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RESEARCH ARTICLE

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The potency of common proinflammatory cytokines measurement for revealing the risk and severity of anxiety and depression in psoriasis patients

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Abstract

Objective: Proinflammatory cytokines mediate anxiety and depression in various ways, such as immunity, inflammation, and the hypothalamic–pituitary–adrenal axis. This study intended to further explore the linkage of common proinflammatory cytokine levels with anxiety and depression in psoriasis patients.

Methods: Totally, 150 psoriasis patients and 50 healthy controls (HCs) were included; the serum samples were collected, then common proinflammatory cytokines were measured by ELISA. Hospital Anxiety and Depression Scale (HADS) was assessed.

Results: HADS-anxiety (HADS-A) score, HADS-depression (HADS-D) score, TNF-α, IL-1β, IL-6, IL-12, IL-17A, and IL-23 were all increased in psoriasis patients compared to HCs (all $p < 0.05$). In psoriasis patients, TNF-α ($p = 0.001$), IL-12 ($p = 0.035$), and IL-17A ($p < 0.001$), but not IL-1β ($p = 0.255$), IL-6 ($p = 0.248$), and IL-23 ($p = 0.216$), were positively linked to HADS-A score. Meanwhile, TNF-α ($p = 0.007$) and IL-17A ($p = 0.007$) were enhanced in psoriasis patients with anxiety in contrast to those without anxiety; whereas IL-1β ($p = 0.178$), IL-6 ($p = 0.360$), IL-12 ($p = 0.239$), and IL-23 ($p = 0.450$) were not different. TNF-α ($p < 0.001$), IL-1β ($p = 0.013$), Il-17A ($p < 0.001$), and IL-23 ($p = 0.023$), but not IL-6 ($p = 0.143$) and IL-12 ($p = 0.158$), were positively linked to HADS-D score. Concurrently, TNF-α ($p = 0.015$), IL-17A ($p < 0.001$), and IL-23 ($p = 0.017$) were climbed in psoriasis patients with depression by comparison to those without depression; whereas IL-1β ($p = 0.113$), IL-6 ($p = 0.237$), IL-12 ($p = 0.660$) did not differ.

Conclusion: TNF-α, IL-17A, and IL-23 increments reflect anabatic anxiety and depression in psoriasis patients, uncovering the potency of proinflammatory cytokines measurement for monitoring or even preventing psoriasis patients' anxiety and depression.

KEYWORDS
anxiety, depression, hospital anxiety and depression scale, proinflammatory cytokines, psoriasis

Nannan Tong and Yu Zhang contributed equally to this work.

1 | INTRODUCTION

Psoriasis is an inflammatory skin disease mediated by immunity, which has a high incidence and prevalence worldwide.[1,2] Although certain progress has been made in the treatment of psoriasis, this disease still cannot be completely cured and often leads to many complications, such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, uveitis, etc.[3–6] In addition to these complications, the body appearance of the psoriasis patient is also affected[7,8]; all of these factors contribute to a huge psychological burden (such as anxiety and depression) on the psoriasis patients, which causes difficulties in rehabilitation and even leads to suicide.[9–11] Therefore, it is necessary to explore potential factors that participate in the pathology of anxiety and depression, which might be helpful for attribution therapy and thereby improve the clinical outcomes of psoriasis patients.

Proinflammatory cytokines are reported to participate in the progression and pathogenesis of anxiety and depression.[12,13] For example, tumor necrosis factor-α (TNF-α) activates the hypothalamic–pituitary–adrenal (HPA) axis and indoleamine 2,3-dioxygenase, which leads to the tryptophan depletion and thereby causes depression.[12] Meanwhile, interleukin (IL)-1, IL-6, IL-8, etc., would activate the kynurenine pathway, which reduces the level of serotonin; thereby inducing anxiety and depression.[13] Clinically, proinflammatory cytokines are linked with anxiety or depression in some autoimmune disease patients, such as multiple sclerosis and rheumatoid arthritis (RA) patients.[14,15] For example, IL-2 is correlated with anxiety; while TNF-α and IL-1β are linked to depression in multiple sclerosis patients.[14] Moreover, a study states that increased IL-17 and IL-6 are linked with depression in RA patients.[15] Hence, it could be hypothesized that proinflammatory cytokines might be linked with these psychological issues in psoriasis patients. However, no study reports that.

Subsequently, this study intended to inspect the prevalence of mental problems (anxiety and depression) and expressions of proinflammatory cytokines, along with their inter-correlations in psoriasis patients.

2 | METHODS

2.1 | Participants

The study enrolled 150 patients with psoriasis who received treatment at our hospital between May 2020 and September 2021. The inclusion criteria for patients were: (1) diagnosed with psoriasis; (2) aged more than 18 years old. The exclusion criteria for patients were: (1) complicated with inflammatory skin diseases other than psoriasis; (2) accompanied with insufficiency of cardiovascular, kidney, and liver system; (3) had malignant tumors or hematological diseases; (4) history of documented mental disorders; (5) pregnant or lactating women. Besides, 50 healthy individuals who received physical examination during the same period were included as health controls (HCs). All HCs had a healthy status determined by physical examination and a record of personal medical history and aged more than 18 years old. The study ethics was approved by the Institutional Review Board. Both psoriasis patients and HCs provided written informed consent.

