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ORIGINAL ARTICLE

Serum levels of angiogenesis-related factors in patients with psoriasis

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Abstract

Psoriasis is characterized by increased dermal vascularity, indicating that aberrant angiogenesis is associated with the pathogenesis of psoriasis. Data on angiogenesis-related factors in psoriasis patients are limited. We explored serum levels of angiogenesis-related factors in patients with psoriasis, and investigated their association with clinical severity and laboratory data. Psoriasis patients visiting our hospital from April 2013 to April 2018 and healthy controls were included in this study. Serum levels of angiopoietin-1, fibroblast growth factor (FGF)-basic, epidermal growth factor (EGF), platelet endothelial cell adhesion molecule (PECAM)-1, placental growth factor, and vascular endothelial growth factor (VEGF) were measured by LEGENDplex. Serum samples obtained from 10 healthy controls, 18 patients with psoriasis vulgaris (PsV), 24 patients with psoriatic arthritis (PsA), and 13 patients with generalized pustular psoriasis (GPP) were analyzed. The serum angiopoietin-1 level was elevated in the PsV, PsA, and GPP patients. GPP patients had a higher serum VEGF level than healthy controls. In contrast, serum levels of EGF and PECAM-1 were lower in the PsV, PsA, and GPP patients than in healthy controls. The serum FGF-basic level was lower in the PsA and GPP patients than in healthy controls. Serum levels of FGF-basic in PsA and GPP patients, PECAM-1 in PsA patients, and VEGF in GPP patients became closer to the respective levels in healthy controls after systemic therapy. The serum FGF-basic level was positively correlated with the psoriasis area and severity index and the number of circulating eosinophils in GPP patients. The serum VEGF level was correlated positively with the serum C-reactive protein (CRP) level and erythrocyte sedimentation rate, and negatively with the serum albumin level in GPP patients. In conclusion, our exploratory study revealed that psoriasis affects serum levels of certain angiogenesis-related factors. Some of these factors could be biomarkers of treatment outcomes, clinical severity, and systemic inflammation.

KEYWORDS
psoriasis, angiogenesis, generalized pustular psoriasis, vascular endothelial growth factor

1 | INTRODUCTION

Psoriasis is a chronic inflammatory dermatitis characterized by abnormal differentiation and proliferation of keratinocytes, massive infiltration of inflammatory cells such as neutrophils, and increased dermal vascularity resulting in clinical manifestations of erythematous and scaly plaques. These features indicate that aberrant angiogenesis is associated with the pathogenesis of psoriasis.[1] Generalized pustular psoriasis (GPP) not only is a skin disease but is associated with systemic inflammation and microvascular hyperpermeability, resulting in fever and edema. Reflecting this, laboratory data of GPP patients demonstrate elevated inflammatory markers and reduced serum level of albumin.[2] The extent of angiogenesis is different in each type of psoriasis.

Various growth factors are involved in angiogenesis. Angiopoietin-1 induces Tie-2 signaling as a receptor activator and maintains blood vessel formation,[3] whereas angiopoietin-2 destabilizes vessels by blocking Tie-2 signaling as an antagonist of angiopoietin-1 and acts with vascular endothelial growth factor (VEGF) to initiate angiogenesis.[4] Epidermal growth factor (EGF) and fibroblast growth factor (FGF)-basic are cytokines that play a key role in the initiation of angiogenesis.[5–7] During angiogenesis, platelet endothelial cell adhesion molecule (PECAM)-1, also known as cluster of differentiation 31, participates in adhesive and/or signaling phenomena required for the motility of endothelial cells and/or their subsequent organization into vascular tubes.[8,9] Placental growth factor (PlGF) is a ligand of VEGF receptor 1, and is an angiogenic factor that belongs to the VEGF family.[9]

Although there are several reports on VEGF levels in patients with psoriasis, data on other angiogenesis-related factors are limited or have not been reported. Furthermore, there has been no report that investigated these serum levels in patients with all three types of psoriasis, i.e., those with psoriasis vulgaris (PsV), those with psoriatic arthritis (PsA), and those with GPP. In this study, we explored the serum levels of angiogenesis-related factors in patients with psoriasis, and investigated the association of the levels of some of these factors with clinical severity and laboratory data.

