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ARTICLE

A Study on the Serum Levels of POSTN and VEGF in Rheumatoid Arthritis Patients and Their Correlations

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Abstract

Aims/Background Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, pannus formation, and neovascularization. Reliable biomarkers for monitoring RA activity are needed to optimize treatment strategies. Periostin (POSTN) and vascular endothelial growth factor (VEGF) contribute to tissue remodeling and angiogenesis in various diseases, but their combined role and clinical significance in RA remain underexplored. This study aimed to evaluate serum POSTN and VEGF levels in RA patients and their correlation with disease activity.

Methods Serum levels of POSTN and VEGF were quantified using enzyme-linked immunosorbent assay (ELISA) in 86 RA patients, 36 osteoarthritis (OA) patients, and 40 healthy volunteers (HV) enrolled between January 2022 and December 2024 at Jinhua Municipal Central Hospital. RA patients were categorized into active (Disease Activity Score-28 [DAS28] >2.6) and stable (DAS28 ≤ 2.6) subgroups. Serum POSTN and VEGF levels were compared across the three study groups and between RA activity subgroups. Correlations between these biomarkers and clinical/laboratory parameters, including DAS28, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), were analyzed.

Results Serum POSTN and VEGF levels were significantly higher in RA patients [(125.21 $\pm$ 35.17) ng/mL, (106.45 $\pm$ 29.54) pg/mL] compared to OA patients [(98.41 $\pm$ 30.09) ng/mL, (82.28 $\pm$ 23.18) pg/mL] and healthy controls [(75.86 $\pm$ 22.81) ng/mL, (71.24 $\pm$ 11.72) pg/mL] (all $p < 0.001$). Furthermore, POSTN and VEGF levels in the active RA group [(144.68 $\pm$ 29.98) ng/mL, (121.75 $\pm$ 27.49) pg/mL] were significantly higher than those in the inactive group [(100.62 $\pm$ 24.23) ng/mL, (87.33 $\pm$ 19.12) pg/mL] (all $p < 0.001$). Spearman's or Pearson's correlation analyses revealed a positive correlation between POSTN and VEGF in RA patients ($r = 0.708$, $p < 0.001$). Serum POSTN levels were positively correlated with DAS28, CRP, and ESR ($r_{DAS28} = 0.753$, $r_{CRP} = 0.623$, $r_{ESR} = 0.437$, $p < 0.001$) so was VEGF ($r_{DAS28} = 0.720$, $r_{CRP} = 0.433$, $r_{ESR} = 0.623$, all $p < 0.001$).

Conclusion POSTN and VEGF levels are elevated in RA patients, correlate with disease activity markers, and may serve as complementary biomarkers for assessing RA activity.

Key words: rheumatoid arthritis; periostin; vascular endothelial growth factor

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial hyperplasia and progressive joint destruction, which can result in joint deformity and irreversible loss of joint function (Aletaha and Smolen, 2018). The global prevalence of RA is estimated to range between 0.5% and 1%, varying across

populations, and it predominantly affects women more than men (Almutairi et al, 2021). The pathogenesis of RA has not been fully clarified. Activation of vascular endothelial growth factor (VEGF) and its receptor signaling pathways, which promote synovitis development and pannus formation, is believed to play a critical role in the onset and progression of RA (Scherer et al, 2020; Rahmati et al, 2024). Periostin (POSTN), also referred to as osteoblast-specific factor 2 (OSF-2), is a highly conserved extracellular matrix protein secreted by osteoblasts and osteoblast-like cells. It is expressed in various human tissues and is closely associated with the proliferation and fibrosis of inflamed tissues, as well as the infiltration and metastasis of malignant tumors (Izuhara et al, 2019). Recent studies have reported elevated POSTN expression in the peripheral blood and synovial tissues of RA patients, indicating its potential involvement in RA pathogenesis (Kerschan-Schindl et al, 2019; Yu et al, 2023). This study aimed to investigate serum expression of POSTN and VEGF levels in the peripheral serum of RA patients, osteoarthritis (OA) patients, and healthy individuals using enzyme-linked immunosorbent assay (ELISA), and also to analyze their correlation with clinical parameters as well as to explore their synergistic role in RA and their association with disease activity.

Methods

General Data

From January 2022 to December 2024, after applying inclusion and exclusion criteria, a total of 86 patients with RA hospitalized and treated at Jinhua Municipal Central Hospital were enrolled in this cross-sectional study. The diagnosis of RA was established according to the 2010 revised classification criteria of the American College of Rheumatology (ACR) (Aletaha et al, 2010). During the same period, 36 patients with OA hospitalized and treated at Jinhua Municipal Central Hospital who met the 2009 European League Against Rheumatism (EULAR) diagnostic recommendations for OA (Zhang et al, 2010) were included as the disease control group. Additionally, 40 healthy individuals undergoing routine physical examinations at Jinhua Municipal Central Hospital without history of autoimmune diseases or joint disorders were enrolled as the healthy control (HC) group. Details are shown in Fig. 1.