2.2 | Clinical data collection

After enrollment, we collected psoriasis patients' demographics, disease features, and treatment information. The demographics included the followings: age; gender (female or male); body mass index (BMI). The disease features included the followings: disease duration; psoriatic body surface area (BSA); Psoriasis Area and Severity Index (PASI) score. The treatment information included the followings: current topical therapy (yes/no); current phototherapy (yes/no); current systemic nonbiologic treatment (yes/no); current biologics treatment (yes/no).

2.3 | Anxiety and depression evaluation

The anxiety and depression were assessed by Hospital Anxiety and Depression Scale (HADS) in psoriasis patients and HCs. The anxiety or depression was classified as no (scored from 0 to 7), mild (scored from 8 to 10), moderate (scored from 11 to 14), and severe (scored from 15 to 21).[16]

2.4 | Enzyme-linked immunosorbent assay (ELISA)

The blood samples (10 ml) were collected into vacuum tubes from all study participants, then left at 37°C for half an hour and centrifuged (4000 revolutions per minute, 5 min) to separate the serum. After collection, the serum concentrations of TNF-α, IL-1β, IL-6, IL-12, IL-17A, and IL-23 were detected by commercial Human ELISA Kits (Thermo Fisher Scientific, China). All procedures were strictly performed according to the manufacturer's protocols.

2.5 | Statistical analysis

SPSS V26.1 (IBM Corp.) was applied for statistical analysis, and GraphPad Prism V7.01 (GraphPad Software Inc.) was applied for graph plotting. The linkage between two non-normally distributed continuous variables was determined using Spearman's rank correlation test. The comparison between two groups was assessed using Student's *t*-test, the Mann–Whitney U-test, the chi-square test, and the Yates'-corrected chi-square test, as appropriate. The potential of variables to predict the risk of anxiety and depression in psoriasis patients was determined by the receiver operating characteristic (ROC) curve. A p-value < 0.05 manifested statistical significance.

TABLE 1 Clinical features of patients with psoriasis

Items	Patients with psoriasis ($N = 150$)
Age (years), mean ± SD	48.0 ± 13.6
Gender, *n* (%)	
Female	57 (38.0)
Male	93 (62.0)
BMI (kg/m^2), mean ± SD	24.3 ± 3.4
Disease duration (years), median (IQR)	9.0 (5.0–15.0)
Psoriatic BSA (%), mean ± SD	20.3 ± 9.1
PASI score, mean ± SD	10.5 ± 4.6
Current topical therapy, *n* (%)	
No	13 (8.7)
Yes	137 (91.3)
Current phototherapy, *n* (%)	
No	29 (19.3)
Yes	121 (80.7)
Current systemic nonbiologic treatment, *n* (%)	
No	50 (33.3)
Yes	100 (66.7)
Current biologics treatment, *n* (%)	
No	134 (89.3)
Yes	16 (10.7)

Abbreviations: BMI, body mass index; BSA, body surface area; IQR, interquartile range; PASI score, psoriasis area and severity index score; SD, standard deviation.

3 | RESULTS

3.1 | Clinical features of psoriasis patients

The mean age of psoriasis patients was 48.0 ± 13.6 years; meanwhile, there were 57 (38.0%) females and 93 (62.0%) males. At the same time, the BMI of psoriasis patients was 24.3 ± 3.4 kg/m^2. The median (interquartile range [IQR]) value of disease duration was 9.0 (5.0–15.0) years. As for the mean values of psoriatic BSA and PASI scores, they were 20.3 ± 9.1 and 10.5 ± 4.6, correspondingly. Other clinical information on psoriasis patients is listed in Table 1.

3.2 | Comparisons of anxiety, depression, and inflammatory cytokine between psoriasis patients and HCs

The HADS-anxiety (HADS-A) score, anxiety rate, and severity were elevated in psoriasis patients compared with HCs (all $p < 0.001$). HADS-depression (HADS-D) score, depression rate, and severity were also enhanced in psoriasis patients in contrast with HCs (all $p < 0.001$). In terms of proinflammatory cytokines, they were climbed in psoriasis patients by contrast with HCs, including TNF-α (median (IQR): 63.4 (50.2–79.4) vs. 55.0 (42.3–69.2) pg/ml, $p = 0.008$), IL-1β (median (IQR): 4.1 (2.5–6.6) vs. 3.1 (1.8–5.0) pg/ml, $p = 0.015$), IL-6 (median (IQR): 39.6 (28.9–51.0) vs. 24.2 (16.6–35.9) pg/ml, $p < 0.001$), IL-12 (median (IQR): 78.0 (60.8–99.4) vs. 61.1 (50.1–83.1) pg/ml, $p = 0.006$), IL-17A (median (IQR): 81.8 (61.2–105.6) vs. 60.5 (46.3–90.5) pg/ml, $p = 0.001$), and IL-23 (median (IQR): 83.4 (62.6–119.2) vs. 75.1 (59.7–95.5) pg/ml, $p = 0.018$) (Table 2).