2 | METHODS

Patients who had been diagnosed with PsV, PsA, or GPP and visited our hospital from April 2013 to April 2018 and healthy controls were included in this study. Serum levels of angiopoietin-1, angiopoietin-2, FGF-basic, EGF, PECAM-1, PlGF, and VEGF were measured using LEGENDplex (BioLegend, San Diego, CA, USA). Clinical severity scores and results of blood tests such as white blood cell counts, numbers of circulating neutrophils and eosinophils, 60-min erythrocyte sedimentation rate (ESR), and serum levels of thymus and activation-regulated chemokine, C-reactive protein (CRP), and albumin were collected retrospectively from the patients' charts. The severity of psoriasis was evaluated by the psoriasis area and severity index (PASI) and the Japanese Dermatological Association (JDA) severity index total score [which ranges from 0 (best) to 17 (worst)],[2] the latter of which has been used in clinical trials in patients with GPP.[10–12] PASI scores and JDA severity scores were evaluated by board-certified dermatologists.

Regarding statistical analyses, normality in each group was evaluated using the Shapiro–Wilk test. Comparisons among three or more groups were made using one-way analysis of variance or Kruskal–Wallis test according to the results of the normality test. Dunnett's multiple comparisons test or Dunn's multiple comparisons test was conducted for multiple comparisons. To compare two related samples, paired t-test or Wilcoxon signed-ranks sum test was used. Correlations were analyzed with the Pearson or Spearman correlation method. Values of $p < 0.05$ were considered to represent significant differences.

Written informed consent was obtained from all of the participants. This study was approved by the institutional review board of Teikyo University (19-086, 09-005-3), and was carried out under the principles of the Declaration of Helsinki.

3 | RESULTS

Serum samples obtained from 10 healthy controls, 18 patients with PsV, 24 patients with PsA, and 13 patients with GPP were analyzed. Their demographics and characteristics are shown in Table 1.

Serum levels of angiogenesis-related factors in healthy controls and psoriasis patients are shown in Figure 1. The serum angiopoietin-1 level was significantly higher in patients with PsV ($p = 0.0016$), those with PsA ($p = 0.0041$), and those with GPP ($p = 0.0319$) than in the healthy controls. The serum levels of angiopoietin-2, EGF, and PECAM-1 were significantly lower in patients with PsV ($p = 0.001$, $p = 0.0003$, $p = 0.0107$, respectively), those with PsA ($p < 0.001$, $p = 0.0022$, $p = 0.0001$, respectively), and those with GPP ($p < 0.001$, $p = 0.0062$, $p = 0.0003$, respectively) than in healthy controls. Patients with PsA and those with GPP had a significantly lower serum FGF-basic level than healthy controls ($p = 0.0043$, $p = 0.0001$). The serum VEGF level was significantly higher in patients with GPP than in healthy controls ($p = 0.0322$). No significant difference was observed in the serum PlGF level among the four groups. Since the mean age of healthy controls was lower than that of patients in this study, we examined whether ages affected serum levels of angiogenesis-related factors by evaluating correlations of ages with these serum levels in healthy controls. No significant correlations were observed between ages and the serum levels except in angiopoietin-2 ($r = -0.6807$, $p = 0.0303$). As the effect of ages cannot be ruled out in the results of the serum angiopoientin-2 level, we excluded it in further investigations. The heatmap of serum levels of angiogenesis-related factors in healthy controls and psoriasis patients is shown in Figure S1. Correlations between serum levels of angiogenesis-related factors in patients with PsV, PsA, and GPP are shown in Tables S1–S3, respectively. No significant positive correlation was observed in GPP patients between serum levels of agiopoietin-1 and VEGF. Significant positive correlation was observed in

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TABLE 1 Demographics and clinical characteristics of psoriasis patients

