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ORIGINAL RESEARCH

Elevated Specific Pro-Inflammatory Cytokines in Peripheral Circulation Indicate an Increased Risk of Anxiety and Depression in Rosacea

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Objective: Pro-inflammatory cytokines mediate the course of rosacea, anxiety, and depression through various means such as immunity and inflammation. This study aims to further explore the relationship between rosacea, anxiety, and depression through changes in the levels of pro-inflammatory cytokines.

Methods: 280 rosacea patients were included in the rosacea group, divided into: rosacea without mental disorders, rosacea with anxiety, rosacea with depression, and rosacea with combined anxiety and depression. The mental control group included 210 anxiety and depression patients, divided into: anxiety, depression, and combined anxiety and depression. The healthy control group consisted of 70 healthy individuals. Serum specimens were collected and ELISA was used to detect major pro-inflammatory cytokines. CEA, IGA, GFSS, RosaQoL, HAMA, and HAMD-24 were used for the diagnosis and severity assessment of rosacea and anxiety and depression.

Results: This study primarily used the Chi-Square test, Kruskal–Wallis *H*-test, generalized linear model, and binary logistic regression to evaluate the data. IL-1β, IL-17, and IL-8 levels in rosacea patients and anxiety/depression patients were higher than those in the healthy population (P<0.001), and TNF-α levels in rosacea patients were higher than those in the healthy population (P<0.001). There was an interaction between rosacea, anxiety, and depression in terms of IL-1β, IL-17, and IL-8 levels (P<0.001). Elevated levels of IL-1β, IL-17, and IL-8 are positively correlated with anxiety and depression in rosacea (all P<=0.05).

Conclusion: It was confirmed that the elevated levels of IL-1β, IL-17, and IL-8 are positively correlated with the onset of anxiety and depression in rosacea. The interaction of the above inflammatory factors suggests a possible common inflammatory mechanism in the coexistence of rosacea and mental disorders. TNF-α only increased in patients with rosacea, combined with the skin-to-mental irreversible phenomenon, indicating that this cytokine may be a key and potential therapeutic target for the onset of rosacea.

Keywords: rosacea, anxiety, depression, pro-inflammatory cytokines, inflammation

Introduction

Rosacea is a chronic, recurring inflammatory skin disease that primarily affects the blood vessels, nerves, hair follicles, and sebaceous gland units of the face, commonly occurring in the central part of the face.[1] Clinical manifestations typically include paroxysmal flushing of the facial skin, persistent erythema or papules, pustules, and capillary dilation, with hyperplastic hypertrophy and ocular changes in some patients.[2] Based on the most recent international meta-analysis of epidemiological data across diverse populations, the average global prevalence rate stands at 5.46%.[3] Numerous patients present with recurring episodes spanning several years or even decades, sometimes manifesting multiple times within a single year. This recurrent nature necessitates multiple rounds of treatments and commonly co-occurs with various comorbidities, particularly neurological disorders.[4,5] Long-term clinical observations have substantiated the association between rosacea and a notable elevation in the susceptibility to depression and anxiety disorders. The stress triggered by social anxiety and psychological strain, frequently manifesting with facial flushing, may reciprocally

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aggravate the severity of rosacea.[2,6] The treatment of rosacea aids in alleviating symptoms of depression and anxiety, while the antipsychotic medication Paroxetine can effectively treat refractory rosacea.[7,8] Hence, the interplay between rosacea and mental disorders should not solely be attributed to cosmetic stressors but could potentially be linked to shared pathological mechanisms.