Inclusion criteria for RA patients: (1) Fulfilment of the ACR 2010 classification criteria for RA; (2) Age $\geq$18 years.

Exclusion criteria for RA patients: (1) Presence of tumors in other locations; (2) Presence of other autoimmune diseases; (3) Severe dysfunction of heart, lungs, liver, or kidneys; (4) Pregnancy or lactation; (5) Incomplete or missing data.

Inclusion criteria for OA patients: (1) Fulfilment of the 2009 EULAR diagnostic recommendations for knee osteoarthritis; (2) Age $\geq$18 years.

Exclusion criteria for OA patients: (1) Presence of other autoimmune diseases; (2) Presence of tumors in any location; (3) Severe dysfunction of the heart, lungs, liver, or kidneys; (4) Pregnancy or lactation; (5) Incomplete or missing clinical or laboratory data.

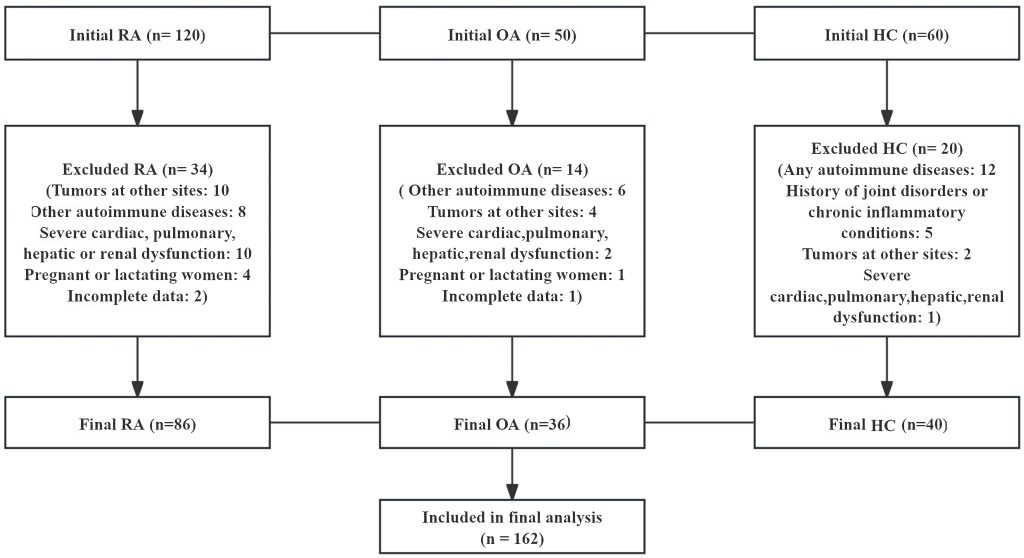

Fig. 1. Flowchart illustrating the inclusion and exclusion process for study participants. RA, rheumatoid arthritis; OA, osteoarthritis; HC, healthy control.

Inclusion criteria for healthy individuals: (1) Underwent physical examination at Jinhua Municipal Central Hospital between January 2022 and December 2024; (2) Age ≥18 years; (3) No history of autoimmune diseases or joint disorders; (4) Normal clinical and laboratory parameters based on standard reference ranges.

Exclusion criteria for healthy individuals: (1) Presence of any autoimmune diseases; (2) History of joint disorders or chronic inflammatory conditions; (3) Presence of tumors in any location; (4) Severe dysfunction of the heart, lungs, liver, or kidneys; (5) Pregnancy or lactation; (6) Incomplete or missing clinical or laboratory data.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Jinhua Municipal Central Hospital (Approval No. 2021-231-001). Written informed consent was obtained from all participants.

Collection of Clinical Indicators

General demographic data, including age and gender, were recorded for all participants. For RA patients, additional data collected included disease duration, body mass index (BMI), comorbidities (hypertension, diabetes, coronary artery disease [CAD]), previous medication history, swollen joint count (SJC), and tender joint count (TJC). Laboratory indicators collected included white blood cell count (WBC), hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody levels, fasting blood glucose (FBG), and total cholesterol (TC).

Disease Activity Scoring

For RA patients, disease activity was assessed using the Disease Activity Score based on 28 joints (DAS28-ESR), calculated using the SJC, TJC, ESR, and the pa-

tient's global health assessment (Prevoo et al, 1995). Patients were categorized into the disease activity group (DAS28 >2.6) and the disease stability group (DAS28 ≤2.6).