	Healthy controls	PsV patients	PsA patients	GPP patients
Number of cases	10	18	24	13
Gender	M, 5; F, 5	M, 12; F, 6	M, 16; F, 8	M, 7; F, 6
Age (year)	36.6 ± 4.67	58.5 ± 16.5	48.4 ± 14.3	62.4 ± 14.3
BMI		24.9 ± 4.0	24.2 ± 4.3	26.2 ± 9.2
PASI		11.7 ± 9.0	18.3 ± 43.1	27.4 ± 12.9
JDA severity score				11.9 ± 4.1
Treatment				
Topical therapy		13	15	2
Phototherapy		2	2	0
Systemic therapy		CyA, 1 CyA+PSL, 1	CyA, 3 CyA+ETR, 1 MTX+CyA, 1 MTX+SASP, 1 SASP, 1	PSL, 3 CyA, 2 MTX, 1 MTX+PSL, 1 Biologics, 1 PSL+ETR+GMA, 1 APR, 1 ETR, 1
Comorbidities				
Hypertension		5 (28%)	3 (13%)	3 (23%)
Diabetes		2 (11%)	2 (8%)	2 (15%)
Hyperlipidemia		11 (61%)	8 (33%)	5 (38%)

Note: Values are presented as mean ± standard deviation.
Abbreviations: APR, apremilast; BMI, body mass index; CyA, cyclosporine; ETR, etretinate; F, female; GMA, granulocyte and monocyte adsorption apheresis; GPP, generalized pustular psoriasis; JDA, Japanese Dermatological Association; M, male; MTX, methotrexate; PASI, psoriasis area and severity index; PsA, psoriasis arthritis; PSL, prednisolone; PsV, psoriasis vulgaris; SASP, salazosulfapyridine.

PsV patients between serum levels of EGF and PECAM-1 ($r = 0.820$, $p = 0.004$), whereas there were no significant correlations in PsA or GPP patients between serum levels of FGF-basic, EGF, and PECAM-1. The consistent association between angiogenesis-related factors was not observed.

We next measured the serum levels of angiopoietin-1, FGF-basic, EGF, PECAM-1, and VEGF, in which significant differences had been observed between healthy controls and psoriatic patients, after systemic therapy, and compared the results with the baseline values (Figure 2). Table 2 shows details of the systemic therapies that the patients received. Most of the patients received biologics. The serum angiopoietin-1 level significantly increased after systemic treatment in the PsA patients ($p = 0.0370$). The serum FGF-basic level significantly increased after systemic therapy in patients with PsA ($p = 0.0215$) and those with GPP ($p = 0.0093$). There was no significant difference in the serum EGF level between before and after systemic therapy in any of the psoriatic groups. The serum PECAM-1 level significantly increased after systemic therapy in patients with PsA ($p = 0.0053$). In patients with GPP, the serum VEGF level significantly decreased after systemic therapy ($p = 0.0117$). After systemic therapy, the serum angiopoietin-1 level in patients with PsA became more divergent from the values in the healthy controls, whereas the serum levels of FGF-basic in patients with PsA and those with GPP, the serum PECAM-1

level in patients with PsA, and the serum VEGF level in patients with GPP became closer to the respective values in the healthy controls.

Regarding the angiogenesis-related factors whose serum levels improved after systemic therapy, i.e., FGF-basic in PsA patients and GPP patients, PECAM-1 in PsA patients, and VEGF in GPP patients, we evaluated the correlation of these factors with clinical severity and laboratory data at baseline (Figure 3). No correlations were observed between the serum FGF-basic level and clinical severity scores or laboratory data among the patients with PsA. In patients with GPP, the serum FGF-basic level was positively correlated with the number of circulating eosinophils ($r = 0.7299$, $p = 0.0066$) and PASI ($r = 0.6222$, $p = 0.0343$). There were no correlations between the serum PECAM-1 level and clinical severity scores or laboratory data among the patients with PsA. The serum VEGF level was correlated positively with the serum CRP level ($r = 0.8611$, $p = 0.0003$) and 60-min ESR values ($r = 0.8270$, $p = 0.0009$), and negatively with the serum albumin level ($r = -0.8467$, $p = 0.0003$) among the patients with GPP.

