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ORIGINAL ARTICLE

Serum hBD-2, IL-36γ, CCL20/MIP-3α, and soluble FGL-2 as innate-immune biomarkers in Iraqi patients with plaque psoriasis: a case-control study with diagnostic-performance evaluation

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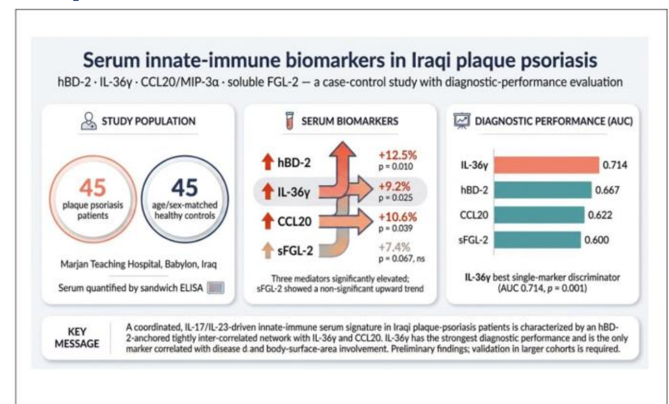
Abstract

Introduction: Plaque psoriasis is driven by an IL-23/IL-17–centred axis in which keratinocyte-derived innate mediators amplify and sustain cutaneous inflammation. Circulating biomarkers that capture this axis in Iraqi patients are poorly characterised. **Objective:** To compare serum human β-defensin-2 (hBD-2), interleukin-36γ (IL-36γ), CCL20/MIP-3α, and soluble fibrinogen-like protein 2 (sFGL-2) between adults with plaque psoriasis and matched healthy controls, and to evaluate their diagnostic performance. **Methods:** This case–control study enrolled 45 patients with clinically diagnosed plaque psoriasis and 45 age- and sex-matched healthy controls at Marjan Teaching Hospital, Babylon Governorate, Iraq (October 2025 – March 2026). Serum biomarkers were quantified by sandwich ELISA. Group comparisons, Pearson correlation, ROC analysis, and logistic regression were performed. **Results:** hBD-2, IL-36γ, and CCL20 were significantly higher in patients than controls (all $p < 0.05$); sFGL-2 showed a non-significant trend. Strong positive correlations were observed between hBD-2 and the other three mediators. IL-36γ had the best diagnostic performance (AUC = 0.714, $p = 0.001$). All four biomarkers were associated with psoriasis in univariate logistic regression, with attenuation in multivariable models consistent with shared pathway regulation. **Conclusion:** A coordinated innate-immune serum signature is present in Iraqi plaque-psoriasis patients; IL-36γ showed the most promising diagnostic utility, although these findings are hypothesis-generating and require validation before clinical use.

Keywords: Plaque psoriasis. Human β-defensin-2. Interleukin-36γ. CCL20. MIP-3α. Fibrinogen-like protein 2. Innate immunity. IL-17/IL-23 axis.

Graphical Abstract



Source: Own authorship.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease with substantial systemic comorbidity and a well-documented adverse impact on quality of life. A systematic review of population-based studies estimated an adult prevalence ranging from 0.51% to 11.4%, with considerable variation by region, latitude and age **[1]**. Psoriasis has been classified by

the World Health Organization as a serious non-communicable disease, and Global Burden of Disease data indicate an upward temporal trend in its age-standardised prevalence. Plaque psoriasis (psoriasis vulgaris) is the predominant clinical phenotype, accounting for approximately 80–90% of cases **[2]**.

The pathogenesis of plaque psoriasis is currently understood as a dysregulated cross-talk between keratinocytes and immune cells, centred on the TNF-α/IL-23/IL-17 axis. Plasmacytoid dendritic cells sense LL-37–nucleic-acid complexes released from damaged keratinocytes, activating myeloid dendritic cells to produce IL-12 and IL-23; IL-23 in turn maintains T-helper-17 (Th17) differentiation and IL-17A production. IL-17A then acts on keratinocytes to induce a large cassette of effector molecules — antimicrobial peptides, neutrophil-attracting chemokines and Th17-recruiting chemokines — that establish a self-perpetuating inflammatory loop **[3]**.

Among the innate mediators induced in this loop, four have attracted particular interest as candidate circulating biomarkers. Human β-defensin-2 (hBD-2) is an antimicrobial peptide whose *DEFB4* gene is one of the most strongly upregulated transcripts in lesional psoriatic skin; serum hBD-2 has repeatedly correlated with PASI and with IL-17A levels in biologic-treated cohorts **[4–6]**. Interleukin-36γ (IL-36γ / IL-1F9) is a keratinocyte-derived IL-1-family cytokine highly enriched in psoriatic lesions; it amplifies IL-23 production by myeloid cells, synergises with TNF-α/IL-17A, and has been proposed as both a tissue and a circulating biomarker for plaque psoriasis **[7–9]**. CCL20 (MIP-3α) is the sole ligand of CCR6 and the principal chemokine that recruits CCR6⁺ Th17 cells, γδT cells and immature dendritic cells into inflamed skin; it is induced in keratinocytes by IL-17A, IL-22 and TNF-α and correlates with PASI and vascular endothelial inflammation in psoriasis **[10–12]**. Soluble fibrinogen-like protein 2 (sFGL-2) is a secreted immunoregulatory protein released by regulatory T cells and activated immune cells; it has dual procoagulant (membrane-bound) and immunomodulatory (soluble) functions and is dysregulated in several chronic inflammatory and autoimmune conditions, although its role in psoriasis has not been well established **[13-14]**.

Despite the strong mechanistic rationale for each of these four molecules, data on their *simultaneous* circulating behaviour in plaque psoriasis — and in Middle-Eastern populations specifically — remain sparse. Recent systematic and scoping reviews of the field have shown that psoriasis biomarkers have largely been evaluated in isolation rather than as integrated panels, and that, despite intensive research, no circulating biomarker has yet entered routine clinical practice for diagnosis, prognosis or treatment monitoring **[15-17]**. Within this gap, the absence of validated multi-marker serum signatures is repeatedly identified as a key unmet need.

This limitation is particularly acute in the regional literature: Iraqi studies have so far focused predominantly on single cytokines or peptides — such as IL-18/TNF-α **[18]**, IL-36 in female patients **[19]**, composite severity markers **[20]**, TGF-β1 **[21]** and IL-36α gene expression **[22]** - rather than a combined innate-immune panel. The innate-immune serum signature combining hBD-2, IL-36γ, CCL20 and sFGL-2 in one cohort of plaque-psoriasis patients has — to our knowledge - not been previously reported in Iraq, and its collective diagnostic performance is unknown.