3.3 | Relation between proinflammatory cytokines and anxiety in psoriasis patients

TNF-α was positively correlated with the HADS-A score ($p = 0.001$, Figure 1A). While IL-1β ($p = 0.255$, Figure 1B) and IL-6 ($p = 0.248$, Figure 1C) were not linked with the HADS-A score. Additionally, IL-12 ($p = 0.035$, Figure 1D) and IL-17A ($p < 0.001$, Figure 1E), but not IL-23 ($p = 0.216$, Figure 1F) were positively linked to the HADS-A score in psoriasis patients.

Subsequently, the difference in proinflammatory cytokines between psoriasis patients with and without anxiety was compared. It was found that TNF-α was climbed in psoriasis patients with anxiety compared to those without anxiety ($p = 0.007$, Figure 2A). Whereas, IL-1β ($p = 0.178$, Figure 2B), IL-6 ($p = 0.360$, Figure 2C), and IL-12 ($p = 0.239$, Figure 2D) were not different between them. IL-17A ($p = 0.007$, Figure 2E), but not IL-23 ($p = 0.450$, Figure 2F) was elevated in psoriasis patients with anxiety compared to those without anxiety.

3.4 | Association between proinflammatory cytokines and depression in psoriasis patients

TNF-α ($p < 0.001$, Figure 3A) and IL-1β ($p = 0.013$, Figure 3B) were positively linked to the HADS-D score. However, IL-6 ($p = 0.143$, Figure 3C) and IL-12 ($p = 0.158$, Figure 3D) were not linked with the HADS-D score. Positive linkage was found in IL-17A ($p < 0.001$, Figure 3E) and IL-23 ($p = 0.023$, Figure 3F) with HADS-D scores in psoriasis patients.

Moreover, the comparison of proinflammatory cytokines between psoriasis patients with and without depression was evaluated. It was discovered that TNF-α was enhanced in psoriasis patients with depression in contrast to those without depression ($p = 0.015$, Figure 4A). IL-1β ($p = 0.113$, Figure 4B), IL-6 ($p = 0.237$, Figure 4C), and IL-12 ($p = 0.660$, Figure 4D) did not differ between them. Regarding IL-17A ($p < 0.001$, Figure 4E) and IL-23 ($p = 0.017$, Figure 4F), they were raised in psoriasis patients with depression in contrast to those without depression.

3.5 | ROC curves based on proinflammatory cytokines for estimating anxiety and depression

TNF-α (area under the curve (AUC) (95% confidence interval [CI]): 0.634 (0.542–0.727), Figure 5A) and IL-17A (AUC (95% CI): 0.635 (0.540–0.730), Figure 5B), but not IL-23 (AUC (95% CI): 0.538 (0.443–0.633), Figure 5C) had a certain ability to discriminate psoriasis patients with anxiety from those without anxiety. While the

TABLE 2 Comparisons of anxiety, depression and inflammatory cytokines between patients with psoriasis and HCs

Items	HCs ($N = 50$)	Patients with psoriasis ($N = 150$)	Statistics (t, χ^2, Z)	p-Value
Anxiety				
HASD-A score, mean ± SD	3.6 ± 2.0	7.6 ± 3.1	−8.320	<0.001
Anxiety, *n* (%)				
No	46 (92.0)	98 (65.3)	13.228	<0.001
Yes	4 (8.0)	52 (34.7)		
Anxiety severity, *n* (%)			−3.749	<0.001
No	46 (92.0)	98 (65.3)		
Mild	4 (8.0)	28 (18.7)		
Moderate	0 (0.0)	16 (10.7)		
Severe	0 (0.0)	8 (5.3)		
Depression				
HASD-D score, mean ± SD	3.5 ± 2.2	8.3 ± 3.4	−9.307	<0.001
Depression, *n* (%)			24.645	<0.001
No	47 (94.0)	83 (55.3)		
Yes	3 (6.0)	67 (44.7)		
Depression severity, *n* (%)			−5.011	<0.001
No	47 (94.0)	83 (55.3)		
Mild	3 (6.0)	30 (20.0)		
Moderate	0 (0.0)	26 (17.3)		
Severe	0 (0.0)	11 (7.3)		
Inflammatory cytokines				
TNF-α (pg/ml), median (IQR)	55.0 (42.3–69.2)	63.4 (50.2–79.4)	−2.648	0.008
IL-1β (pg/ml), median (IQR)	3.1 (1.8–5.0)	4.1 (2.5–6.6)	−2.421	0.015
IL-6 (pg/ml), median (IQR)	24.2 (16.6–35.9)	39.6 (28.9–51.0)	−5.764	<0.001
IL-12 (pg/ml), median (IQR)	61.1 (50.1–83.1)	78.0 (60.8–99.4)	−2.773	0.006
IL-17A (pg/ml), median (IQR)	60.5 (46.3–90.5)	81.8 (61.2–105.6)	−3.297	0.001
IL-23 (pg/ml), median (IQR)	75.1 (59.7–95.5)	83.4 (62.6–119.2)	−2.360	0.018