4 | DISCUSSION

Serum levels of some angiogenesis-related factors in psoriasis patients differed from those in healthy controls. The serum angiopoietin-1
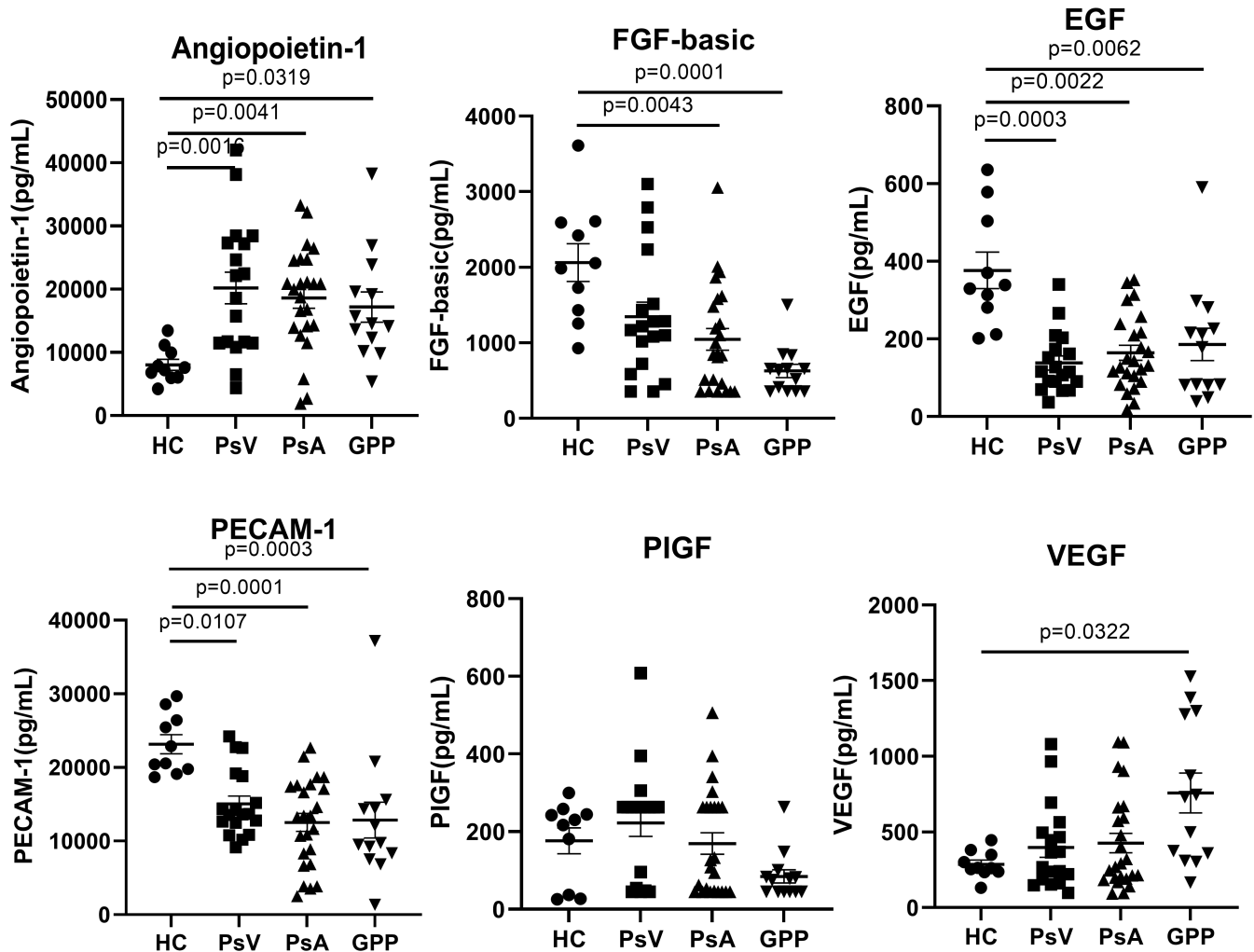
FIGURE 1 Serum levels of angiogenesis-related factors in healthy controls and psoriasis patients. Data are presented as mean ± standard deviation in the figures. EGF, epidermal growth factor; FGF, fibroblast growth factor; GPP, generalized pustular psoriasis; HC, healthy controls; PECAM-1, platelet endothelial cell adhesion molecule-1; PlGF, placental growth factor; PsA, psoriatic arthritis; PsV, psoriasis vulgaris; VEGF, vascular endothelial growth factor.

level was elevated in patients with psoriasis including PsV, PsA, and GPP. GPP patients demonstrated a higher serum VEGF level than healthy controls. These factors could contribute to the pathogenesis of angiogenesis in psoriasis. In contrast, serum levels of EGF and PECAM-1 were lower in patients with psoriasis including PsV, PsA, and GPP than in healthy controls. The serum FGF-basic level was lower in patients with PsA and those with GPP than in healthy controls. The decreased levels of these angiogenesis-related factors might be accounted for by the feedback from increased angiogenesis in psoriasis patients. Further investigation is needed to clarify this.