Detection of Serum POSTN and VEGF

Fasting peripheral venous blood (10 mL) was collected from all participants, centrifuged, and the supernatant was stored at –70 °C for subsequent analysis. Centrifugation was performed using a TGL-2150 centrifuge (MY-19, Sichuan Shuke Instrument Co., Ltd., Chengdu, China) at 2500 revolutions per minute (rpm) for 10 minutes. Serum POSTN and VEGF levels were measured using ELISA kits (Wuhan Huamei Bioengineering Co., Ltd., Wuhan, China; POSTN: Cat. No. CSB-E16444h; VEGF: Cat. No. CSB-E11718h). The POSTN kit employed a monoclonal anti-human POSTN antibody (detection limit: 1.56 ng/mL; intra-assay coefficient of variation (CV): <8%; inter-assay CV: <10%). The VEGF kit used a monoclonal anti-human VEGF antibody (detection limit: 7.8 pg/mL; intra-assay CV: <8%; inter-assay CV: <10%). All procedures strictly followed the manufacturer's instructions.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of distribution for continuous variables. Normally distributed continuous variables are expressed as mean ± standard deviation (mean ± SD), and comparisons between two groups were conducted using independent samples tests. Comparisons among three or more groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) post hoc test when variances were homogeneous (Levene's test). Non-normally distributed continuous data are expressed as median (interquartile range (IQR): 1st Quartile (Q1), 3rd Quartile (Q3)), with intergroup comparisons using the Mann-Whitney U test (two groups) or the Kruskal-Wallis H test (three or more groups). When the Kruskal-Wallis H test was significant, Dunn's test with Bonferroni correction was used for post hoc pairwise comparisons. Categorical variables are expressed as frequencies and proportions (n, %), with intergroup comparisons performed using the Chi-square (χ^2) test or Fisher's exact test when expected cell counts were <5. For continuous variables with normal distribution, Pearson's correlation coefficient was used to evaluate linear associations. For non-normally distributed variables, the Spearman rank correlation coefficient was applied. A two-tailed p-value < 0.05 was considered statistically significant.

Sample Size Calculation

An a priori power analysis was performed to determine the minimum sample size required to detect statistically significant differences in serum POSTN and VEGF levels among the three study groups (Rheumatoid Arthritis, Osteoarthritis, and Healthy Controls). Based on preliminary data from 15 participants per group, a moderate effect size was observed (Cohen's f = 0.28 for POSTN and 0.25 for

VEGF) in biomarker levels between groups, which aligns more closely with typical clinical studies than the initially assumed large effect size. The calculation was conducted using G*Power software (version 3.1.9.7; Franz Faul, Universität Kiel, Kiel, Schleswig-Holstein, Germany).

The sample size was calculated using the formula for comparing means across multiple groups (ANOVA):

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \times k \times \sigma^2}{\Delta^2}$$

Where, n represents the sample size per group, $Z_{(1-\alpha/2)} = 1.96$ (for $\alpha = 0.05$), adjusted to 0.025 for the two primary biomarkers (POSTN and VEGF) using Bonferroni correction, $Z_{(1-\beta)} = 0.84$ (for 80% power); k = 3 (number of groups: RA, OA, HC); σ is the pooled standard deviation (estimated as 35 for POSTN and 29 for VEGF from preliminary data); and Δ is the expected mean difference (set at 25 for POSTN and 20 for VEGF). This yielded a minimum of approximately 36 participants per group. To account for potential non-normality in outcome measures (e.g., CRP, ESR) that may require non-parametric tests, the sample size was increased by 15%, resulting in a target of 42 participants per group. Our actual sample sizes (RA: 86, OA: 36, HC: 40; total n = 162) exceeded this requirement, ensuring adequate power. Post-hoc power analysis confirmed >90% power to detect the observed differences in both POSTN and VEGF levels with the final sample sizes.

Results

General Data of RA Patients

A total of 86 RA patients, 36 OA patients, and 40 healthy controls (HC) were included in this study. The baseline characteristics of the RA cohort, stratified by disease activity, are presented in Table 1. Among RA patients, 48 were classified into the disease activity group (DAS28 >2.6) and 38 into the disease stability group (DAS28 ≤2.6). The mean age of RA patients was 49.05 ± 11.39 years, including 23 males (26.74%) and 63 females (73.26%). The disease activity group comprised 15 males and 33 females (mean age 48.90 ± 10.43 years), whereas the disease stability group included 8 males and 30 females (mean age 49.24 ± 12.65 years). Medication history, POSTN, VEGF, DAS28 score, SJC, TJC, CRP, and ESR were significantly different between the disease stability and disease activity groups ($p < 0.05$), while no significant differences were observed in the remaining variables ($p > 0.05$) (Table 1).

