severity			0.998	0.606
Grade I	18	25		
Grade II	22	20		
Grade III	10	10		
Education level			2.829	0.092
\geq Senior High School	30	45		
$<$ Senior High School	20	15		
Monthly income			0.216	0.641
≥ 5000 RMB	25	30		
< 5000 RMB	25	25		
Smoking history			0.021	0.883
YES	13	15		
NO	37	40		
History of alcoholism			0.498	0.480
YES	5	8		
NO	45	47		

compared to CG (P = 0.017, **Table 2**).

Changes of serum IL-1 β and IL-6 in patients before and after treatment

After treatment, IL-1 β and IL-6 of the two groups of patients both went markedly lower than those before treatment (both P $<$ 0.05), and levels of those in RG were obviously lower than those in CG (both P $<$ 0.05, **Figure 1**).

Comparison of adverse reactions in patients

The adverse reactions of the two groups of patients were counted, and they were found to be evidently higher in CG than in RG (P = 0.023, **Table 3**).

Changes of skin physiological indexes and symptom scores before and after treatment

After treatment, the inflammatory skin lesion score, facial seborrhea score and TEWL of RG were lower than those of CG, while its hydration of the stratum corneum was higher comparatively (**Figure 2**, P $<$ 0.05).

Statistics on recurrence

By querying the 1-year outpatient records and electronic medical records, we found that 17 patients had recurrence, including 10 patients in the control group and 7 patients in the research group, and no statistical difference was observed between the two groups (P = 0.312, **Table 4**). In addition, K-M curve analysis found that there was no statistical difference in recurrence between the two groups (P = 0.346, **Figure 3**).

Analysis of risk factors affecting recurrence in patients

The patients were grouped according to their relapse status. Through univariate analysis, it

patients with acne vulgaris, and the receiver operating curve (ROC) was drawn to analyze the value of risk factors in predicting the recurrence of patients. P $<$ 0.05 was taken as the significance level.

Results

Baseline information

Subjects were comparable due to insignificant differences observed regarding gender, age, course of disease, acne severity, education level, monthly income, smoking history, and alcoholism history between the two groups (all P $>$ 0.05, **Table 1**).

Comparison of therapeutic effect of patients

Comparing the clinical efficacy of two groups after treatment, it was found that RG held an evidently higher total rate of clinical efficacy

Analysis of risk factors for short-term recurrence after acne treatment

Table 2. Comparison of clinical efficacy between the two groups

Grouping	Recovery	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n = 50)	12 (24.00)	18 (36.00)	7 (14.00)	12 (24.00)	38 (76.00)
Research group (n = 55)	25 (45.45)	20 (36.36)	6 (10.91)	4 (7.28)	55 (92.72)
χ^2					5.674
P					0.017

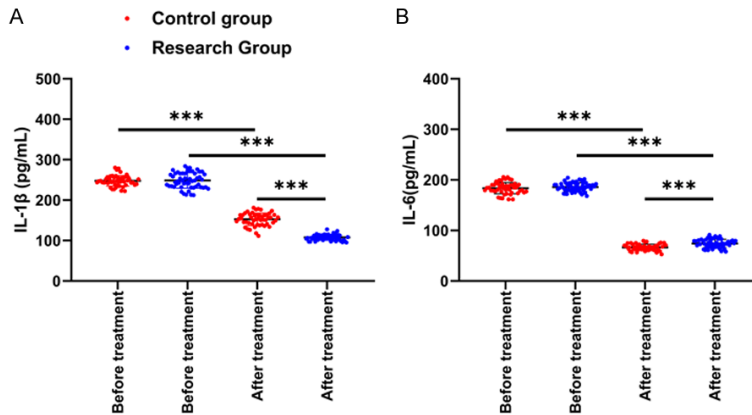


Figure 1. Changes of serum IL-1 β and IL-6 levels in patients before and after treatment. A. Changes of IL-1 β levels in the two groups before and after the treatment. B. Changes of IL-6 levels in the two groups before and after the treatment. Note: *** means P<0.001. IL-1 β : interleukin-1 β ; IL-6: interleukin-6.

was found that age, gender, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 were the factors affecting the recurrence of patients (Table 5). In order to further analyze the results (Table 6), we then conducted multivariate logistic regression analysis and found that age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 were independent risk factors for recurrence (P<0.05, Tables 6, 7).