Abbreviations: HADS-A, hospital anxiety and depression scale for anxiety; HADS-D, hospital anxiety and depression scale for depression; HCs, health controls; IL-12, interleukin-12; IL-17A, interleukin-17A; IL-23, interleukin-23; IL-1β, interleukin-1-beta; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation; TNF-α, tumor necrosis factor-alpha.

combination of TNF-α, IL-17A, and IL-23 improved this discriminating ability to some extent (AUC (95% CI): 0.670 (0.580–0.760), Figure 5D). Meanwhile, TNF-α (AUC (95% CI): 0.616 (0.526–0.706), Figure 5E), IL-17A (AUC (95% CI): 0.674 (0.587–0.760), Figure 5F), and IL-23 (AUC (95% CI): 0.614 (0.524–0.704), Figure 5G) also showed a certain capacity to distinguish psoriasis patients with depression from those without depression. Additionally, the combination of TNF-α, IL-17A, and IL-23 also enhanced the distinguishing capacity to some extent (AUC (95% CI): 0.701 (0.618–0.784), Figure 5H).

3.6 | Linkage of proinflammatory cytokines with treatments in psoriasis patients

Increased IL-12 ($p = 0.045$) and IL-23 ($p = 0.026$) were linked to current topical therapy. Nevertheless, no relation was found between proinflammatory cytokines and current phototherapy (all $p > 0.05$). Decreased TNF-α ($p = 0.002$) and IL-12 ($p = 0.018$) were related to current systemic nonbiologic treatment. Declined IL-12 ($p = 0.048$) and IL-17A ($p = 0.002$) were linked to current biologics treatment (Table S1).

4 | DISCUSSION

Autoimmune disease patients often suffer from psychological problems, such as anxiety and depression.[17–19] For instance, ankylosing spondylitis patients have higher anxiety rates compared to healthy individuals.[20] Meanwhile, in contrast with healthy populations, RA patients exhibit higher anxiety and depression levels.[20] Additionally, a study claims that anxiety and depression are prevalent in inflammatory bowel disease (IBD) patients.[21] Conclusively, these