To date, reports on serum levels of angiogenesis-related factors in psoriasis patients have been limited. To the best of our knowledge, data on serum levels of angiopoietin-1 and PECAM-1 in psoriasis patients have not been reported yet. Reports on serum levels of other factors in patients with PsA and GPP are limited. Furthermore, although there are a few data on serum levels of angiogenesis-related factors in patients with PsV, some of the results are not consistent[13–17] and contradict our results. The difference in the results

could be due to the different background and characteristics of the patients including age, ethnicity, severity, and so on. Further accumulation of studies is needed to reach a consistent conclusion.

Serum levels of FGF-basic in patients with PsA and those with GPP, PECAM-1 in those with PsA, and VEGF in those with GPP became closer to the levels in healthy controls after systemic therapy. They could be potential biomarkers of psoriasis in evaluating treatment outcomes. In this study, we could not obtain detailed data after systemic therapy. It will be elucidated in the next study.

The serum FGF-basic level was positively correlated with PASI and the number of circulating eosinophils in GPP patients. However, the serum FGF-basic level was lower in GPP patients than in healthy controls. In psoriasis, the production of FGF-basic may be generally suppressed by certain factors. Under such circumstances, severe skin manifestation in GPP patients might induce production of FGF-basic. FGF-basic is overexpressed in involved psoriasis skin.[18] Positive immunoreactivities for FGF-basic were observed in the basal cells and several supra-basal layers at rete ridges.[19] The increased production
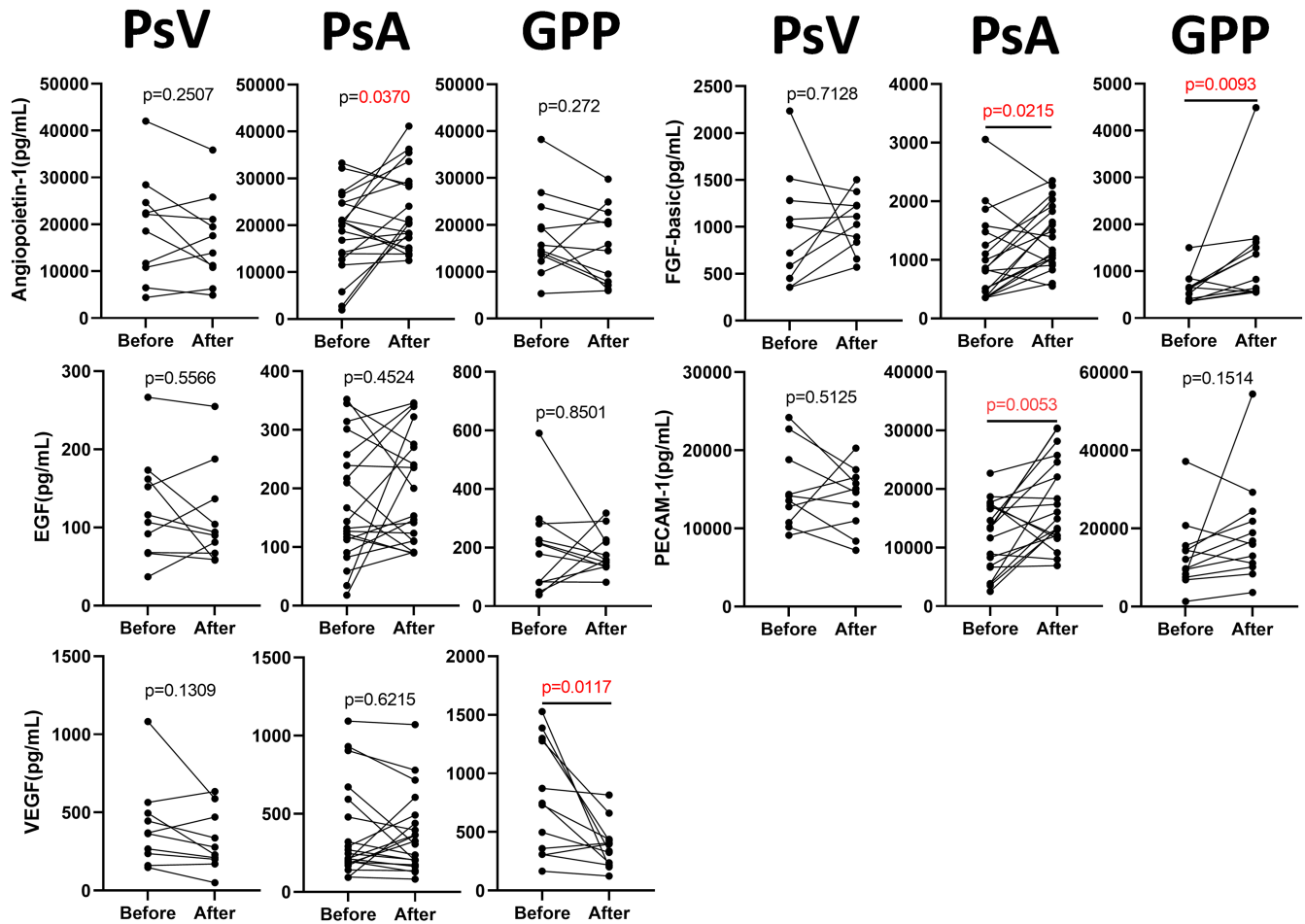
FIGURE 2 Changes in serum levels of angiogenesis-related factors in psoriasis patients before and after systemic therapies. EGF, epidermal growth factor; GPP, generalized pustular psoriasis; PsA, psoriatic arthritis; PsV, psoriasis vulgaris; VEGF, vascular endothelial growth factor.