The present study therefore aimed to: (i) measure and compare serum hBD-2, IL-36γ, CCL20/MIP-3α and sFGL-2 between Iraqi adults with plaque psoriasis and age- and sex-matched healthy controls; (ii) examine correlations among these biomarkers and with clinical severity parameters (disease duration and body surface area involvement); and (iii) evaluate the diagnostic performance of each biomarker, individually and in a multivariable logistic-regression framework, for discriminating plaque psoriasis from controls.

Materials and Methods

Study design and ethical approval

This was a single-centre, hospital-based, age- and sex-matched case-control study conducted in accordance with the ethical principles of the Declaration of Helsinki (as amended by the 75th WMA General Assembly, Helsinki, October 2024) **[23]**. The study protocol was reviewed and approved by the Research Administration Unit of the Training and Human Development Center, Babylon Health Directorate, Iraqi Ministry of Health, under reference number 1630, subsequent to the formal letter of the Graduate Studies Division, College of Medicine, University of Babylon (reference No. 88756 dated 27 October 2025). Institutional approval for patient recruitment was obtained from the administration of Marjan Teaching Hospital, Babylon Governorate, Iraq. Written informed consent was obtained from every participant (or from a legal guardian where appropriate) before any study-related procedure, and participants were informed of their right to withdraw at any time without penalty. Personal data were handled confidentially and only de-identified data were used for analysis. The study is reported in accordance with the STROBE statement for observational research **[24]**.

Study setting and duration

Cases were recruited from the Dermatology Outpatient Clinic of Marjan Teaching Hospital, Hillah, Babylon Governorate, Iraq, between 27 October 2025 and 25 March 2026 (total recruitment duration ≈ 5 months). Controls were recruited concurrently from the hospital's general-health-screening service and staff volunteers.

Participants

Cases were consecutive adults aged ≥ 18 years who attended the clinic during the recruitment period and in whom a clinical diagnosis of chronic plaque psoriasis had been established by a certified dermatologist on the basis of recognised clinical criteria (well-demarcated, erythematous plaques with silvery scaling over extensor surfaces, scalp and/or trunk), in keeping with current international consensus [2].

Inclusion criteria (cases): (1) age 18–65 years; (2) clinically confirmed plaque psoriasis of at least 6-month duration; (3) willingness to provide written informed consent.

Exclusion criteria (cases): (1) non-plaque variants (guttate, erythrodermic, generalised pustular, palmoplantar pustulosis, inverse); (2) concurrent psoriatic arthritis requiring systemic therapy; (3) use of systemic immunomodulators, biologic agents, oral retinoids, methotrexate, cyclosporine or phototherapy within the preceding 4 weeks; (4) use of potent/very-potent topical corticosteroids, vitamin-D analogues or calcineurin inhibitors within the preceding 2 weeks; (5) any other chronic inflammatory or autoimmune disease (rheumatoid arthritis, systemic lupus, inflammatory bowel disease, systemic vasculitis); (6) acute or chronic infection within the preceding 2 weeks; (7) chronic hepatitis B or C, HIV, or active tuberculosis; (8) active malignancy; (9) pregnancy or lactation; (10) uncontrolled diabetes mellitus, uncontrolled hypertension, or known ischaemic heart disease.

Controls were apparently healthy adults, matched to the case group by age (± 5 years) and sex. Controls had no personal or first-degree family history of psoriasis, no chronic inflammatory or autoimmune disease, no active infection within the previous 2 weeks, and were not taking immunomodulatory medication.

Sample-size considerations and statistical justification

The recruitment target of 45 cases and 45 controls was determined a priori as the maximum number of eligible, consenting participants who could realistically be enrolled and have serum analysed within the available 5-month single-centre window, while remaining adequately powered for the primary between-group comparison. A formal a priori power calculation for the two-independent-sample comparison of means (independent-samples t-test) was performed using the standard formula $n = 2(z_{1-\alpha/2} + z_{1-\beta})^2/d^2$, where d is the standardised effect size (Cohen's d). With a two-sided $\alpha = 0.05$ ($z = 1.96$) and power of 80% ($z = 0.84$), a sample of 45 per group is sufficient to detect a standardised mean difference of Cohen's d ≈ 0.60 (i.e., a moderate effect). This target effect size is consistent with, and slightly more conservative than, the serum hBD-2 and IL-36γ effect sizes reported in prior plaque-psoriasis cohorts [4,7], which informed the assumption. The achieved effect size for the primary biomarker (hBD-2, d = 0.59) closely matched this design assumption, supporting the adequacy of the sample for the principal comparison. The power calculation was performed in G*Power 3.1, and post-hoc verification was conducted in MedCalc; smaller effects (e.g., the sFGL-2 difference, d = 0.41) were, as expected, underpowered at this sample size and are interpreted accordingly in the Discussion.

Clinical assessment and data collection

Demographic data (age, sex), smoking history (current/former vs never), disease duration

(years) and body surface area (BSA) involvement were recorded on a standardised case-report form. Disease duration was calculated from the date of first clinically documented diagnosis to the date of study inclusion. BSA was estimated by the dermatologist using the "rule-of-nines" and the patient's palm-surface method, consistent with routine clinical practice [25,26]. The Psoriasis Area and Severity Index (PASI) was calculated where complete lesion mapping was available.

Blood sampling and processing

After an overnight fast of ≥ 8 hours, a venous blood sample (5 mL) was collected between 08:00 and 11:00 a.m. from each participant into a plain serum-separator tube under aseptic conditions. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3,000 × g for 10 minutes. Serum was aliquoted into labelled Eppendorf tubes and stored at −80 °C until batched analysis, avoiding repeated freeze–thaw cycles, in accordance with manufacturer recommendations.

Quantification of serum biomarkers

All four biomarkers were quantified by enzyme-linked immunosorbent assay (ELISA) using

commercially available sandwich ELISA kits manufactured by BT LAB (Bioassay Technology Laboratory, Jiaxing, Zhejiang, China), following the manufacturer's protocol exactly. All samples were run in duplicate; mean values were used for analysis. Absorbance was read at 450 nm on a microplate reader, and concentrations were calculated from a freshly constructed four-parameter standard curve. Intra-assay and inter-assay coefficients of variation were < 8% and < 10%, respectively, as per manufacturer specifications. The kit-specific characteristics are summarised in Table 1.

Table 1. Characteristics of the commercial ELISA kits used to quantify the four serum biomarkers.