Clinical value of risk factors in predicting acne recurrence

According to the results of risk factors, we drew the ROC curves of age, monthly income, IL-1 β before treatment, and IL-6 before treatment in predicting acne recurrence and found that the areas under the curve (AUCs) were 0.687, 0.670, 0.707, and 0.730, respectively. Among them, the AUC of IL-1 β and IL-6 before treatment exceeding 0.7 has certain clinical value (Figure 4; Table 8).

Discussion

Acne vulgaris is a common chronic inflammatory disease involving the pilosebaceous glands

[14]. Retinoids or antibiotics were commonly used for the treatment, but the clinical effect was not noteworthy due to factors like long treatment, bacterial resistance and various adverse reactions [15]. Therefore, there is a strong need to find safer and more effective treatment methods to improve the degree of skin lesions in patients.

In this study, it was confirmed that alternating red and blue light irradiation combined with collagen effectively improved the treatment efficacy in patients with acne vulgaris, as well as the changes of skin

physiological indicators and symptom scores, and reduced the incidence of adverse events. Red and blue light irradiation promotes the synthesis of adenosine triphosphate (ATP) through actinic action, increases cell metabolism, promotes cell proliferation, accelerates the release of growth factors, improves local blood circulation, and promotes local repair of fibroblasts, thereby promoting wound healing to a certain extent [16]. Collagen patch, a moisturizing dressing made of collagen stock solution and non-woven fabric, is suitable for skin in sub-healthy state and has the ability to quickly restore the water retention capacity of the stratum corneum [17]. What's more, studies have also found that collagen dressings could promote cell differentiation, movement, chemotaxis and repair of connective tissue; it was convenient for leukocyte mediators to mediate the role of phagocytes, increase local bacterial power, and improve the speed of epidermal regeneration [18, 19]. In the study of Nityavardhana et al. [20], it was found that alternating red and blue light evidently ameliorated the inflammation in patients with moderate and severe acne vulgaris. Another one by Kharazi et

Analysis of risk factors for short-term recurrence after acne treatment

Table 3. Comparison of adverse reactions between the two groups

Grouping	Mild redness	Facial tightness	Erythema	Ache	Exudation	Total incidence
Control group (n = 50)	2 (4.00)	2 (4.00)	2 (4.00)	2 (4.00)	2 (4.00)	10 (20.00)
Research group (n = 55)	1 (1.82)	1 (1.82)	0 (0.00)	0 (0.00)	1 (1.82)	3 (5.46)
χ^2						5.108
P						0.023

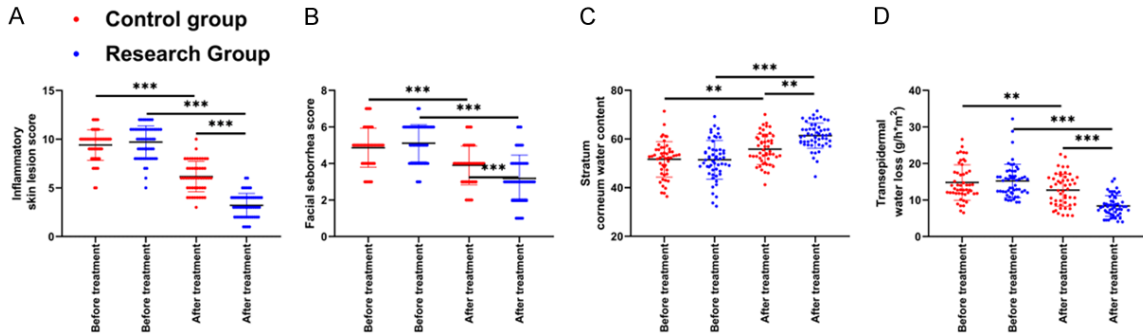


Figure 2. Changes of skin physiological indexes and symptom scores of patients before and after treatment. A. Changes of inflammatory lesion score in the two groups before and after treatment. B. Changes of facial seborrhea score in the two groups before and after treatment. C. Changes of stratum corneum hydration in the two groups before and after treatment. D. Changes of transepidermal water loss in the two groups before and after treatment. Note: ** means $P < 0.01$, *** means $P < 0.001$.