Baseline characteristics of all three groups (RA, OA, HC) are summarized in Table 2. The total study population comprised 162 individuals. The mean age was 49.05 ± 11.39 years for RA patients (n = 86), 48.44 ± 7.69 years for OA patients (n = 36), and 46.45 ± 9.73 years for HCs (n = 40), with no statistically significant difference among groups ($p = 0.418$). Gender distribution and BMI were also comparable across the three groups ($p = 0.266$ and $p = 0.157$, respectively).

Table 1. Baseline characteristics of RA patients stratified by disease activity.

Variables	RA (n = 86)	Stable RA (n = 38)	Active RA (n = 48)	Statistic	*p*-value
Age, years (mean ± SD)	49.05 ± 11.39	49.24 ± 12.65	48.90 ± 10.43	$t = 0.14$	0.891
Gender, n (%)				$\chi^2 = 1.13$	0.289
Male	23 (26.74)	8 (21.05)	15 (31.25)		
Female	63 (73.26)	30 (78.95)	33 (68.75)		
BMI, kg/m^2 (mean ± SD)	24.92 ± 4.31	24.69 ± 4.63	25.09 ± 4.08	$t = –0.43$	0.670
Disease duration, months (median, Q1, Q3)	7.5 (4.0, 12.0)	7.0 (3.5, 11.5)	8.0 (4.5, 12.5)	$Z = –0.82$	0.412
Hypertension, n (%)				$\chi^2 = 2.76$	0.097
No	60 (69.77)	23 (60.53)	37 (77.08)		
Yes	26 (30.23)	15 (39.47)	11 (22.92)		
Diabetes, n (%)				$\chi^2 = 1.87$	0.171
No	73 (84.88)	30 (78.95)	43 (89.58)		
Yes	13 (15.12)	8 (21.05)	5 (10.42)		
CAD, n (%)					0.744
No	76 (88.37)	33 (86.84)	43 (89.58)		
Yes	10 (11.63)	5 (13.16)	5 (10.42)		
Medication history				$\chi^2 = 6.06$	0.014
No	14 (16.28)	2 (5.26)	12 (25.00)		
Yes	72 (83.72)	36 (94.74)	36 (75.00)		
WBC, $\times 10^9$/L (mean ± SD)	5.81 ± 1.88	5.90 ± 1.86	5.73 ± 1.90	$t = 0.40$	0.690
Hb, g/L (mean ± SD)	121.42 ± 15.84	124.21 ± 15.78	119.21 ± 15.70	$t = 1.46$	0.147
TC, mmol/L (mean ± SD)	4.87 ± 0.75	4.80 ± 0.73	4.92 ± 0.77	$t = –0.70$	0.485
FBG, mmol/L (mean ± SD)	5.13 ± 0.76	5.15 ± 0.62	5.12 ± 0.85	$t = 0.22$	0.823
POSTN, ng/mL (mean ± SD)	125.21 ± 35.17	100.62 ± 24.23	144.68 ± 29.98	$t = –7.35$	<0.001
VEGF, pg/mL (mean ± SD)	106.54 ± 29.54	87.33 ± 19.12	121.75 ± 27.49	$t = –6.83$	<0.001
DAS28 (mean ± SD)	2.80 ± 0.99	1.93 ± 0.51	3.49 ± 0.68	$t = –11.73$	<0.001
SJC (median, Q1, Q3)	6.00 (5.00, 7.75)	5.00 (3.25, 6.00)	7.00 (6.00, 8.00)	$Z = –5.75$	<0.001
TJC (median, Q1, Q3)	8.00 (6.00, 10.00)	6.00 (5.00, 7.00)	10.00 (8.00, 12.00)	$Z = –6.44$	<0.001

Table 1. Continued.

Variables	RA (n = 86)	Stable RA (n = 38)	Active RA (n = 48)	Statistic	*p*-value
CRP, mg/L (median, Q1, Q3)	17.35 (8.35, 29.12)	12.85 (2.32, 22.55)	26.20 (13.80, 33.62)	Z = –3.38	<0.001
ESR, mm/h (median, Q1, Q3)	35.50 (20.25, 49.00)	19.50 (9.25, 32.25)	43.00 (34.75, 53.50)	Z = –5.02	<0.001
RF, IU/mL (median, Q1, Q3)	42.25 (27.45, 61.15)	47.45 (29.95, 68.42)	37.95 (25.55, 57.08)	Z = –1.53	0.126
Anti-CCP, AU/mL (median, Q1, Q3)	50.20 (23.18, 110.52)	50.40 (26.72, 112.65)	50.10 (22.70, 96.97)	Z = –0.10	0.921

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide antibody; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; Hb, hemoglobin; POSTN, periostin; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TC, total cholesterol; VEGF, vascular endothelial growth factor; WBC, white blood cell count.
Notes: *t*, independent samples *t*-test; Z, Mann-Whitney U test; χ^2, Chi-square test; SD, standard deviation; Q1, 1st Quartile; Q3, 3rd Quartile.