Biomarker	Manufacturer	Catalogue No.	Standard curve range	Analytical sensitivity	CV (intra/ inter)
Human β-defensin-2 (hBD2)	BT LAB, China	E1936Hu	10 – 4000 ng/L	5.31 ng/L	< 8% / < 10%
Human interleukin-36γ (IL-36γ / IL-1F9)	BT LAB, China	E4404Hu	30 – 9000 ng/L	16.54 ng/L	< 8% / < 10%
Human MIP-3α (CCL20)	BT LAB, China	E0086Hu	10 – 2000 ng/L	4.23 ng/L	< 8% / < 10%
Human soluble FGL-2 (sFGL-2)	BT LAB, China	E7626Hu	2.5 – 160 ng/mL	1.11 ng/mL	< 8% / < 10%

All kits use a sandwich ELISA principle with streptavidin-HRP detection and TMB substrate; absorbance measured at 450 nm. CV — coefficient of variation. Source: Compiled by the authors from the manufacturer's (BT LAB) kit specifications.

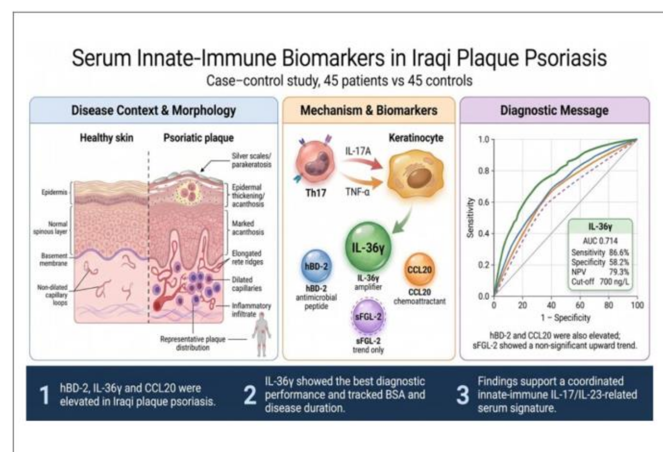
Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA) and MedCalc Software, version 23.1 (MedCalc Software Ltd., Ostend, Belgium). The normality of continuous variables was examined using the Shapiro–Wilk test. Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and compared between groups with the independent-samples t-test; non-normally distributed variables are expressed as median (interquartile range, IQR) and compared with the Mann–Whitney U test. Categorical variables are reported as frequencies (percentages) and compared using the χ^2 test or Fisher's exact test as appropriate. Between-group effect sizes for continuous variables were reported as Cohen's d calculated from the pooled standard deviation (interpreted as small ≈ 0.2, medium ≈ 0.5, large ≈ 0.8). Associations between continuous variables were assessed by Pearson correlation.

Receiver-operating-characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of each biomarker, reporting the area under the curve (AUC) with 95% confidence interval (Hanley–McNeil method), optimal cut-off (Youden index), sensitivity, specificity, and positive and negative predictive values (PPV and NPV). Binary logistic regression was used to model psoriasis status (1 = case, 0 = control) as a function of each biomarker, with age and sex as covariates in the multivariable model. Regression results are reported as odds ratios (OR) with 95% CI. Model fit was assessed by McFadden's pseudo-R^2. Because smoking showed complete separation (no smokers in the control group), it could not be estimated by maximum likelihood and was therefore excluded from the multivariable model; a sensitivity analysis using Firth's penalised (bias-reduced) logistic regression is recommended for future work [27]. A two-sided p-value < 0.05 was considered statistically significant.

Results

Framework and overall results



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Demographic and clinical characteristics

A total of 90 participants were enrolled, comprising 45 patients with plaque psoriasis and 45 age- and sex-matched healthy controls. The two groups were comparable with respect to age (37.1 ± 14.6 vs. 39.3 ± 12.1 years; p = 0.442) and sex distribution (males: 53.3% vs. 44.4%; p = 0.228). A significantly higher proportion of smokers was observed in the patient group (28.9% vs. 0%; p < 0.001). Among patients, the median disease duration was 5.0 years (IQR 2.0–16.5) and the median body surface area (BSA) involvement was 0.25% (IQR 0.085–0.70) (Table 2).

Table 2. Demographic and clinical characteristics of patients with plaque psoriasis and healthy controls.

Variable		Patients (n = 45)	Controls (n = 45)	p-value
Age (years)	Mean ± SD	37.1 ± 14.6	39.3 ± 12.1	0.442
	Range	18 – 65	18 – 65	—
Sex, n (%)	Male	24 (53.3)	20 (44.4)	0.228
	Female	21 (46.7)	25 (55.6)	—
Smoking, n (%)	Yes	13 (28.9)	0 (0.0)	**< 0.001**
	No	32 (71.1)	45 (100.0)	—
Disease duration (years)	Median (IQR)	5.0 (2.0 – 16.5)	—	—
Body surface area (%)	Median (IQR)	0.25 (0.085 – 0.70)	—	—

Independent-samples t-test for age; χ² test for categorical variables. Bold $p < 0.05$. SD — standard deviation; IQR — interquartile range. Source: Prepared by the authors from the present study's data.

Serum biomarker levels in patients and controls

Serum concentrations of three innate-immune mediators were significantly elevated in patients with plaque psoriasis compared with healthy controls (Table 3, Figure 1). hBD-2 was higher in patients than in controls (345.1 ± 67.7 vs. 306.7 ± 63.3 ng/L; $p = 0.010$; Cohen's $d = 0.59$). CCL20/MIP-3α (200.4 ± 47.5 vs. 181.2 ± 33.0 ng/L; $p = 0.039$; $d = 0.47$) and IL-36γ (766.8 ± 134.7 vs. 702.1 ± 149.8 ng/L; $p = 0.025$; $d = 0.45$) were also significantly increased. Serum sFGL-2 showed a trend toward higher levels in patients (26.1 ± 4.54 vs. 24.3 ± 4.15 ng/mL; $p = 0.067$; $d = 0.41$) without reaching statistical significance.

Subgroup analyses within the patient group revealed no statistically significant differences in any biomarker according to sex or smoking status (all $p > 0.05$; Supplementary Tables S1–S2), indicating that the observed elevations were not driven by these factors.

Table 3. Comparison of serum biomarker concentrations between patients with plaque psoriasis and healthy controls.