Table 4. Recurrence of the two groups of patients

Grouping	Relapse	Non-relapse
Control group (n = 50)	10	40
Research group (n = 55)	7	48
χ^2	1.021	
P	0.312	

al. [21] also claimed that patients' conditions was obviously improved after the therapy. Consequently, we speculated that red and blue light irradiation could kill Propionibacterium acnes in the pilosebaceous glands to the maximum extent, and collagen, on the other hand, could promote skin wound healing and reduce adverse reactions such as flushing, burning, and dryness in patients. Apart from that, it could also improve the blood circulation of the skin, and maintain the moisture of the stratum corneum and the integrity of fiber structure. We believe the combination of the two has synergistic effect and improves the therapeutic effect.

Cytokines IL-1 β and IL-6, mainly produced by monocytes-macrophages, are the key substances to initiate immune response. The lev-

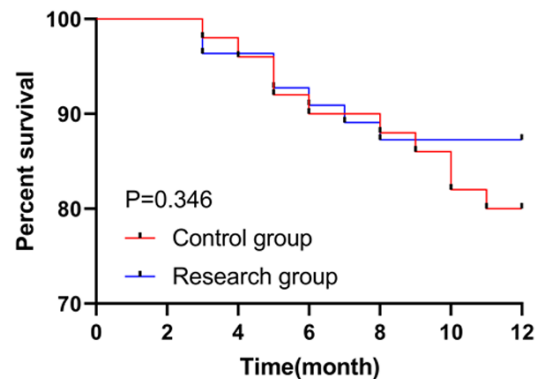


Figure 3. Statistics of recurrence of patients after treatment.

els of them in skin lesions can serve as reliable indicators to reflect the state of skin inflammation [22-24]. In the study of Ahmed et al. [25], it was concluded that serum levels of IL-6 and tumor necrosis factor (TNF- α) were evidently reduced in patients treated with active vitamin D. In our study, we compared the levels of IL-1 β and IL-6 of patients before and after intervention, and found that they were markedly reduced in both groups after treatment, yet RG held an even lower level compared to CG. This suggested that the combined treatment of red

Analysis of risk factors for short-term recurrence after acne treatment

Table 5. Univariate analysis of the factors affecting the acne recurrence

Indicators	Relapse group (n = 17)	Non-relapse group (n = 88)	χ^2/t	P
Age			7.718	0.005
≥ 20 years old	6	62		
< 20 years old	11	26		
Gender			5.611	0.017
Male	11	30		
Female	6	58		
Course of disease			0.038	0.844
≥ 2 years	12	60		
< 2 years	5	28		
Acne severity			1.415	0.493
Grade I	6	37		
Grade II	6	36		
Grade III	5	15		
Education level			0.811	0.367
\geq Senior High School	10	65		
$<$ Senior High School	7	28		
Monthly income			6.769	0.009
≥ 5000 RMB	4	51		
< 5000 RMB	13	37		
Smoking history			0.078	0.779
YES	5	23		
NO	12	65		
History of alcoholism			0.518	0.471
YES	3	10		
NO	14	78		
Before treatment IL-1 β (pg/mL)	257.21 \pm 12.60	246.21 \pm 16.48	2.603	0.010
Before treatment IL-6 (pg/mL)	191.27 \pm 7.51	183.46 \pm 9.87	3.088	0.002

Table 6. Assignment table

Factors	Assignment
Age	Belonging to continuous variables using raw data analysis
Gender	Male = 1, Female = 0
Monthly income	≥ 5000 yuan = 1, < 5000 yuan = 0
Before treatment IL-1 β	Belonging to continuous variables using raw data analysis
Before treatment IL-6	Belonging to continuous variables using raw data analysis
Recurrence	Recurrence = 1, No recurrence = 0

and blue light and collagen dressing had the effect of improving inflammation in patients just as active vitamin D did. When the blue light source is irradiated on the surface of the patient's skin, it can accelerate the growth of endothelial cells and fibroblasts in the affected area, reduce the inflammatory response in the local area, and thus play a therapeutic effect.