Table 2. Serum levels of POSTN and VEGF levels in RA, OA, and healthy control groups.

Variables	Total (n = 162)	Healthy controls (n = 40)	OA patients (n = 36)	RA patients (n = 86)	Statistic	*p*-value
Age, years (mean ± SD)	48.27 ± 10.27	46.45 ± 9.73	48.44 ± 7.69	49.05 ± 11.39	F = 0.88	0.418
Gender, n (%)					χ^2 = 2.65	0.266
Male	51 (31.48)	13 (32.50)	15 (41.67)	23 (26.74)		
Female	111 (68.52)	27 (67.50)	21 (58.33)	63 (73.26)		
BMI, kg/m^2 (mean ± SD)	24.32 ± 4.22	23.59 ± 3.82	23.70 ± 4.32	24.92 ± 4.31	F = 1.87	0.157
Disease duration, months (median, Q1, Q3)	4.00 (1.50, 8.00)	0.00 (0.00, 0.00)	3.00 (1.00, 5.00)	7.50 (4.00, 12.00)	H = 62.14	<0.001
Hypertension,n (%)					χ^2 = 1.89	0.388
No	116 (71.60)	27 (67.50)	29 (80.56)	60 (69.77)		
Yes	46 (28.40)	13 (32.50)	7 (19.44)	26 (30.23)		
Diabetes, n (%)					χ^2 = 0.61	0.736
No	140 (86.42)	36 (90.00)	31 (86.11)	73 (84.88)		
Yes	22 (13.58)	4 (10.00)	5 (13.89)	13 (15.12)		

Table 2. Continued.

Variables	Total (n = 162)	Healthy controls (n = 40)	OA patients (n = 36)	RA patients (n = 86)	Statistic	*p*-value
CAD, n (%)					-	0.744
No	142 (87.65)	36 (90.00)	30 (83.33)	76 (88.37)		
Yes	20 (12.35)	4 (10.00)	6 (16.67)	10 (11.63)		
Medication history, n (%)					$\chi^2 = 43.01$	<0.001
No	54 (33.33)	30 (75.00)	10 (27.78)	14 (16.28)		
Yes	108 (66.67)	10 (25.00)	26 (72.22)	72 (83.72)		
WBC, $\times 10^9$/L (mean ± SD)	5.80 ± 1.91	5.65 ± 1.82	5.94 ± 2.12	5.81 ± 1.88	F = 0.22	0.802
Hb, g/L (mean ± SD)	120.01 ± 15.44	120.53 ± 15.41	116.08 ± 14.18	121.42 ± 15.84	F = 1.56	0.214
TC, mmol/L (mean ± SD)	4.82 ± 0.74	4.65 ± 0.63	4.89 ± 0.81	4.87 ± 0.75	F = 1.36	0.259
FBG, mmol/L (mean ± SD)	5.12 ± 0.70	5.01 ± 0.54	5.20 ± 0.72	5.13 ± 0.76	F = 0.78	0.460
POSTN, ng/mL (mean ± SD)	107.07 ± 37.56	75.86 ± 22.81	98.41 ± 30.09	125.21 ± 35.17	F = 35.41	<0.001
VEGF, pg/mL (mean ± SD)	92.43 ± 29.18	71.24 ± 11.72	82.28 ± 23.18	106.54 ± 29.54	F = 31.36	<0.001
SJC, count (median, Q1, Q3)	4.00 (1.00, 6.00)	0.00 (0.00, 0.00)	3.00 (2.00, 4.00)	6.00 (5.00, 7.75)	H = 113.78	<0.001
TJC, count (median, Q1, Q3)	5.00 (1.00, 8.00)	0.00 (0.00, 0.00)	3.50 (2.00, 5.00)	8.00 (6.00, 10.00)	H = 115.59	<0.001
CRP, mg/L (median, Q1, Q3)	5.95 (2.45, 20.30)	3.05 (2.40, 4.00)	4.40 (1.90, 7.43)	17.35 (8.35, 29.12)	H = 43.35	<0.001
ESR, mm/h (median, Q1, Q3)	20.00 (11.00, 37.75)	10.00 (8.00, 13.00)	17.00 (12.00, 22.25)	35.50 (20.25, 49.00)	H = 51.84	<0.001

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide antibody; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; Hb, hemoglobin; HC, healthy controls; OA, osteoarthritis; POSTN, periostin; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TC, total cholesterol; TJC, tender joint count; VEGF, vascular endothelial growth factor; WBC, white blood cell count.

Statistics: F, one-way ANOVA; H, Kruskal-Wallis test; χ^2, Chi-square test; -, Fisher's exact test. Q1, 1st Quartile; Q3, 3rd Quartile. All continuous variables are presented as mean ± SD or median (Q1, Q3). *p*-values for ANOVA and the Kruskal-Wallis test indicate overall group differences. Post-hoc tests were performed where appropriate.