Pro-inflammatory cytokines are involved in the development of rosacea, anxiety, and depression. Interleukin (IL)-17 not only directly promotes angiogenesis and vasodilation in patients with rosacea, but also stimulates the production of tumor necrosis factor (TNF)-α, IL-1β, and IL-6. It collaborates with the aforementioned cytokines to upregulate vascular endothelial growth factor and IL-8.[9,10] Moreover, IL-17 enhances the activation of neurons in the inner frontal cortex, contributing to the development of anxiety and depression.[11] IL-8 and TNF-α mediate the formation of pustules and papules in rosacea and downstream vascular effects;[12] TNF-α activates the hypothalamic-pituitary-adrenal (HPA) axis and indoleamine 2,3-dioxygenase, leading to depletion of tryptophan, thereby causing anxiety and depression; IL-17, IL-1β, IL-6, IL-8, eg., activate the kynurenine pathway, reduce 5-hydroxytryptamine (5-HT) levels, and cause symptoms of anxiety and depression.[13,14] However, the case-control data from the UK indicate that a prior history of depression does not increase the risk of developing rosacea.[4] It indicates that rosacea may have unique inflammatory pathways leading to the pathogenic spirit of the skin, while the spirit cannot cause skin disease. Further exploration into the potential mechanisms connecting rosacea with anxiety and depression may facilitate the development of tailored treatments, ultimately enhancing the clinical outcomes for individuals with rosacea. To date, there have been no studies elucidating the aforementioned issues from the standpoint of pro-inflammatory cytokines and inflammation.

This study aims to assess the pro-inflammatory cytokine levels and symptom severity in patients with rosacea and mental disorders, in order to explore the causal sequence of onset between rosacea and mental disorders, as well as the potential common-acting inflammatory nodes between them.

Methods

Study Population

This study retrospectively enrolled 280 patients diagnosed with rosacea who underwent treatment in the Department of Dermatology outpatient clinic at the Second Affiliated Hospital of Kunming Medical University from January 2019 to December 2023; During the same period, 210 patients diagnosed with anxiety and depression received treatment at the Psychiatric Hospital of Yunnan Province.

The inclusion criteria for the rosacea group were: (1) diagnosed with rosacea;[1] (2) aged more than 18 years old; (3) the scores on the HAMA and HAMD-24 scales are both below 21 points.

The inclusion criteria for the mental control group were: (1) diagnosed with anxiety / depression / anxiety and depression;[15] (2) aged more than 18 years old; (3) the scores on the HAMA and HAMD-24 scales are both below 21 points.

The exclusion criteria for the rosacea group and the mental control group were: (1) with a previous family history of psychosis; (2) with severe cognitive impairments, dementia, significant aphasia, agnosia, and other mental illnesses excluding depression, anxiety disorders; (3) combining with insufficiency of cardiovascular, liver, and kidney system; (4) pregnant or lactating women; (5) anxiety and depression caused by psychoactive substances, addictive substances; (6) with a previous history of stroke; (7) complicated with inflammatory skin diseases other than rosacea.

70 healthy individuals who underwent medical examinations during the same period were included as healthy controls. All healthy controls were determined to be in a healthy state through physical examinations and personal medical history records, with ages all above 18 years old. The study's ethics were approved by the institutional review board. Patients with rosacea, mental disorders, and healthy individuals all provided written informed consent.

Clinical Data collection

Upon collecting the clinical data for the study, we obtained demographic information and disease characteristics of individuals with rosacea, mental disorders, and healthy participants. The demographic data encompassed age, gender (female or male), and educational attainment.

Anxiety and Depression Evaluation

The evaluation of anxiety and depression in all patients are based on the HAMA and HAMD-24 scales. A score of HAMA≥8 indicates the presence of anxiety, whereas a score of HAMA<8 indicates no anxiety. A score of HAMD-24≥8 indicates the presence of depression, while the score of HAMD-24<8 indicates no depression.[15]

Disease Characteristics of the Rosacea Group: CEA, IGA, GFSS, RosaQoL, HAMA and HAMD-24