Recurrence of acne vulgaris is commonly seen in clinical practice [26]. We compared the recur-

rence rates of two groups in this study and found no evident difference in terms of recurrence rates after treatment. But in attempts to further identify the risk factors affecting relapse in patients, we conducted a systematic analysis and found that age, monthly income, pre-treatment IL1 β and pre-treatment IL-6 were risk factors for relapse. Endocrine disorders are prone to occur among young patients because they are in the period of physical development. At this stage, hormones normally increase and

Analysis of risk factors for short-term recurrence after acne treatment

Table 7. Multivariate logistic regression analysis of the factors affecting the acne recurrence

Factors	β	SE	χ^2	P	OR	95% CI	
						Lower limit	Upper limit
Age	-0.11	0.05	4.778	0.029	0.896	0.812	0.989
Gender	0.988	0.666	2.204	0.138	2.686	0.729	9.904
Monthly income	-1.476	0.687	4.612	0.032	0.229	0.059	0.879
Before treatment IL-1 β	0.053	0.023	5.511	0.019	1.055	1.009	1.103
Before treatment IL-6	0.093	0.038	5.938	0.015	1.097	1.018	1.182

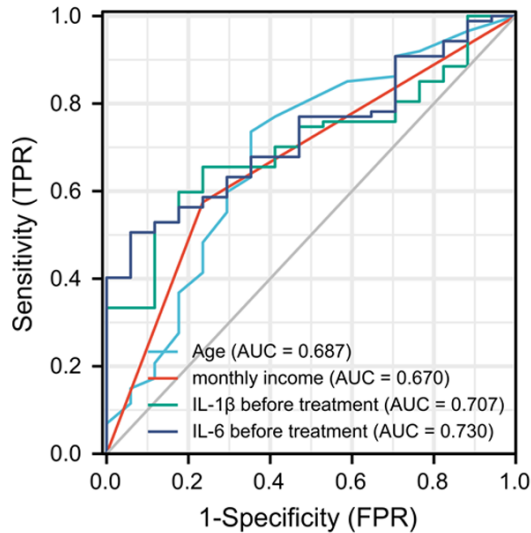


Figure 4. ROC curve of risk factors in predicting acne recurrence.

very likely promote active sebum secretion, thereby leading to the recurrence of disease, which was previously confirmed in the study of Quéréux et al. [27]. Interestingly, what we found was that high monthly income was a protective factor for the recurrence of acne vulgaris, which was mainly because high-income people have higher requirements for self-generated appearance, and are able to afford more skin care products. In addition, high levels of pre-treatment inflammatory factors may also affect patient relapse, as inflammation is an important part of the pathogenesis of ulcers [28]. There is a specific immune response observed in acne vulgaris patients that can be involved in the pathogenic process of acne and promote the formation of acne inflammation. And it is acknowledged that abnormal up-regulation of inflammatory factors induces the occurrence of acne. Therefore, effectively controlling the inflammatory response in patients is an effective means to improve acne vulgaris [29]. At the

end of the study, we analyzed the value of age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 in predicting relapse in patients. Through ROC curve analysis, it was found that the AUCs of IL1 β and IL-6 before treatment were all greater than 0.7, which were good clinical predictors.

In this study, we determined through statistical analysis that alternating red and blue light irradiation combined with collagen application could improve the treatment efficacy in patients with acne vulgaris, and that age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 were all risk factors for recurrence. However, this study still has some limitations. First, due to the nature of retrospective study, we failed to follow up patients in long-term. Second, research samples were not as homogeneous as randomized controlled trials. Therefore, we hope to carry out more experiments and long-term follow-up in future studies to refine our conclusions.

To sum up, alternating red and blue light irradiation combined with collagen dressing can improve the treatment efficacy in patients with acne vulgaris, and factors such as age, monthly income, pre-treatment IL-1 β and pre-treatment IL-6 were risk factors affecting the recurrence of patients.

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Disclosure of conflict of interest

None.

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Analysis of risk factors for short-term recurrence after acne treatment

Table 8. ROC parameters

Factors	Area under the curve	Confidence interval	Specificity	Sensitivity	Youden index
Age	0.687	0.537-0.837	0.647	0.736	0.383
Monthly income	0.670	0.553-0.786	0.765	0.575	0.339
Before treatment IL-1 β	0.707	0.594-0.821	0.824	0.598	0.421
Before treatment IL-6	0.730	0.622-0.838	0.941	0.506	0.447

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Analysis of risk factors for short-term recurrence after acne treatment

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