Biomarker	Group	Mean ± SD	95% CI	p-value	Cohen's d
hBD-2 (ng/L)	Patients (n=45)	345.1 ± 67.7	324.8 – 365.4	0.010	0.59
	Controls (n=45)	306.7 ± 63.3	287.7 – 325.7		
CCL20/MIP-3α (ng/L)	Patients (n=45)	200.4 ± 47.5	186.1 – 214.7	0.039	0.47
	Controls (n=45)	181.2 ± 33.0	171.3 – 191.1		
IL-36γ (ng/L)	Patients (n=45)	766.8 ± 134.7	726.3 – 807.3	0.025	0.45
	Controls (n=45)	702.1 ± 149.8	657.1 – 747.1		
sFGL-2 (ng/mL)	Patients (n=45)	26.1 ± 4.54	24.74 – 27.46	0.067	0.41
	Controls (n=45)	24.3 ± 4.15	23.05 – 25.55		

Values are mean ± SD with 95% CI of the mean. Independent-samples t-test. Bold $p < 0.05$. Source: Prepared by the authors from the present study's data.

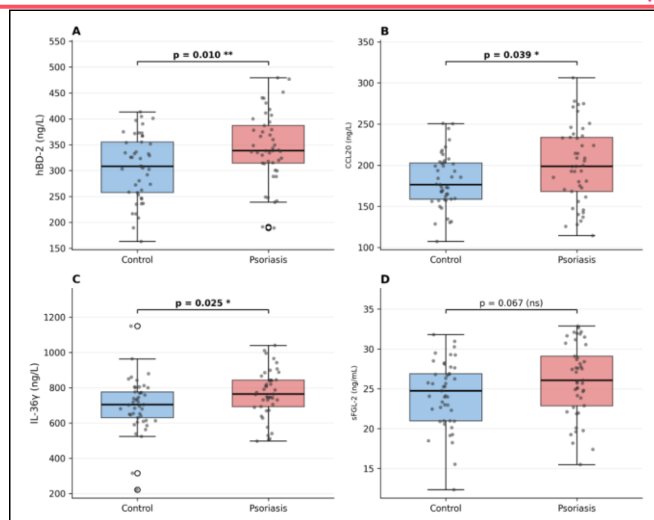

Figure 1. Comparison of serum concentrations of the four innate-immune biomarkers in patients with plaque psoriasis (n = 45) and healthy controls (n = 45). Panels: (A) hBD-2 (ng/L); (B) CCL20/MIP-3α (ng/L); (C) IL-36γ (ng/L); (D) sFGL-2 (ng/mL). In each panel the x-axis denotes the study group (patients vs. healthy controls) and the y-axis denotes the serum concentration of the corresponding biomarker in the units indicated. Data are presented as box-and-whisker plots (box = interquartile range; central line = median; whiskers = 1.5 × IQR) overlaid with individual data points. Between-group comparisons were performed using independent-samples t-tests; significance is indicated as *$p < 0.05$; **$p \leq 0.01$; ns = not significant. Source: Prepared by the authors from the present study's data.

Correlations among biomarkers and with clinical parameters

Pearson correlation analysis revealed significant positive correlations among the three elevated biomarkers (Table 4, Figure 2). hBD-2 was strongly correlated with CCL20 ($r = 0.536$, $p < 0.001$), sFGL-2 ($r = 0.534$, $p < 0.001$), and IL-36γ ($r = 0.474$, $p = 0.001$). CCL20 and sFGL-2 were also significantly correlated ($r = 0.431$, $p = 0.005$), suggesting shared activation of innate inflammatory pathways. With respect to clinical severity, disease duration correlated significantly with hBD-2 ($r = 0.344$, $p = 0.026$) and IL-36γ ($r = 0.325$, $p = 0.036$), whereas BSA correlated significantly only with IL-36γ ($r = 0.364$, $p = 0.018$) (Figure 3).

Table 4. Pearson correlation coefficients among serum biomarkers and clinical severity parameters in patients with plaque psoriasis (n = 45).

Variable	hBD-2	IL-36γ	CCL20	sFGL-2	Disease duration
hBD-2	—	r=0.474; p=0.001*	r=0.536; p<0.001**	r=0.534; p<0.001**	r=0.344; p=0.026*
IL-36γ	r=0.474; p=0.001*	—	r=0.177; p=0.261	r=0.266; p=0.088	r=0.325; p=0.036*
CCL20	r=0.536; p<0.001**	r=0.177; p=0.261	—	r=0.431; p=0.005*	r=0.192; p=0.228

sFGL-2	r=0.534; p<0.001**	r=0.266; p=0.088	r=0.431; p=0.005*	—	r=0.242; p=0.123
BSA (%)	r=0.100; p=0.531	r=0.364; p=0.018*	r=0.088; p=0.584	r=0.173; p=0.279	—

*p < 0.05, **p < 0.01. BSA — body surface area. Source: Prepared by the authors from the present study's data.

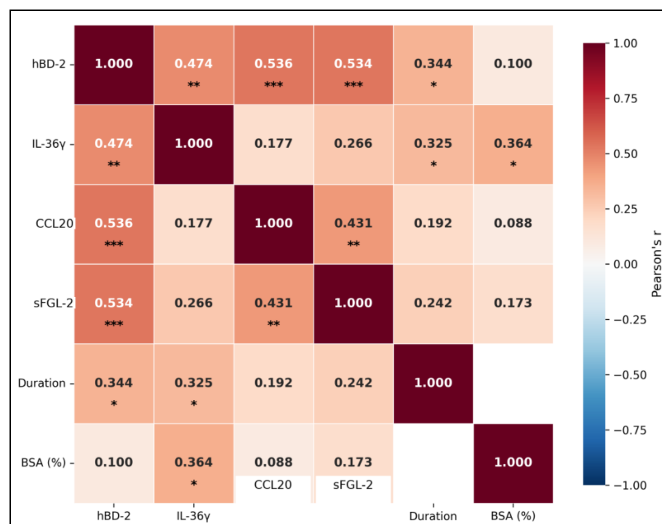

Figure 2. Correlation heatmap of the four serum biomarkers (hBD-2, IL-36γ, CCL20 and sFGL-2) and two clinical severity parameters (disease duration and BSA) in patients (n = 45). Both axes list the variables; each cell shows the pairwise Pearson correlation coefficient (r), and the colour scale encodes the magnitude and direction of r (warmer = stronger positive correlation). Asterisks denote statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001. Source: Prepared by the authors from the present study's data.