Based on the presence or absence of anxiety and depression, the rosacea group was further divided into: A. rosacea without mental disorders group (HAMA<8, HAMD-24<8), B. rosacea with comorbid anxiety and depression group (HAMA≥8, HAMD-24≥8), C. rosacea with comorbid anxiety group (HAMA≥8, HAMD-24<8), D. rosacea with comorbid depression group (HAMA<8; HAMD-24≥8). Each group includes 70 patients.[1,15–18]

Disease Characteristics of the Mental Control Group: HAMA, HAMD-24

Based on the presence or absence of anxiety and depression, the mental control group was further divided into: E. anxiety group (HAMA≥8, HAMD<8), F. depression group (HAMA<8, HAMD≥8), G. anxiety and depression group (HAMA≥8, HAMD≥8). Each group includes 70 patients.[15]

Healthy Control Group: H. Healthy Control Group. The Group Includes 70 Healthy Individuals

Enzyme-Linked Immunosorbent Assay (ELISA, Dual Antibody Sandwich Method)

Blood samples (10mL) of the median cubital vein from all study participants were collected into vacuum tubes, then placed at 37°C for half an hour and centrifuged at a speed of 4000 rpm for 5 minutes to separate the serum. After collection, serum levels of IL-1β, IL-6, TNF-α, IL-17, and IL-8 were detected using reagent kits (Enzyme-free biology, China) provided by Kunming Jinyu Medical Co., Ltd. All procedures were strictly performed according to the manufacturer's protocols.

Statistical Analysis

First, for categorical variables, we presented them as frequencies and percentages, and differences between groups were compared using the Chi-square test. For continuous variables that all did not follow a normal distribution, we used the median and interquartile range (IQR) to describe central tendency and dispersion. Differences among multiple independent samples were analyzed using the Kruskal–Wallis *H*-test. When significant differences were identified, pairwise comparisons were performed with a Bonferroni correction to adjust for multiple comparisons. The generalized linear model (GLM) was also used to look into how rosacea, anxiety, and depression affect inflammatory markers such as IL-1β, IL-6, TNF-α, IL-17, and IL-8, as well as how they interact with each other. Finally, the association between anxiety, depression, and the inflammatory markers IL-1β, IL-6, TNF-α, IL-17, and IL-8 was further investigated using binary logistic regression. A p-value of less than 0.05 was considered statistically significant in this study. Statistical analysis was conducted using SPSS version 25.0.

Results

Basic Information and Disease Characteristics of Enrolled Samples

There were no significant statistical differences in gender, age, and level of education among groups A to H, as shown in Table 1. Groups A to D had rosacea, with no significant statistical differences in CEA, IGA, GFSS, and RosaQoL scale levels between groups, as shown in Table 2. Groups B, C, E, and G had anxiety, with no significant statistical differences in HAMA scale levels between groups; Groups B, D, F, and G had depression, with no significant statistical differences in HAMD-24 scale levels between groups, as shown in Table 3 and Supplementary Table 1.

Table 1 Basic Data comparison[1]

	Gender		Age (Years)	Level of Education				
	Male	Female		Primary School and Below	Junior High School	High School/ Vocational School	University	Master's Degree or Above
A	30 (42.86)	40 (57.14)	37.50(30.00 ~ 45.00)	10 (14.29)	12 (17.14)	17 (24.29)	28 (40.00)	3 (4.29)
B	32 (45.71)	38 (54.29)	35.00(31.00 ~ 44.00)	10 (14.29)	11 (15.71)	17 (24.29)	20 (28.57)	12 (17.14)
C	28 (40.00)	42 (60.00)	35.00(28.00 ~ 41.00)	7 (10.00)	19 (27.14)	18 (25.71)	18 (25.71)	8 (11.43)
D	31 (44.29)	39 (55.71)[1]	35.00(27.00 ~ 43.00)	8 (11.43)	17 (24.29)	18 (25.71)	20 (28.57)	7 (10.00)
E	31 (44.29)	39 (55.71)	34.00(28.00 ~ 41.00)	12 (17.14)	14 (20.00)	16 (22.86)	17 (24.29)	11 (15.71)
F	30 (42.86)	40 (57.14)	35.00(29.00 ~ 41.00)	10 (14.29)	18 (25.71)	22 (31.43)	15 (21.43)	5 (7.14)
G	32 (45.71)	38 (54.29)	35.50(29.00 ~ 41.00)	9 (12.86)	17 (24.29)	14 (20.00)	22 (31.43)	8 (11.43)
H	30 (42.86)	40 (57.14)	34.00(27.00 ~ 42.00)	9 (12.86)	7 (10.00)	24 (34.29)	25 (35.71)	5 (7.14)
χ^2/H-value	0.697		3.863	29.192				
P-value	0.998		0.795	0.403				