TABLE 2 Systemic therapies that the psoriasis patients received

	PsV group (n = 10)	PsA group (n = 20)	GPP group (n = 12)
Cyclosporine	1	1	0
Methotrexate	0	3	0
Biologics			
TNF inhibitor	5	13	2
IL-17 inhibitor	2	3	10
IL-23 inhibitor	2	0	0

Abbreviations: GPP, generalized pustular psoriasis; IL, interleukin; PsA, psoriasis arthritis; PsV, psoriasis vulgaris; TNF, tumor necrosis factor.

of FGF-basic in lesional skin might lead to its increased serum level in GPP patients. Regarding eosinophils, some GPP patients show a high number of circulating eosinophils and increased infiltration of eosinophils in lesional skin.[20] The FGF and eotaxin signaling pathways share activation through the ERK pathway; together, they could act to increase eosinophil activation and prolong the half-life of eosinophils in local tissues of the esophagus in patients with eosinophilic esophagitis.[21] The correlation between the serum FGF-basic level and the number of circulating eosinophils might be due to a similar mechanism, although there are no data on the association between the FGF-basic level and number of eosinophils in GPP patients.

The serum VEGF level increased only in GPP patients in this study and in severe psoriatic patients in the previous literature,[15,22-26] whereas the serum angiopoitin-1 level increased in PsV, PsA, and GPP patients. Furthermore, the significant positive correlation was not observed in psoriatic patients between serum levels of VEGF and angiopoietin-1, which indicates that the roles of VEGF and angiopoietin-1 in the pathogenesis of psoriasis are different. In terms of angiogenesis, one of the major differences between GPP and other types of psoriasis is vascular permeability. Angiopoietin-1 maintains blood vessel formation, whereas VEGF not only induces angiogenesis but also disrupts vascular barrier function in diseased tissues.[27,28] Moreover, our study demonstrated that the serum VEGF level was significantly correlated negatively with the serum albumin level among the patients with GPP. It suggests that angiopoietin-1 plays an important role in the angiogenesis in the psoriatic plaque, and that VEGF contributes to the vascular permeability in addition to angiogenesis in GPP.