Comparison of Serum POSTN and VEGF Levels Among RA Patients, OA Patients, and Healthy Individuals

Serum POSTN levels differed significantly among the three groups. Post hoc analysis revealed that RA patients (n = 86) had markedly higher POSTN levels (125.21 ± 35.17 ng/mL) than both OA patients (n = 36; 98.41 ± 30.09 ng/mL, $p < 0.001$) and healthy controls (HCs) (n = 40; 75.86 ± 22.81 ng/mL, $p < 0.001$). Additionally, OA patients had significantly higher POSTN levels than HCs ($p < 0.05$). Similarly, serum VEGF levels were significantly different across the three groups. RA patients exhibited significantly higher VEGF levels (106.54 ± 29.54 pg/mL) compared to OA patients (82.28 ± 23.18 pg/mL, $p < 0.001$) and HCs (71.24 ± 11.72 pg/mL, $p < 0.001$). No statistically significant difference in VEGF levels was observed between OA patients and HCs ($p = 0.133$) (Table 2).

Correlation Analysis of Serum POSTN and VEGF Levels With Disease Activity in RA Patients

Among RA patients (n = 86), serum POSTN and VEGF levels were significantly higher in the active disease group (DAS28 >2.6; n = 48) compared to the disease stability group (DAS28 ≤2.6; n = 38). POSTN levels were 144.68 ± 29.98 ng/mL in the active group versus 100.62 ± 24.23 ng/mL in the stable group ($p < 0.001$). VEGF levels were 121.75 ± 27.49 pg/mL in the active group versus 87.33 ± 19.12 pg/mL in the stable group ($p < 0.001$) (Table 1).

Correlation Analysis of Serum POSTN and VEGF Levels With Clinical Features and Laboratory Indicators in RA Patients

In RA patients, Spearman's or Pearson correlation analysis showed a strong positive correlation between serum POSTN and VEGF levels ($r = 0.708$, $p < 0.001$). Serum POSTN also correlated positively with medication use ($r = 0.189$, $p = 0.016$), SJC ($r = 0.618$, $p < 0.001$), TJC ($r = 0.546$, $p < 0.001$), ESR ($r = 0.437$, $p < 0.001$), CRP ($r = 0.623$, $p < 0.001$), and DAS28 score ($r = 0.753$, $p < 0.001$). Likewise, serum VEGF was positively associated with BMI ($r = 0.158$, $p = 0.045$), medication use ($r = 0.239$, $p = 0.002$), SJC ($r = 0.535$, $p < 0.001$), TJC ($r = 0.510$, $p < 0.001$), ESR ($r = 0.623$, $p < 0.001$), CRP ($r = 0.433$, $p < 0.001$), and DAS28 score ($r = 0.720$, $p < 0.001$). No significant correlations were observed between POSTN or VEGF levels and age, gender, hypertension, diabetes, CAD, disease duration, TC, FBG, WBC, hemoglobin, RF, or anti-CCP antibody levels (all $p > 0.05$) (Table 3).

Discussion

RA is a systemic, chronic autoimmune disease characterized by synovial inflammation, hyperplasia, and neovascularization, leading to progressive joint damage if not adequately controlled (Di Matteo et al, 2023). Pannus, composed of newly formed capillaries, proliferating fibroblast-like synoviocytes, inflammatory cells, and organized fibrin, is a hallmark throughout the course of RA and is considered the primary cause and pathological basis of joint erosion and destruction (D'Orazio et al, 2024; Zhang et al, 2024). Angiogenesis, the formation of new blood vessels, is a critical process in the development and maintenance of RA synovitis,

Table 3. Correlation between serum POSTN and VEGF levels with clinical and laboratory parameters in RA patients.

Characteristics	POSTN		VEGF	
	r	*p*-value	r	*p*-value
Age	r_p= –0.010	0.092	r_p= 0.022	0.841
Gender	r_s= 0.128	0.927	r_s= –0.146	0.181
BMI	r_p= 0.153	0.052	r_p= 0.158	0.045
Hypertension	r_s= –0.194	0.073	r_s= –0.199	0.066
Diabetes	r_s= –0.056	0.146	r_s= –0.086	0.433
CAD	r_s= 0.146	0.179	r_s= 0.086	0.430
Disease duration	r_s= –0.119	0.274	r_s= –0.046	0.673
Medication history	r_s= 0.189	0.016	r_s= 0.239	0.002
SJC	r_s= 0.618	<0.001	r_s= 0.535	<0.001
TJC	r_s= 0.546	<0.001	r_s= 0.510	<0.001
TC	r_p= –0.010	0.930	r_p= –0.007	0.951
FBG	r_p= 0.016	0.840	r_p= 0.040	0.617
WBC	r_p= –0.058	0.594	r_p= 0.007	0.948
Hemoglobin	r_p= –0.247	0.078	r_p= –0.111	0.310
ESR	r_s= 0.437	<0.001	r_s= 0.623	<0.001
CRP	r_s= 0.623	<0.001	r_s= 0.433	<0.001
RF	r_s= 0.017	0.880	r_s= 0.014	0.898
Anti-CCP antibody	r_s= –0.146	0.181	r_s= –0.118	0.278
DAS28 score	r_p= 0.753	<0.001	r_p= 0.720	<0.001
VEGF	r_p= 0.708	<0.001	1	/