Note: [1]χ^2: Chi-Square Statistic.

Table 2 Comparison of the CEA, IGA, GFSS, and RosaQoL Scale Scores Among the Four ABCD Groups

	CEA	IGA	GFSS	RosaQoL
A	2.00(2.00 ~ 3.00)	1.00(1.00 ~ 2.00)	37.00(13.00 ~ 52.00)	31.50(20.00 ~ 43.00)
B	2.00(2.00 ~ 3.00)	1.00(1.00 ~ 2.00)	38.00(15.00 ~ 50.00)	35.50(21.00 ~ 44.00)
C	2.00(1.00 ~ 3.00)	1.00(0.00 ~ 2.00)	30.50(14.00 ~ 51.00)	32.50(19.00 ~ 43.00)
D	2.00(1.00 ~ 3.00)	1.00(0.00 ~ 2.00)	34.00(20.00 ~ 53.00)	33.50(18.00 ~ 48.00)
H-value	0.329	0.760	0.478	0.680
P -value	0.954	0.859	0.924	0.878

Table 3 HAMA, HAMD-24 Groups Comparison

	HAMA	HAMD
A	2.00(1.00 ~ 4.00)	2.00(0.00 ~ 3.00)
B	14.00(11.00 ~ 18.00)	14.50(11.00 ~ 18.00)
C	14.00(11.00 ~ 17.00)	3.00(1.00 ~ 5.00)
D	3.00(2.00 ~ 5.00)	14.00(11.00 ~ 17.00)
E	14.00(12.00 ~ 16.00)	3.00(2.00 ~ 5.00)
F	3.00(2.00 ~ 5.00)	15.00(12.00 ~ 17.00)
G	14.00(11.00 ~ 17.00)	15.00(13.00 ~ 18.00)
H-value	364.326	364.173
P-value	<0.001	<0.001

Comparison of Pro-Inflammatory Cytokines Between the Rosacea Group, Mental Control Group, and Healthy Control Group

(1) The levels of IL-1β, IL-17, and IL-8 in the rosacea (groups A-D) and the anxiety/depression (groups E-G) were higher compared to healthy individuals (group H) (all P<0.001). Additionally, the levels of TNF-α in the rosacea (groups A-D) were higher compared to healthy individuals (H group) (all P<0.001), as shown in Table 4 and Supplementary Table 2.

(2) The levels of IL-6 in the rosacea (groups A-D) showed no significant statistical difference compared to healthy individuals (group H) (all P>0.05). Moreover, The levels of IL-6 and TNF-α in the anxiety/depression (groups E-G) showed no significant statistical difference compared to healthy individuals (group H) (all P>0.05), as shown in Table 4 and Supplementary Table 2.