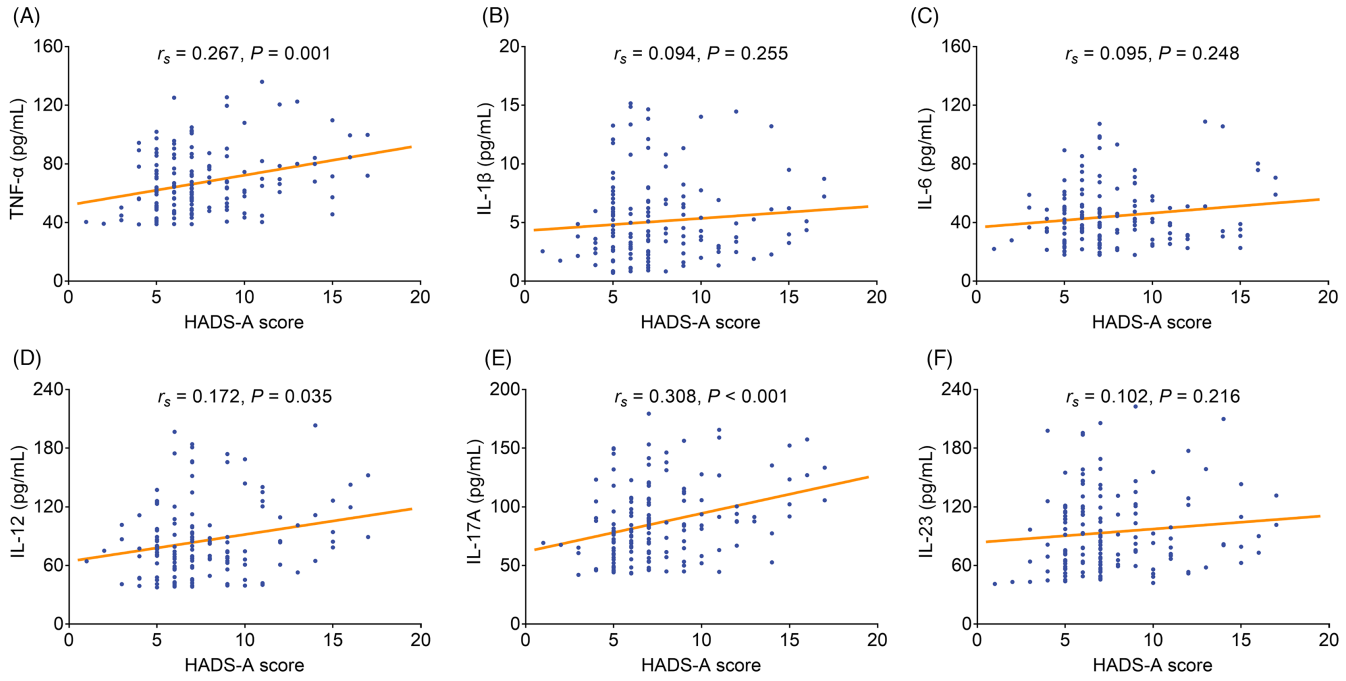

FIGURE 1 TNF-α, IL-12, and IL-17A were positively linked to HADS-A scores in psoriasis patients. Association of TNF-α (A), IL-1β (B), IL-6 (C), IL-12 (D), IL-17A (E), and IL-23 (F) with HADS-A score in psoriasis patients

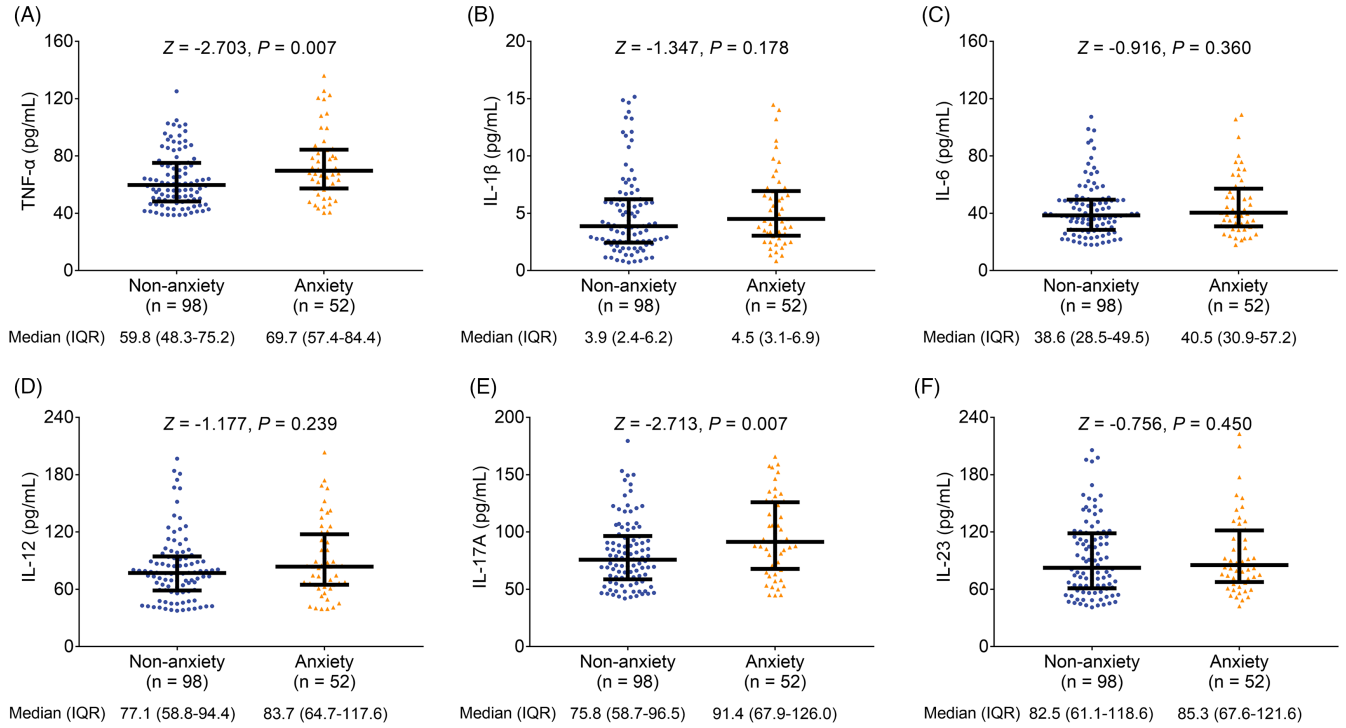

FIGURE 2 TNF-α and IL-17A were climbed in psoriasis patients with anxiety in contrast to those without anxiety. Comparison of TNF-α (A), IL-1β (B), IL-6 (C), IL-12 (D), IL-17A (E), and IL-23 (F) between psoriasis patients with and without anxiety

proinflammatory cytokines are related to anxiety or depression in these autoimmune disease patients; however, it remains unknown in psoriasis patients. The present study discovered that anxiety and depression were enhanced in psoriasis patients compared to HCs. It could be argued that compared with healthy individuals, psoriasis patients were more likely to suffer comorbidities and the body appearance damaged, which decreased the quality of life and social activities of psoriasis patients,[3,4,6,22] thus the prevalence of anxiety and depression was increased in psoriasis patients by contrast with HCs. Additionally, the inflammation status was generally higher in psoriasis patients; meanwhile, inflammation outbreaks were linked with the prevalence of anxiety and depression[13]; therefore, anxiety