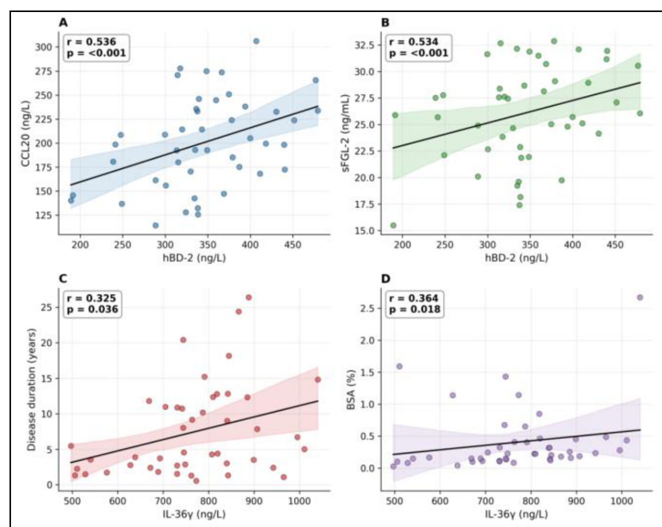

Figure 3. Scatter plots of the most clinically relevant correlations in patients (n = 45): (A) hBD-2 (x-axis, ng/L) vs. CCL20 (y-axis, ng/L); (B) hBD-2 (x-axis, ng/L) vs. sFGL-2 (y-axis, ng/mL); (C) IL-36γ (x-axis, ng/L) vs. disease duration (y-axis, years); (D) IL-36γ (x-axis, ng/L) vs. BSA (y-axis, %). In each panel the solid line is the linear-regression fit and the shaded band is the 95% bootstrap confidence interval; the Pearson r and p-value for each pair are reported in Section 3.3 and Table 4. Source: Prepared by the authors from the present study's data.

Diagnostic performance of biomarkers

Receiver-operating-characteristic (ROC) analysis was performed to evaluate the discriminative capacity of each biomarker (Table 5, Figure 4). IL-36γ demonstrated the highest diagnostic performance, with an AUC of 0.714 (95% CI 0.608–0.820; p = 0.001); at a cut-off of 700.0 ng/L, sensitivity and specificity were 86.6% and 58.2%, with a negative predictive value of 79.3%. hBD-2 achieved an AUC of 0.667 (95% CI 0.555–0.779; p = 0.005) at a cut-off of 334.8 ng/L (sensitivity 63.6%, specificity 61.5%). CCL20 showed modest discrimination (AUC = 0.622; 95% CI 0.506–0.738; p = 0.050), while sFGL-2 did not reach statistical significance (AUC = 0.600; 95% CI 0.483–0.717; p = 0.112).

Table 5. ROC-curve diagnostic performance of serum biomarkers for discriminating plaque psoriasis from healthy controls.

Biomarker	Cut-off	AUC (95% CI)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	p-value
IL-36γ	700.0 ng/L	0.714 (0.608–0.820)	86.6	58.2	75.0	79.3	0.001
hBD-2	334.8 ng/L	0.667 (0.555–0.779)	63.6	61.5	64.4	60.5	0.005
CCL20	189.2 ng/L	0.622 (0.506–0.738)	66.6	63.8	69.8	60.5	0.050
sFGL-2	24.9 ng/mL	0.600 (0.483–0.717)	69.7	47.3	60.0	58.1	0.112

Cut-offs identified by the Youden index. 95% CIs computed by the Hanley–McNeil method. Biomarkers ranked in descending order of AUC. Bold p < 0.05. Source: Prepared by the authors from the present study's data.

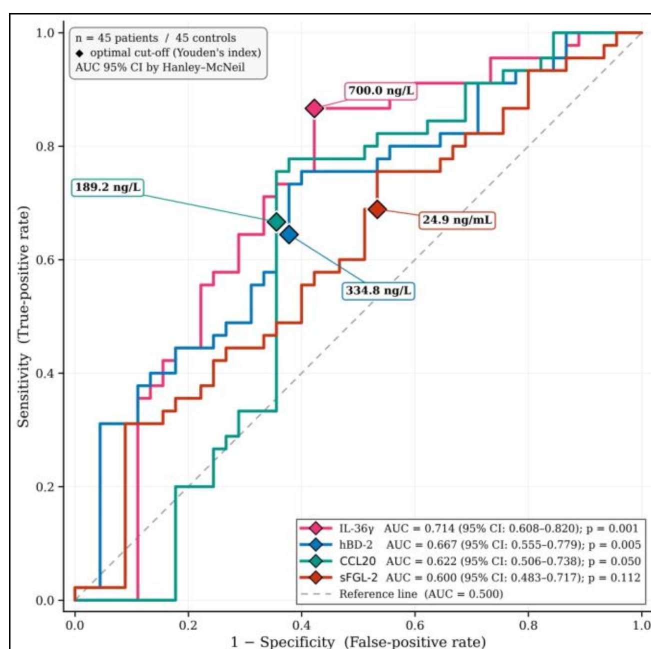

Figure 4. ROC curves of the four biomarkers for discriminating patients (n = 45) from controls (n = 45). The

x-axis is 1 − specificity (false-positive rate) and the y-axis is sensitivity (true-positive *rate); each coloured curve corresponds to one biomarker (hBD-2, IL-36γ, CCL20, sFGL-2) with its AUC reported in the legend and in Table 5. Filled diamonds mark the Youden-optimal cut-off for each curve with the annotated concentration, and the grey dashed diagonal is the no-discrimination reference line (AUC = 0.500). Source: Prepared by the authors from the present study's data.*

Univariate and multivariable logistic regression

To identify independent predictors of plaque psoriasis, univariate and multivariable binary logistic regression analyses were performed (Table 6). Univariately, each of the four biomarkers was associated with the odds of plaque psoriasis, with hBD-2 showing the strongest significance (OR = 1.010; 95% CI 1.009–1.016; p = 0.013). In the multivariable model adjusting for the other biomarkers, age and sex, the effect sizes retained their expected direction but the individual biomarker coefficients were attenuated - a finding consistent with the substantial inter-correlations among the biomarkers (Table 4). This pattern suggests that the four mediators partially reflect a shared innate-immune inflammatory signature rather than fully independent biological processes. Smoking was excluded from the multivariable model owing to complete separation (no smokers among controls); a sensitivity analysis using Firth's bias-reduced logistic regression is recommended. The overall model had a McFadden's pseudo-R^2 of 0.099, consistent with a modest but non-trivial contribution of the biomarker panel to psoriasis classification beyond demographic factors.

Table 6. Univariate and multivariable binary logistic regression for serum biomarkers, age and sex as predictors of plaque psoriasis.