Table 4 Comparison of Pro-Inflammatory Cytokines

Group	IL-1β	IL-6	TNF-α	IL-17	IL-8
A	68.96(62.36 ~ 78.37)	32.10(24.84 ~ 37.59)	45.57(40.85 ~ 53.33)	42.92(31.77 ~ 46.83)	83.35(72.28 ~ 94.10)
B	124.22(115.62 ~ 139.48)	32.87(25.99 ~ 37.91)	48.25(42.43 ~ 55.14)	92.57(83.93 ~ 100.37)	160.19(153.07 ~ 173.11)
C	108.08(98.45 ~ 115.10)	30.13(22.41 ~ 38.91)	48.24(37.70 ~ 58.62)	74.02(61.75 ~ 79.83)	120.28(111.37 ~ 129.05)
D	103.17(94.90 ~ 114.01)	31.91(20.81 ~ 42.24)	49.33(37.68 ~ 56.60)	70.57(62.72 ~ 82.46)	118.38(104.64 ~ 133.61)
E	68.76(57.63 ~ 81.18)	31.29(25.67 ~ 34.72)	34.81(29.69 ~ 43.37)	38.76(33.91 ~ 46.35)	82.01(72.34 ~ 91.01)
F	72.42(65.44 ~ 78.45)	31.11(26.18 ~ 35.85)	34.28(25.95 ~ 46.84)	41.22(33.93 ~ 47.18)	80.13(74.68 ~ 87.95)
G	88.06(76.55 ~ 94.13)	31.46(26.01 ~ 37.96)	35.53(28.97 ~ 45.66)	50.92(42.87 ~ 61.78)	96.73(88.18 ~ 106.50)
H	35.91(29.94 ~ 43.17)	29.53(24.83 ~ 35.53)	36.17(29.07 ~ 41.27)	26.32(24.12 ~ 28.99)	66.46(60.17 ~ 71.58)
H-value	471.954	4.202	119.789	458.383	457.009
P-value	<0.001	0.756	<0.001	<0.001	<0.001

Comparison of Pro-Inflammatory Cytokines in the Rosacea Without Mental Disorders Group, the Rosacea Combined with Mental Disorders Group, and the Mental Control Group

(1) The levels of IL-1β, IL-17, IL-8 in the rosacea combined with anxiety and depression (group B) were elevated compared to the rosacea without mental disorders (group A) (P<0.001; P<0.001; P<0.001), the rosacea combined with anxiety (group C) (P=0.044<0.05; P=0.023<0.05; P=0.001<0.01), the rosacea combined with depression (group D) (P=0.011<0.05; P=0.011<0.05; P=0.001<0.01), the anxiety (group E) (P<0.001; P<0.001; P<0.001), the depression (group F) (P<0.001; P<0.001; P<0.001), the anxiety and depression (group G) (P<0.001; P<0.001; P<0.001); The levels of TNF-α in the rosacea (groups A-D) were significantly higher in those with the anxiety/depression (groups E-G) (all P<0.001); The rosacea combined with anxiety (group C) showed higher levels of IL-1β, IL-17, and IL-8 compared to the anxiety and depression (group G) (all P<0.001); The rosacea combined with depression (group D) showed higher levels of IL-1β, IL-17, and IL-8 compared to the anxiety and depression (group G) (P=0.001<0.01; P<0.001; P=0.001<0.01); The levels of IL-1β, IL-17, IL-8 in the anxiety and depression (group G) were elevated compared to the anxiety (group E) (P=0.001<0.01; P=0.002<0.01; P=0.001<0.01), the depression (group F) (P=0.005<0.01; P=0.007<0.01; P=0.001<0.01); The anxiety and depression (group G) showed higher levels of IL-1β, IL-17, and IL-8 compared to the rosacea without mental disorders (group A) (P=0.002<0.01; P=0.012<0.05; P=0.011<0.05). Refer to Table 4 and Supplementary Table 2.