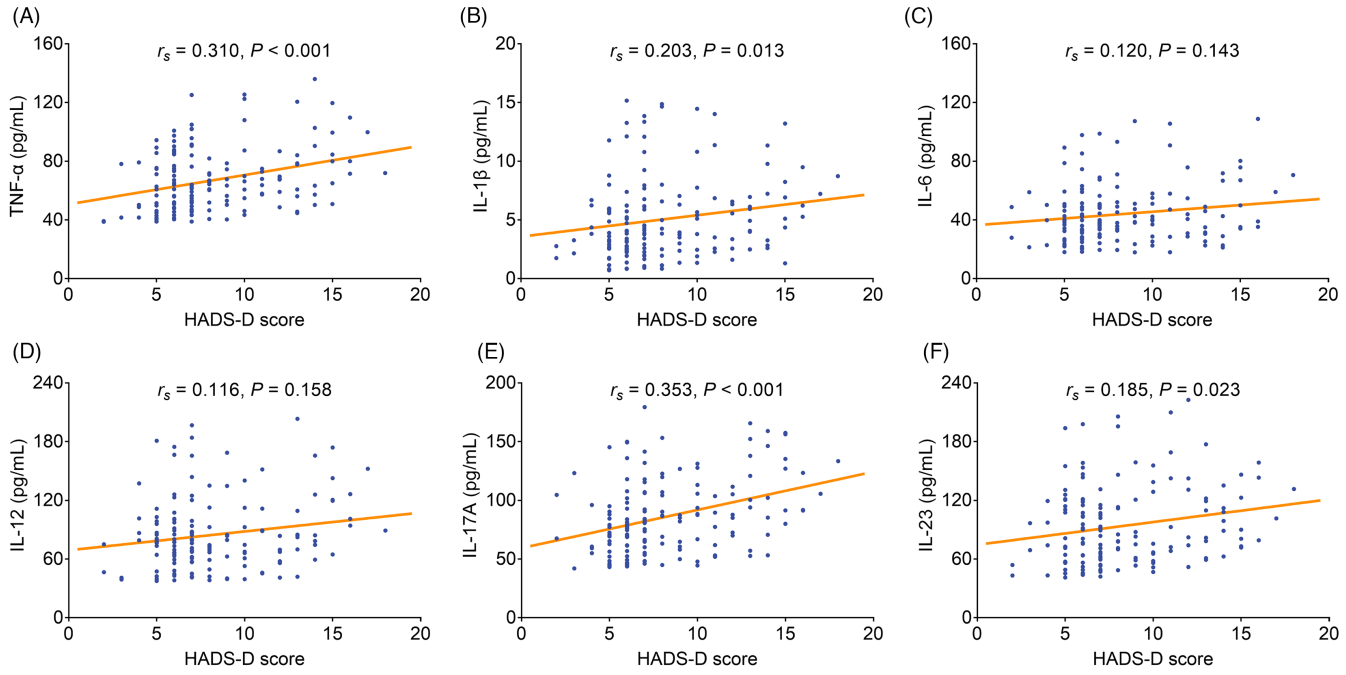

FIGURE 3 TNF-α, IL-1β, IL-17A, and IL-23 were positively linked with HADS-D scores in psoriasis patients. Correlation of TNF-α (A), IL-1β (B), IL-6 (C), IL-12 (D), IL-17A (E), and IL-23 (F) with HADS-D score in psoriasis patients