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide antibody; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; POSTN, periostin; RF, rheumatoid factor; SJC, swollen joint count; TC, total cholesterol; TJC, tender joint count; VEGF, vascular endothelial growth factor; WBC, white blood cell count.
Notes: r_p represents Pearson correlation coefficient; r_s represents Spearman rank correlation coefficient.

supplying oxygen and nutrients to the expanding synovial tissue and facilitating the infiltration of inflammatory cells (Balogh et al, 2019). VEGF is a primary mediator of angiogenesis and has been reported to be upregulated in RA synovial tissue and synovial fluid, with levels correlating with disease activity (Yi et al, 2016; Lee et al, 2024; Boldeanu et al, 2023). Previous studies have demonstrated that VEGF concentrations are significantly elevated in the synovial fluid of RA patients and are positively correlated with RF, CRP, and ESR, thereby suggesting its utility as a potential biomarker of disease severity (Wu et al, 2016; Kendrew et al, 2011).

Our findings are consistent with previous studies, demonstrating that serum VEGF levels in RA patients were significantly higher than those in OA patients and healthy controls. Furthermore, serum VEGF levels in RA patients correlated positively with DAS28, CRP, and ESR, further supporting its role as a marker of

inflammatory activity in RA. Although these correlations were statistically significant, the strength of some associations (e.g., with CRP) was moderate, suggesting that while VEGF contributes to inflammation, other factors also play a pivotal role in modulating inflammatory markers.

POSTN, an extracellular matrix protein, is involved in tissue remodeling, inflammation, and fibrosis. It is increasingly recognized for its diverse roles in inflammatory and fibrotic conditions, including RA (Wang et al, 2022). In RA, POSTN is highly expressed in inflamed synovial tissue and contributes to the regulation of fibroblast-like synoviocyte (FLS) behavior, local inflammation, and tissue remodeling (Li et al, 2024; Mangoni and Zinellu, 2025). Our study revealed that serum POSTN levels were significantly elevated in RA patients compared to both OA patients and healthy controls. Additionally, POSTN levels positively correlated with RA disease activity indicators, including DAS28, CRP, ESR, and joint counts. Notably, we identified a significant positive correlation between serum POSTN and VEGF levels, suggesting a potential synergistic interplay between these biomarkers in the immunoinflammatory cascade and pannus development characteristic of RA. This interplay may contribute to synovial angiogenesis, FLS activation, and persistent inflammation, highlighting their combined relevance in RA pathophysiology.

Our clinical findings, demonstrating a significant correlation between serum POSTN and VEGF levels in RA patients, suggest a potential functional interplay between matricellular signaling and angiogenic pathways in synovial pathology. Periostin has been shown to bind integrins $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 6\beta 4$ on fibroblasts and endothelial cells, initiating downstream focal adhesion kinase (FAK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling cascades that promote cellular proliferation, migration, and angiogenesis. Zhang et al (2015) reported that elevated periostin expression in keloid fibroblasts activates FAK and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways, leading to increased secretion of VEGF and angiopoietin-1, thereby driving neovascularization in fibrotic tissue. Similarly, in various tumor microenvironments, POSTN engagement with $\alpha v\beta 3/\alpha v\beta 5$ integrins has been shown to trigger PI3K/Akt-mediated and FAK-dependent phosphorylation, resulting in upregulation of VEGF family growth factors and enhanced vascular density (Wasik et al, 2022).

Within RA synovium, fibroblast-like synoviocytes (FLS) are the predominant source of VEGF, contributing to pannus formation and progressive joint destruction (Paleolog, 2002). Periostin-mediated integrin activation may further synergize with pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are markedly elevated in RA, to induce VEGF expression via hypoxia-inducible factor-1 alpha (HIF-1α)-dependent transcriptional mechanisms (Elshabrawy et al, 2015). These convergent pathways, direct integrin-mediated signaling and cytokine-driven transcriptional amplification, provide a biologically plausible mechanism for the strong correlation between POSTN and VEGF observed in our cohort. Although these findings support a mechanistic link between POSTN and VEGF, direct functional validation in RA-specific experimental models is warranted. Future investigations should include RA-FLS-targeted POSTN knockdown or integrin blockade studies *in vitro*, as well as POSTN-deficient or

integrin-mutant animal models, to confirm causality and assess the therapeutic potential of disrupting this axis.