(2) The rosacea (groups A-D) and the anxiety/depression (groups E-G) have no significant differences in IL-6 levels (all P>0.05). There were no significant statistical differences in TNF-α and IL-6 among the four groups: the rosacea without mental disorders (group A), the rosacea combined with anxiety and depression (group B), the rosacea combined with anxiety (group C), and the rosacea combined with depression (group D) (all P>0.05). In the comparison of TNF-α and IL-6 levels among the anxiety (E group), the depression (group F), and the anxiety and depression (group G), there were no significant statistical differences (P>0.05). There were no significant statistical differences in IL-1β, IL-17, and IL-8 levels between the rosacea combined with anxiety (group C) and the rosacea combined with depression (group D) (all P>0.05). Similarly, there were no significant statistical differences in IL-1β, IL-17, and IL-8 levels between the anxiety (group E) and the depression (group F) (all P>0.05); There were no significant statistical differences in the levels of IL-1β, IL-17, and IL-8 among the three groups: the rosacea without mental disorders (group A), the anxiety (group E), and the depression (group F) (all P>0.05). Refer to Table 4 and Supplementary Table 2.

The Interaction of Rosacea, Anxiety, and Depression in the Expression of Pro-Inflammatory Cytokine Levels

Rosacea, anxiety, and depression were interactive in the levels of IL-1 β, IL-17, and IL-8 (P<0.001), shown in Table 5.

Table 5 Generalized Linear Model Estimates the Main Effects and Interaction Benefits of Rosacea, Anxiety, and depression[1]

Effects	IL-1β		IL-6		TNF-α		IL-17		IL-8	
	χ^2	P-value	χ^2	P-value	χ^2	P-value	χ^2	P-value	χ^2	P-value
Rosacea	966.658	<0.001	2.556	0.11	111.398	<0.001	914.537	<0.001	795.507	<0.001
Anxiety	539.145	<0.001	0.366	0.545	1.113	0.291	423.336	<0.001	330.73	<0.001
Depression	532.449	<0.001	1.258	0.262	0.520	0.471	410.412	<0.001	342.782	<0.001
Rosacea * Anxiety * Depression	56.668	<0.001	0.135	0.713	0.169	0.681	27.233	<0.001	12.584	<0.001

Notes: [1]Rosacea * Anxiety * Depression: interaction benefits of rosacea, anxiety, and depression.

Table 6 The Association Between Anxiety and Depression and IL-1β, IL-6, TNF-α, IL-17, and IL-8 Within Rosacea (ABCD Groups) Was Investigated Using Binary Logistic Regression

	Anxiety		Depression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
IL-1β	1.05 (1.02 ~ 1.08)	0.001	1.03 (1.00 ~ 1.06)	0.050
IL-6	0.99 (0.96 ~ 1.02)	0.532	0.99 (0.97 ~ 1.02)	0.685
TNF-α	1.00 (0.97 ~ 1.03)	0.751	1.00 (0.97 ~ 1.03)	0.977
IL-17	1.04 (1.02 ~ 1.07)	0.003	1.03 (1.01 ~ 1.06)	0.017
IL-8	1.03 (1.01 ~ 1.04)	0.011	1.04 (1.02 ~ 1.06)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval.

The Correlation Between Pro-Inflammatory Cytokines and the Risk of Anxiety/Depression in Rosacea

Elevated levels of IL-1β, IL-17, and IL-8 are positively correlated with the risk of anxiety/depression in rosacea (groups A-D)(all P<=0.05), while the levels of IL-6 and TNF-α are not significantly correlated with the risk of anxiety/depression in rosacea (all P>0.05), shown in Table 6.

Discussion

An increasing body of evidence suggests that rosacea is not only a unique inflammatory skin disease characterized by skin lesions concentrated in the central part of the face, but may also have a systemic origin, serving as a marker for an increased risk of systemic diseases.[4] Mylonas et al detected elevated levels of IL-1β and IL-17 mRNA in the skin of patients with rosacea.[19] In the present study, it was found that the levels of IL-1β, TNF-α, IL-17, and IL-8 in the peripheral blood of rosacea patients were significantly elevated compared to healthy individuals, further indicating that the inflammation of rosacea is not limited to the facial skin but involves systemic inflammation throughout the body. While rosacea is not a life-threatening disease, enhancing awareness of potential systemic complications and early identification could improve quality of life and extend the lives of patients.[4]