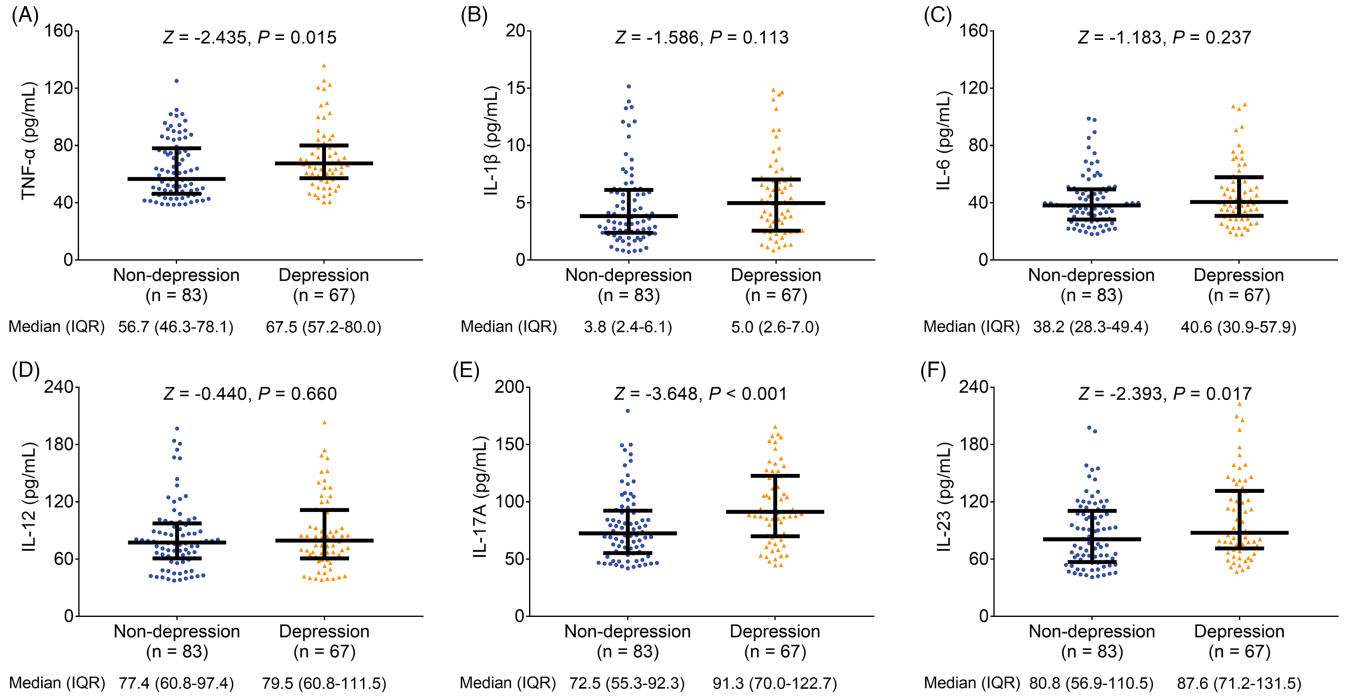

FIGURE 4 TNF-α, IL-17A, and IL-23 were raised in psoriasis patients with depression in contrast to those without depression. Comparison of TNF-α (A), IL-1β (B), IL-6 (C), IL-12 (D), IL-17A (E), and IL-23 (F) between psoriasis patients with and without depression

and depression were aggravated in psoriasis patients. In addition, this study also discovered that 34.7% of psoriasis patients had anxiety and 44.7% of psoriasis patients had depression. According to a previous stud, the prevalence of anxiety and depression is 36.0% and 19%, respectively.[23] Our finding suggested that anxiety prevalence was similar (34.7% vs. 36%) to previous data, however, the depression prevalence was increased (44.7% vs. 19%) in psoriasis patients. These indicated that anxiety and depression were serious issues in psoriasis patients.

Besides, the expressions of proinflammatory cytokines in psoriasis patients and HCs were further measured. In accordance with previous studies, this study found that common proinflammatory cytokines,