Variable	Univariate OR	p-value	β	OR (95% CI)	SE	p-value (multi)
hBD-2 (per 1 ng/L)	1.010 (1.009–1.016)	0.013	0.0039	1.004 (0.995–1.013)	0.0044	0.377
IL-36γ (per 1 ng/L)	1.003 (1.000–1.006)	0.025	0.0025	1.002 (0.999–1.006)	0.0018	0.156
CCL20 (per 1 ng/L)	1.010 (1.001–1.020)	0.039	0.0070	1.007 (0.994–1.020)	0.0064	0.275
sFGL-2 (per 1 ng/mL)	1.099 (0.994–1.216)	0.067	0.0602	1.062 (0.941–1.199)	0.0620	0.331
Age (per 1 year)	0.988 (0.960–1.017)	0.442	–0.0094	0.991 (0.957–1.025)	0.0175	0.589
Sex (M vs F)	1.429 (0.804–2.538)	0.228	0.4685	1.598 (0.628–4.066)	0.4766	0.326
Smoking (Y vs N) [a]	Inestimable	< 0.001	—	Excluded	—	—

Outcome: psoriasis status (1 = case, 0 = control). McFadden's pseudo-R^2 (multivariable) = 0.099. [a] Smoking showed complete separation (28.9% of patient vs 0% of controls); the ML estimate diverges, so smoking was excluded from the multivariable model. Firth's bias-reduced logistic regression is recommended as a sensitivity analysis. Source: Prepared by the authors from the present study's data.

Discussion

Principal findings

In this case-control study of Iraqi adults, we observed that three of four innate-immune serum biomarkers — hBD-2, IL-36γ and CCL20/MIP-3α — were significantly elevated in plaque-psoriasis patients compared with healthy controls, with small-to-moderate effect sizes (Cohen's d = 0.45–0.59). sFGL-2 showed a trend in the same direction without reaching statistical significance. The elevations were independent of sex and smoking status within the patient group. Pearson correlation analysis identified hBD-2 as the hub of a tightly correlated innate-immune network connecting all three other biomarkers, and IL-36γ was the only biomarker simultaneously correlated with both disease duration and body surface area. In ROC analysis, IL-36γ demonstrated the most discriminative performance (AUC = 0.714), followed by hBD-2 (0.667). Finally, in logistic-regression analysis, all four biomarkers were univariately associated with psoriasis but lost their individual independence in the multivariable model — a pattern that is biologically consistent with collinearity among members of a single IL-17/IL-23-driven innate-immune axis.

These findings contribute three observations to the literature: (a) the first simultaneous quantification of hBD-2, IL-36γ, CCL20 and sFGL-2 in an Iraqi plaque-psoriasis cohort; (b) reinforcement of IL-36γ as the serum biomarker with the best single-marker diagnostic performance; and (c) preliminary evidence that sFGL-2 — an immunoregulatory molecule not previously well studied in psoriasis — trends upward in this population and is tightly correlated with hBD-2 and CCL20.

hBD-2: antimicrobial peptide as a disease-activity surrogate

hBD-2 is one of the most upregulated transcripts in lesional psoriatic epidermis and is induced in keratinocytes by the synergistic action of IL-17A and TNF-α through NF-κB and IκBζ-dependent pathways **[3,28]**. Our finding of significantly higher serum hBD-2 in patients (345.1 ± 67.7 ng/L) than controls (306.7 ± 63.3 ng/L; p = 0.010, d = 0.59) is directionally consistent with the seminal work of Jansen et al. **[4]**, who demonstrated that serum hBD-2 protein levels correlated strongly with PASI score in European patients and reached very high concentrations in severely affected individuals. Kolbinger et al. **[5]** subsequently showed in a large multi-disease validation

cohort that BD-2 levels are most strongly elevated in patients with psoriatic skin lesions, correlate with IL-17A and PASI, and decline with secukinumab therapy. Jin et al. **[6]** reported that hBD-2 falls in parallel with PASI during JAK inhibition, supporting its responsiveness to treatment. The absolute magnitude of our mean difference is smaller than that reported by Jansen et al. **[4]** - plausibly because our cohort had very low median BSA (0.25%), indicating a predominantly mild-to-moderate disease phenotype, whereas Jansen's dose - response signal was driven largely by patients with severe PASI. Our data therefore reinforce the view that even comparatively mild plaque psoriasis carries a measurable systemic hBD-2 signal, and that hBD-2 may be better characterised as a graded surrogate of cutaneous IL-17A activity than as a binary diagnostic marker.

IL-36γ: IL-1-family amplifier and Iraqi-cohort diagnostic leader

IL-36γ (IL-1F9) is a keratinocyte-derived IL-1-family member that signals through the IL-36R / IL-1RAcP complex to activate NF-κB and MAPK pathways **[7,29]**. It participates in a positive feedback loop with IL-17A and TNF-α, induces the production of further pro-inflammatory mediators including CCL20, and enhances myeloid-cell production of IL-23 in psoriatic macrophages **[9]**. D'Erme et al. **[7]** originally established IL-36γ as the most discriminative transcript distinguishing psoriasis from other inflammatory dermatoses and showed that serum IL-36γ correlates with disease activity and falls after anti-TNF therapy. Traks et al. **[8]** further demonstrated that genetic variants in IL36G are associated with plaque-psoriasis susceptibility in a large European cohort. In our study, IL-36γ showed the highest AUC (0.714, p = 0.001) of the four biomarkers, the highest sensitivity at the Youden-optimal cut-off (86.6%), and was the only biomarker simultaneously correlated with both disease duration (r = 0.325, p = 0.036) and BSA (r = 0.364, p = 0.018). Together with the Iraqi findings of Khazem and Ibraheem, who reported significantly elevated serum IL-36 in Iraqi female psoriasis patients compared with controls **[19]**, and of Mahmood and colleagues, who observed altered IL-36α gene expression in Iraqi psoriatics **[22]**, these data position IL-36γ as the single most promising serum biomarker in our local context. Clinically, the strong sensitivity (86.6%) and acceptable NPV (79.3%) of a 700 ng/L cut-off could be useful as a ruling-out marker if validated in larger, severity-stratified cohorts; specificity (58.2%) remains insufficient for stand-alone diagnostic use.

CCL20/MIP-3α: Th17 chemoattractant in circulation

CCL20 is the sole chemokine ligand of CCR6, and the CCL20–CCR6 axis is central to the recruitment of Th17, Tc17, γδT, ILC3 and immature dendritic cells into psoriatic lesional skin. Keratinocytes upregulate CCL20 in response to IL-17A, IL-22 and TNF-α, creating a self-sustaining loop **[10,11]**. Our patients had higher mean serum CCL20 than controls (200.4 ± 47.5 vs 181.2 ± 33.0 ng/L; p = 0.039, d = 0.47), a moderate effect size consistent with published estimates. Elnabawi et al. **[12]** identified CCL20 as one of the most upregulated circulating proteins in plaque psoriasis among 273 analytes screened and reported a correlation with PASI, with an independent association with vascular endothelial inflammation. The modest discriminative performance of CCL20 in our study (AUC 0.622, p = 0.050) is compatible with literature data and reflects the fact that serum levels integrate skin-derived production with pleiotropic chemokine activity at other mucosal sites. Importantly, CCL20 was strongly correlated with hBD-2 (r = 0.536) and with sFGL-2 (r = 0.431), reinforcing the interpretation that it is part of a coherent innate-immune network rather than an independent signal.