Several studies have investigated and confirmed the connection between rosacea and mental disorders.[20] Data from two national outpatient surveys conducted in the United States between 1995 and 2002 showed that among patients with rosacea, 65.1% experienced psychological complications such as depression, compared to only 29.9% in the general population.[21] Similarly, in a Danish nationwide rosacea cohort study, the occurrence of anxiety and depression was more than twice as high compared to the normal control population.[4,6] Some of the previous studies reported an association between decreased quality of life and conditions of depression and anxiety in patients with rosacea.[22–24] Traditional views believe that the main source of anxiety and depression in rosacea is the social stigma caused by the impact on facial appearance.[25] However, anxiety and depression may be related to the release of pro-inflammatory cytokines.[2,26] Tong N et al discovered a correlation between elevated levels of TNF-α, IL-17, and IL-23 and the worsening of

depression and anxiety in patients with psoriasis.[14,27] However, these studies did not exclude potential confounding factors, such as physical appearance. Therefore, this study confirmed that the elevation of peripheral blood IL-1β, IL-17, and IL-8 is positively correlated with the occurrence of anxiety and depression in patients with rosacea after unifying the factors of physical appearance and quality of life. In addition, the study observed that the levels of peripheral blood IL-1β, IL-17, and IL-8 in patients with rosacea, anxiety, and depression are higher than those in healthy individuals, which aligns with the viewpoint in previous literature that the comorbidities of rosacea may share common innate inflammatory factors with rosacea.[28–31] Moreover, it was confirmed from the level of inflammatory factors that there may be overlapping inflammatory mechanisms related to IL-1β, IL-17, and IL-8 in rosacea, anxiety, and depression. These pro-inflammatory cytokines can cause rosacea or anxiety and depression by activating the HPA axis or influencing neurotransmitter metabolism.[14] At the same time the research group observed that in patients with rosacea and comorbid anxiety/depression/anxiety and depression, levels of peripheral blood IL-1β, IL-17, and IL-8 were higher compared to patients with rosacea without mental disorders and those with only anxiety/depression/anxiety and depression, and confirmed that there is an interaction between rosacea, anxiety, and depression in the elevation of the aforementioned pro-inflammatory cytokines. This indirectly confirms that comorbidity trigger events will further promote the progression of rosacea and mental comorbidities through accelerating inflammation.

The overlapping pathological mechanisms need further study to clarify the causal sequence of rosacea, anxiety and depression, in order to deepen our understanding of the pathological mechanisms of rosacea and achieve comorbidity control and attributive treatment. In this research, by comparing the pro-inflammatory cytokines of the rosacea without mental disorders group and the mental control group, it can be seen that TNF-α is elevated only in rosacea, and there is no significant difference in its appearance in anxiety and depression. Although theoretically TNF-α is also involved in the progression of anxiety and depression through inflammatory responses,[14,32] in this study, the degree of anxiety and depression in all the patients diagnosed with mental disorders were mild. This is based on the fact that during the screening of patients with rosacea in the preliminary stages of the experiment, there were hardly any patients with severe levels of anxiety and depression. Furthermore, this study used peripheral median cubital vein blood samples instead of cerebrospinal fluid samples. Therefore, it can be speculated that in mild anxiety and depression, TNF-α in the peripheral blood circulation has not yet participated in the systemic upregulation of inflammation in both conditions. Combining the confirmed findings from previous large-sample epidemiological studies, the onset of anxiety and depression does not increase the risk of rosacea, suggesting that peripheral blood TNF-α may play a unique inflammatory role in the pathogenesis of rosacea, providing compelling evidence for the possibility of skin-first, mental-second in pathogenesis.