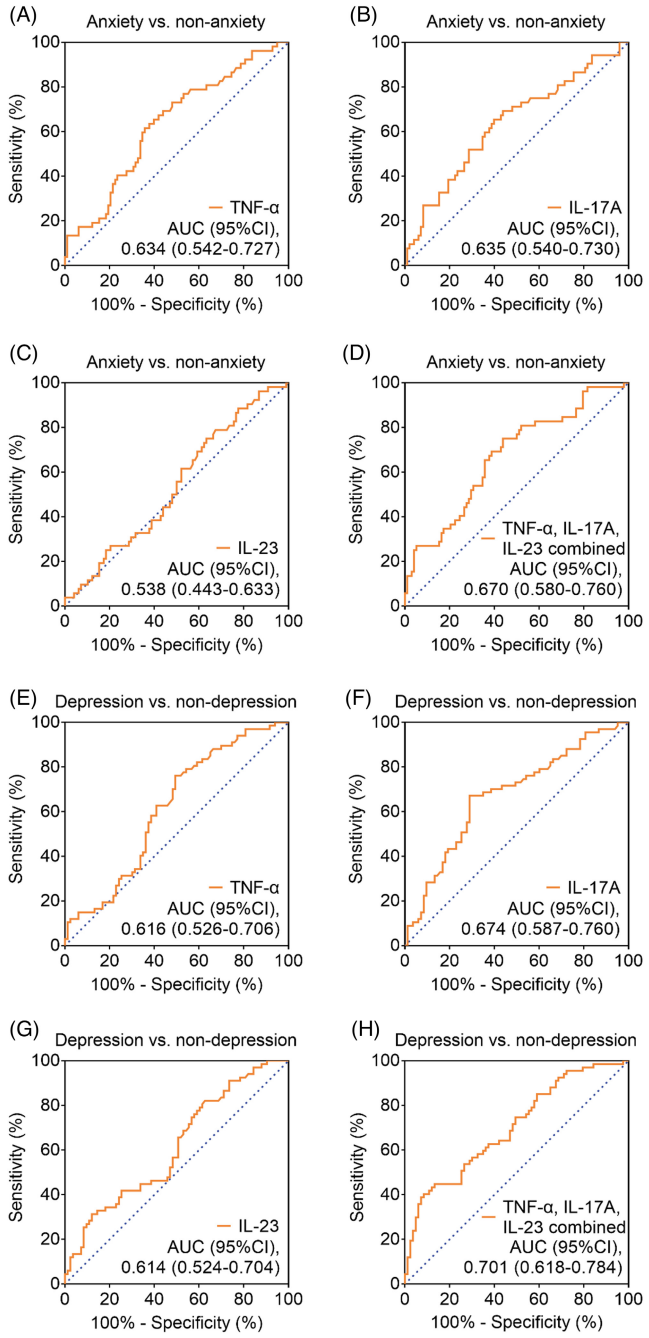

FIGURE 5 TNF-α, IL-17A, and IL-23, and their combination for estimating anxiety and depression in psoriasis patients. ROC curves of TNF-α (A), IL-17A (B), IL-23 (C), and their combination (D) for discriminating psoriasis patients with anxiety from those without anxiety; ROC curves of TNF-α (E), IL-17A (F), IL-23 (G), and their combination (H) for discriminating psoriasis patients with anxiety from those without anxiety

containing TNF-α, IL-1β, IL-6, IL-12, IL-17A, and IL-23, were enhanced in psoriasis patients compared to HCs.[1,24,25] The possible explanation would be that: proinflammatory cytokines participated in the progression and pathogenesis of psoriasis; for example, IL-1 mediated inflammation of psoriasis by activating macrophages to secrete IL-36[26]; meanwhile, IL-23 contributed to dermatitis pathogenesis of psoriasis through activating the signal transducer and activator of transcription 3-retinoid-related orphan receptor-γ T pathway to induce the release of IL-17A in macrophages[27]; therefore, TNF-α, IL-1β, IL-6, IL-12, IL-17A, and IL-23 were elevated in psoriasis patients compared to HCs.

Anxiety or depression may be linked to the release of proinflammatory cytokines in autoimmune disease patients.[15,28,29] For instance, depression symptom is discovered in RA patients with elevated serum IL-6 and IL-17[30]; at the same time, IL-6 and IL-17 not only cause arthritis but also induce depression in RA patients.[15] This study exhibited that IL-17A and TNF-α were positively linked to anxiety, while TNF-α, IL-17A, along with IL-23 were positively linked to depression in psoriasis patients. The possible reason might be that: proinflammatory cytokines might trigger anxiety and depression in various ways, for example, enhanced proinflammatory cytokines might activate the kynurenine pathway, leading to tryptophan depletion and reduced serotonin levels, which further causes depressive symptoms[13,31]; meanwhile, proinflammatory cytokines might also activate the HPA axis or affect the neurotransmitter metabolism, thereby causing anxiety or depression.[32] Therefore, TNF-α, IL-17A, and IL-23 increments were linked with aggravated depression and anxiety in psoriasis patients.

Several limitations existed in this study: (1) the HADS score for estimating anxiety and depression was a self-assessed questionnaire, which might exist an assessment bias; (2) although the linkage of proinflammatory cytokines with anxiety and depression was revealed, the detailed mechanism of these proinflammatory cytokines underlying anxiety and depression in psoriasis patients remained unclear; (3) using psoriatic tissues as samples might be more representative; subsequent studies could make improvements based on this consideration; (4) the pathogenesis of proinflammatory cytokines for regulating anxiety and depression might be different from other autoimmune diseases, further studies could take this into account and investigate the specific mechanisms; (5) some intermediate products, such as indoleamine 2,3-dioxygenase and serotonin were interacted with proinflammatory cytokines to regulate anxiety and depression; therefore, it was meaningful to detect these intermediate products as well; this could be the direction of further studies; (6) this study only assessed anxiety and depression after enrollment; further studies could explore the longitudinal changes in anxiety and depression by multiple points evaluation in psoriasis patients; (7) the linkage of proinflammatory cytokines with anxiety and depression in patients with other autoimmune diseases needed to be further explored; (8) this study revealed the linkage between proinflammatory cytokines and treatment modalities; however, whether the proinflammatory cytokines caused by treatments would further lead to anxiety and depression remained unclear; further studies could explore the linkage based on this consideration; (9) the treatments would directly modulate the levels of proinflammatory cytokines; therefore, this study evaluated the linkage between proinflammatory cytokines and treatment modalities; however, whether this regulation would further regulate anxiety and depression needed to be further explored.

In summary, TNF-α, IL-17A, and IL-23 increments might reflect anabatic anxiety and depression in psoriasis patients. This finding indicates the potential value of proinflammatory cytokines

measurement for monitoring or even preventing anxiety and depression in psoriasis patients.

FUNDING INFORMATION

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

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

INFORMED CONSENT

Both psoriasis patients and HCs provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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