While both molecules have been extensively studied in oncology for their roles in tumor progression and angiogenesis, leading to clinical applications of anti-VEGF therapies (Liu et al, 2023), their combined assessment and therapeutic targeting in RA warrant further investigation. Our findings that POSTN and VEGF levels are significantly elevated in active RA and correlate with disease activity underscore their potential, possibly in combination, as clinically valuable biomarkers for assessing disease activity and monitoring therapeutic response. Elevated POSTN levels have also been associated with more severe joint damage and radiographic progression in RA (Heckert et al, 2023; Bykerk, 2014), suggesting potential prognostic value. Given their synergistic implications, targeting the POSTN-VEGF axis may represent a novel therapeutic avenue. For instance, therapeutic strategies aimed at neutralizing POSTN or inhibiting its interaction with integrins might not only directly attenuate FLS activation and extracellular matrix (ECM) remodeling but also indirectly suppress VEGF-driven angiogenesis and inflammation (Zhu et al, 2024; Wang et al, 2023). These approaches could complement or enhance the effects of existing therapies, including those that may indirectly affect VEGF pathways.

However, the clinical application of POSTN and VEGF in RA requires further validation. While our study provides preliminary evidence of their utility as biomarkers, larger, prospective studies are needed to establish their sensitivity, specificity, and predictive value across diverse RA populations.

Our study has several limitations. First, although we observed strong correlations between serum POSTN/VEGF levels and RA disease activity indices (DAS28, CRP, ESR), we did not perform multivariate regression analyses to adjust for potential confounders. Variables such as age, BMI, comorbidities (e.g., hypertension, diabetes, coronary artery disease), and medication history may influence systemic inflammation and biomarker expression, potentially affecting the observed associations. While we analyzed univariate correlations between these clinical variables and serum POSTN/VEGF levels, residual confounding cannot be excluded. Future studies employing multivariable statistical models or propensity score adjustment are warranted to better clarify the independent associations of POSTN and VEGF with RA disease activity. Second, the specificity of POSTN and VEGF for RA was not evaluated against other autoimmune diseases such as systemic lupus erythematosus (SLE) or psoriatic arthritis, limiting conclusions about disease specificity. Third, our cross-sectional design and modest control group sizes (OA: 36, HC: 40) restrict causal inference and generalizability. Finally, synovial fluid or tissue levels of POSTN and VEGF were not evaluated, which could provide more direct mechanistic insights into their roles in RA pathogenesis.

Future research should focus on larger, multicenter prospective cohorts to validate these findings and to investigate the predictive value of POSTN and VEGF for disease progression or treatment response in RA. Mechanistic studies, both *in vitro* using RA FLS and endothelial cells, and *in vivo* using animal models of arthritis, are also needed to elucidate the synergistic pathways through which POSTN and VEGF contribute to RA pathogenesis. Moreover, investigating whether therapeutic

interventions targeting POSTN, VEGF, or their interaction could mitigate disease progression represents an important avenue for future exploration.

Conclusion

Our study demonstrates that serum levels of POSTN and VEGF are significantly elevated in patients with RA compared to those with OA and healthy controls. Both biomarkers show strong positive correlations with established measures of RA disease activity, including DAS28, CRP, and ESR, and are markedly higher in patients with active RA. The positive correlation between POSTN and VEGF suggests a potential synergistic role in the immunoinflammatory pathways and pannus formation characteristic of RA. These findings highlight the potential utility of POSTN and VEGF, individually and in combination, as complementary biomarkers for assessing RA activity. However, further validation in larger, prospective, and multi-disease cohorts is necessary to confirm their diagnostic and prognostic value.

Key Points

- POSTN and VEGF levels are significantly higher in RA patients compared to OA and healthy controls.
- Both biomarkers correlate with DAS28, ESR, and CRP, reflecting the inflammatory burden.
- Active RA patients exhibit higher POSTN and VEGF levels than those with stable disease, indicating an association with disease severity.
- POSTN and VEGF may serve as complementary biomarkers for RA activity but require validation in broader disease cohorts.
- Future research should include larger, multicenter studies and mechanistic investigations to clarify their roles in RA pathogenesis.

Availability of Data and Materials

All data and materials included in this study are available upon request by contacting the corresponding author.

Author Contributions

LJS, YHL, YPY and MF contributed to the study design. LJS and YHL conducted the literature search. YPY acquired the data. MF wrote the article. YPY and LJS performed data analysis. LJS revised the article. All authors contributed to important editorial changes in the manuscript. All authors have given final approval of the current version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Jinhua Municipal Central Hospital (2021-231-001), and all participants provided written informed consent. This study followed international and national regulations in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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