Overall, peripheral blood levels of IL-1β, IL-17, and IL-8 can simultaneously reflect the comorbid risks of anxiety and depression in patients with rosacea, while the elevation of TNF-α is specific to rosacea. Treatment targeted at the same inflammatory node may be more effective in treating rosacea and its associated psychiatric comorbidities. Paroxetine has been shown to reduce levels of IL-1β, IL-6, and possibly TNF-α in the treatment of anxiety and depression. The decrease in inflammation levels post-treatment correlates with improvements in anxiety and depression, and patients who experience greater reductions in pro-inflammatory cytokines levels also show greater improvements in anxiety and depression severity. This supports the role of paroxetine in combating anxiety and depression through potential inflammatory pathways.[33–37] Meanwhile, Paroxetine has been proven to effectively address the limitations and rebound side effects of traditional medications such as doxycycline for refractory rosacea erythema symptoms.[8] Paroxetine's effects on pro-inflammatory cytokines in patients with rosacea have not been clearly studied. However, combining the above conclusions, it can be speculated that paroxetine may act on the pro-inflammatory cytokines in patients with rosacea, becoming an effective treatment method through its anti-inflammatory effects, significantly helping to improve patients' quality of life, and effectively reducing or improving psychiatric comorbidities. In rosacea, peripheral blood TNF-α is independent of anxiety and depression. Does its uniqueness suggest that further exploration of the pathogenesis and related anti-inflammatory treatments targeting TNF-α may lead to earlier and more effective treatment for rosacea?

There are several limitations to this study: (1) Although the relationship between pro-inflammatory cytokines and rosacea, anxiety, and depression has been revealed, the detailed mechanisms by which these pro-inflammatory cytokines trigger anxiety and depression in rosacea are still unclear; (2) Among the patients with rosacea included in this study,

there were no cases showing nasal hypertrophy, and further research can be conducted to investigate this manifestation subsequently; (3) Based on the anxiety and depression status of outpatients with rosacea in this study, the levels of anxiety and depression in the mental control were limited to mild. The pathological mechanism of moderate to severe anxiety and depression is more complex. Further research can take this into consideration and incorporate the impact of the quality of life burden of rosacea as well as the severity of flushing on varying degrees of anxiety and depression, exploring their specific mechanisms; (4) Some intermediate products, such as 5-HT, can interact with pro-inflammatory cytokines, regulating rosacea and anxiety, depression. The detection of these intermediate products may be a direction for further research.

Conclusion

In conclusion, our research unified the effects of appearance and quality of life, adding the control of anxiety and depression patients, and revealed the significant value of the pro-inflammatory cytokines IL-1β, IL-17, and IL-8 in rosacea and psychiatric comorbidity, as well as the uniqueness of TNF-α in the inflammation of rosacea; confirmed rosacea as a systemic inflammatory disease, linking rosacea with anxiety and depression from an inflammatory perspective and attracting clinicians' attention to rosacea and psychiatric comorbidity. This aligns with previous studies mentioning the consideration of neural aspects in rosacea intervention, providing a partial clinical theoretical basis for subsequent anti-inflammatory treatments of rosacea and comorbid mental disorders. Whether it is providing new therapeutic targets based on clearly defined pathological mechanisms of rosacea, monitoring, or even preventing psychiatric comorbidities, pro-inflammatory cytokines are indispensable.

Abbreviations

CEA, clinician erythema assessment; IGA, investigator global assessments; GFSS, global flushing severity score; RosaQoL, rosacea quality of life index; HAMA, Hamilton Anxiety Scale; HAMD-24, Hamilton Depression Scale-24.

Data Sharing Statement

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

Ethics Statement

The study complies with the Declaration of Helsinki. The Medical Ethics Committee of the Second Affiliated Hospital of Kunming Medical University approval has been obtained to publish the study details (ethics number: Shen-PJ-Ke-2024-10).

Informed Consent

All the rosacea patients, mental controls and healthy controls provided written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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