In conclusion, our exploratory study revealed that psoriasis affects the serum levels of certain angiogenesis-related factors. Some of them could be biomarkers of treatment outcomes, clinical severity and systemic inflammation. Since the number of patients examined in
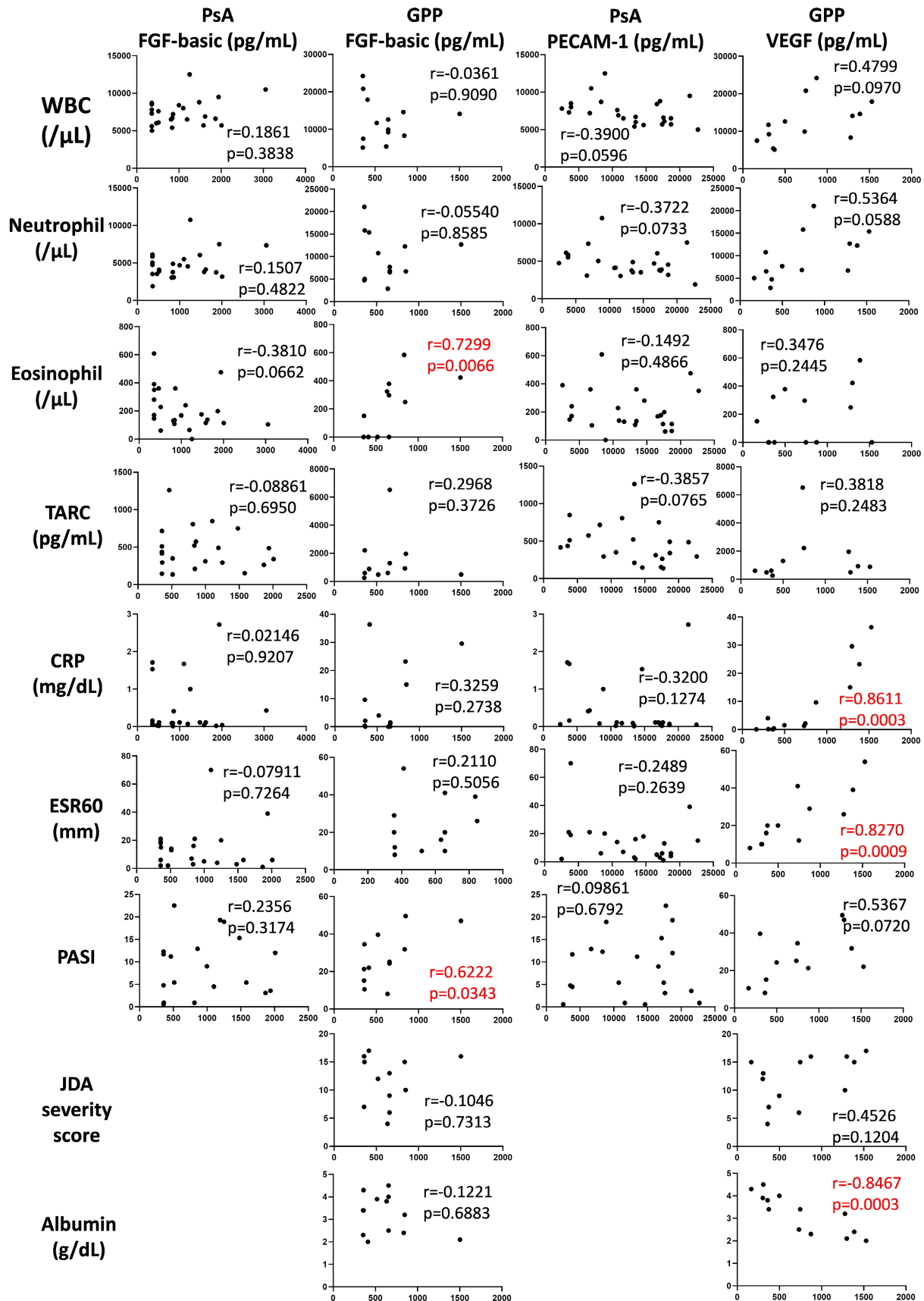
FIGURE 3 Correlations of serum levels of angiogenesis-related factors with laboratory data and clinical severity in psoriasis patients. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FGF, fibroblast growth factor; GPP, generalized pustular psoriasis; JDA, Japanese Dermatological Association; PASI, psoriasis area and severity index; PECAM-1, platelet endothelial cell adhesion molecule-1; PsA, psoriasis arthritis; TARC, thymus and activation-regulated chemokine; VEGF, vascular endothelial growth factor; WBC, white blood cell count.

this study was small, which is one of the limitations in our study, further accumulation of data is needed to clarify and validate our results.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

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