Soluble FGL-2: an exploratory finding in plaque psoriasis

Soluble FGL-2 is a member of the fibrinogen-related protein superfamily with pleiotropic functions: its membrane-bound form has immune-associated prothrombinase activity, while the secreted form (sFGL-2) acts as a regulatory immunomodulator — an effector molecule of $CD4^{+}CD25^{+}$ regulatory T cells capable of suppressing T-cell proliferation and dendritic-cell maturation **[13,14]**. sFGL-2 is dysregulated in viral hepatitis, inflammatory bowel disease, allograft rejection, glioma and systemic autoimmunity, but data in psoriasis are remarkably scarce. We observed a non-significant trend toward higher sFGL-2 in patients (26.1 ± 4.54 vs 24.3 ± 4.15 ng/mL; p = 0.067), a tight correlation with hBD-2 (r = 0.534) and a significant correlation with CCL20 (r = 0.431). Given these correlations, the direction of effect, and the underpowered nature of a 45-vs-45 comparison for detecting a small-to-moderate shift, our data should be interpreted as hypothesis-generating: they are compatible with the biologically plausible notion that an expanded or over-active regulatory T-cell pool is co-mobilised in response to Th17-driven cutaneous inflammation. A closely related protein, FGL-1, was recently identified as an inversely correlated biomarker of psoriasis severity in a large Chinese

cohort **[30]**, reinforcing that fibrinogen-like proteins as a class merit further dedicated study in psoriasis. Our findings do not support use of sFGL-2 as a diagnostic marker (AUC 0.600, $p = 0.112$).

Inter-biomarker correlations: evidence of a shared innate-immune signature

The strongest and most consistent observation in our correlation matrix is that hBD-2 connects all three other biomarkers ($r = 0.474$–0.536, all $p \leq 0.001$). IL-36γ, CCL20 and sFGL-2 are weakly related to each other. This pattern is biologically intelligible: hBD-2 and CCL20 are both downstream IL-17A/TNF-α targets in keratinocytes and share transcription-factor regulation by NF-κB and IκBζ **[10,28]**; IL-36γ in turn reinforces IL-17A signalling and induces CCL20 **[9]**; and sFGL-2 may reflect a Treg-axis counter-regulatory response engaged in parallel **[14]**. The attenuation of individual biomarker coefficients when all four are placed together in a multivariable model — and the modest McFadden pseudo-R^2 of 0.099 — is therefore expected and, rather than being a weakness, constitutes internal evidence that the four biomarkers are partially redundant read-outs of a single inflammatory axis.

Comparison with Iraqi studies

Our work extends a growing body of Iraqi psoriasis biomarker research. Khazem and Ibraheem studied IL-36 and IL-10 in Iraqi female psoriasis patients and reported significant elevation of IL-36 in cases versus controls — directly concordant with our IL-36γ finding **[19]**. Sabri and Ibraheem reported elevated procalcitonin but non-significant shifts in lysozyme, illustrating that not every putative inflammatory marker discriminates psoriasis from controls **[20]**. Ahmed and colleagues showed a TGF-β1 gene polymorphism and altered serum TGF-β1 levels in psoriasis vulgaris among Iraqi people **[21]**. Yahya and colleagues, in an Iraqi cohort of ustekinumab-treated patients in Baghdad, showed that higher hs-CRP, IL-17, IL-22 and IL-23 levels distinguished suboptimal responders — corroborating the centrality of the IL-23/IL-17 axis in Iraqi psoriasis **[31]**. Al-Hamadani and colleagues reported IL-1β promoter polymorphisms and serum IL-1β levels in Iraqi plaque-psoriasis patients and related both to etanercept response **[32]**. Jasim documented higher IL-18, TNF-α and hs-CRP levels in Iraqi psoriatic patients that correlated with disease severity **[18]**. Mahmood and colleagues further characterised IL-36α gene expression and polymorphism in Iraqi psoriasis patients **[22]**. Our data add an innate-immune-axis perspective — hBD-2 and CCL20 in combination with IL-36γ — that has not previously been described in Iraqi patients, and specifically extend the evidence base from the Baghdad governorate to Babylon Governorate.

Comparison with international studies

Our between-group mean differences and diagnostic AUCs are modestly lower than those reported in seminal European cohorts. Jansen et al. demonstrated a strong correlation between serum hBD-2 and PASI in European patients **[4]**; Kolbinger et al. **[5]** reported a significant correlation between BD-2 and PASI in a large validation set; D'Erme et al. **[7]** established IL-36γ as a serum biomarker tracking disease activity. The most likely drivers of this difference are (a) the comparatively mild-to-moderate severity spectrum of our cohort (median BSA 0.25%) relative to trial-enrolment populations and (b) smaller sample size, which limits power to detect steeper severity gradients. Sun et al. observed that FGL-1 declined with disease severity in a large Chinese psoriasis cohort **[30]**; by contrast, we observed a non-significant trend toward elevated serum sFGL-2 in Iraqi plaque-psoriasis patients. This apparent discordance emphasises that FGL-1 and FGL-2, despite belonging to the same family, have distinct biological roles - FGL-1 being a LAG-3 ligand and FGL-2 a Treg-effector — and cannot be regarded interchangeably. In the context of vascular inflammation, Elnabawi et al. found that circulating CCL20 predicted endothelial dysfunction in psoriasis independent of PASI, a clinically meaningful downstream implication that may be relevant to cardiovascular risk stratification in Iraqi patients and should be investigated in future work **[12]**.

Mechanistic integration and clinical implications

Taken together, our findings support a mechanistic model in which IL-17A/TNF-α-driven keratinocyte activation generates a coordinated systemic biomarker signature comprising the antimicrobial peptide hBD-2, the IL-1-family amplifier IL-36γ, the Th17-recruiting chemokine CCL20/MIP-3α, and the co-mobilised immunoregulator sFGL-2. Clinically, three implications warrant consideration: (1) in settings where biologic monitoring is not feasible, a combined ELISA panel of hBD-2 + IL-36γ + CCL20 could provide an affordable, pathway-specific read-out of disease activity, pending validation; (2) IL-36γ's graded elevation and correlation with both BSA and disease duration is consistent with its emergent status as a therapeutic target, as evidenced by the clinical efficacy of anti-IL-36R biologics (spesolimab, imsidolimab) in pustular-spectrum psoriasis **[29,33]**; and (3) the exploratory elevation of sFGL-2 deserves prospective validation because of the known link

between this protein family and both immunoregulation and vascular/coagulation biology, all of which are highly relevant to the cardiometabolic comorbidity burden of psoriasis **[34]**.

Smoking warrants particular attention. Our cohort showed a very high smoking-rate differential (28.9% of patient vs 0% of controls, $p < 0.001$). A 2020 meta-analysis of observational studies reported pooled odds ratios of 1.63 for current smokers and 1.36 for former smokers for developing psoriasis **[35]**. Although Mendelian randomisation suggests that the observational smoking–psoriasis association may not be causal at a population level **[36]**, smoking is nevertheless mechanistically linked to oxidative stress and NF-κB activation in keratinocytes and is associated with poorer treatment response **[35]**. The complete separation that forced exclusion of smoking from our multivariable model is itself a noteworthy epidemiological observation in Babylon Governorate.

Strengths

The study has several strengths. First, it is, to our knowledge, the first simultaneous assessment of hBD-2, IL-36γ, CCL20/MIP-3α and sFGL-2 in an Iraqi plaque-psoriasis cohort. Second, the case–control design was rigorously age- and sex-matched, minimising confounding from demographic imbalance. Third, all samples were processed with standardised pre-analytical handling (fasting state, standardised collection window, rapid centrifugation, storage at −80 °C without freeze–thaw cycles), in duplicate, with kit-specified CV performance. Fourth, we report effect sizes (Cohen's d), 95% CIs, ROC-based cut-offs with Youden optimisation, and transparent handling of the complete-separation issue for smoking — all in accordance with the STROBE checklist for observational studies **[24]**. Fifth, our analytic plan was explicit about the biological non-independence of the biomarkers and interpreted multivariable attenuation accordingly rather than over-interpreting it.

Limitations

Several limitations should be acknowledged. First, the single-centre design limits external validity beyond Babylon Governorate and cases may over-represent hospital-attending patients. Second, the sample size ($n = 45$ per group) provides adequate power only for moderate effect sizes; a non-significant trend in sFGL-2 ($p = 0.067$) could reflect type-II error. Third, PASI scoring was not uniformly available in all records; BSA was used as the principal severity metric, which captures lesion extent but not erythema, induration and scaling. Fourth, clinical covariates known to influence inflammatory biomarkers — body-mass index, lipid profile, metabolic-syndrome status, alcohol intake, vitamin D and comorbid depression — were not collected. Fifth, we did not measure canonical upstream cytokines (IL-17A, IL-22, IL-23, TNF-α), which limits formal mediation analysis. Sixth, all four biomarkers were quantified with kits from a single manufacturer (BT LAB); cross-platform validation against a second assay or a mass-spectrometry-based approach would strengthen analytical confidence, especially for sFGL-2 where our finding is exploratory. Seventh, the complete separation of smoking status necessitated exclusion from the multivariable model; the recommended Firth's penalised logistic regression sensitivity analysis should be implemented in a subsequent report. Eighth, the cross-sectional design precludes any inference regarding temporal dynamics or treatment response.

Future directions

Future work should (a) validate these biomarker levels and cut-offs in a larger, multicentre Iraqi cohort stratified by PASI categories (mild, moderate, severe) and by plaque versus non-plaque variants; (b) incorporate a longitudinal arm in which biomarker trajectories are tracked during topical, conventional systemic and biologic therapy to determine responsiveness and treatment-monitoring potential, mirroring the secukinumab work of Kolbinger et al. **[5]** and the JAK-inhibitor work of Jin et al. **[6]**; (c) examine the relationship between this innate-immune panel and cardiovascular surrogates such as carotid intima-media thickness, high-sensitivity CRP and endothelial-function indices, building on the vascular-inflammation work of Elnabawi et al. **[12]**; (d) formally test the FGL-2 hypothesis in psoriasis through dedicated powered studies, ideally with paired lesional-skin transcriptomics; (e) conduct mechanistic Firth-penalised sensitivity analyses for the smoking variable; and (f) integrate the four biomarkers with Iraqi genotype data (e.g., IL-36RN, IL36G, DEFB copy-number, CCR6 variants) to explore gene–environment contributions to the innate-immune phenotype observed here.

Conclusion

In this case–control study of adults attending Marjan Teaching Hospital in Babylon Governorate, Iraq, plaque psoriasis was associated with significant elevations in serum hBD-2, IL-36γ and CCL20/MIP-3α, and a non-significant trend toward higher sFGL-2, relative to age- and sex-matched healthy controls. Among the markers tested, IL-36γ demonstrated the best single-marker diagnostic performance (AUC = 0.714) and was uniquely correlated with both disease

duration and body-surface-area involvement. The strong inter-correlations among the biomarkers and the attenuation observed in multivariable analysis are consistent with a partially overlapping, IL-17/IL-23-driven innate-immune signature rather than four fully independent signals. Because the study was single-centre, cross-sectional and modestly sized, these findings should be regarded as preliminary and hypothesis-generating; they do not establish causality and do not justify the use of any single biomarker as a stand-alone diagnostic tool. Validation in larger, severity-stratified, longitudinal Iraqi cohorts with adjustment for metabolic and lifestyle covariates is required before any clinical application.

CRediT

Author contributions: KAM: Conceptualization, methodology, investigation, data collection, laboratory work, formal analysis, data interpretation, writing—original draft, and correspondence. AHA: Supervision, conceptualization, methodology, validation, data interpretation, writing— review and editing. WAA: Clinical assessment of patients, patient recruitment, diagnosis confirmation, clinical data acquisition, and writing—review and editing. All authors contributed to the article, revised it critically for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Ethical Approval

Approved by the Research Administration Unit of the Training and Human Development Center, Babylon Health Directorate, Iraqi Ministry of Health (Ref. No. 1630), subsequent to Graduate-Studies-Division, College of Medicine, University of Babylon letter No. 88756 dated 27 October 2025. The study was conducted in accordance with the Declaration of Helsinki (2024 revision). Written informed consent was obtained from every participant prior to enrolment.

Informed Consent

It was applicable.

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Data sharing statement

The datasets generated and analysed during the current study are not publicly available because they contain potentially identifying clinical information, but the de-identified dataset supporting the conclusions of this article is available from the corresponding author (Karam Alaa Mudhar, med519.karam.alaa@student.uobabylon.edu.iq) upon reasonable request and subject to approval by the Research Administration Unit of the Babylon Health Directorate and compliance with applicable data-protection and ethical regulations. No public repository accession or web link applies to this dataset at the time of submission.

Conflict of Interest

The authors declare no competing interests. All authors have completed the ICMJE Disclosure of Interest form.

Similarity Check

It was applied by Ithenticate@.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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