**RESEARCH ARTICLE**

# bFGF could be a biomarker of malignancy in RS₃PE syndrome: an ambispective single-center cohort analysis of 51 patients

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## Abstract

**Objectives:** Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) is a rare inflammatory arthritis, with a higher incidence of malignancy. The aim of this study is to identify biomarkers for predicting malignancy in RS₃PE.

**Methods:** A total of 51 patients with RS₃PE from September 2007 to May 2019 were retrospectively reviewed and followed for up to 5 years, with 15 patients with osteoarthritis (OA) and 14 patients with elderly-onset rheumatoid arthritis (EORA) as disease controls. Serum levels of angiogenesis cytokines were measured by electrochemiluminescent immunoassay and Luminex Human Magnetic Assay. Clinical data and laboratory parameters were analyzed to identify risk factors for malignancy.

**Results:** A total of forty-eight RS₃PE patients (94.1%) were available with follow-up data; 8 patients (16.7%) were diagnosed with malignancy, of which 6 patients were hematological tumor; and 2 patients were solid tumors. Serum levels of basic fibroblast growth factor (bFGF) were exclusively higher in RS₃PE patients with malignancy [14.21 (7.52, 23.18) ng/mL] than RS₃PE patients without malignancy [4.32 (2.88, 7.42) ng/mL], OA [3.20 (2.20, 5.30) ng/mL], and EORA [3.20 (2.20, 5.30) ng/mL]. The optimal cut-off value of bFGF for malignancy was 10ng/mL in RS₃PE. Logistic regression analysis indicated that elevation of bFGF was a risk factor for malignancy in RS₃PE.

**Conclusions:** This study indicated that bFGF was elevated in RS₃PE patients with malignancy and could serve as a biomarker for predicting paraneoplastic RS₃PE.

**Keywords:** RS₃PE, Malignancy, bFGF

## Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) is a rare elderly-onset inflammatory arthritis, characterized by symmetrical involvement of small joints and marked pitting edema on the dorsum of the hands and feet [1, 2]. In addition, a higher incidence of malignancy was reported in RS₃PE after the first symptom onset or during follow-up [2–4]. However,

no significant demographic or clinical differences were observed between idiopathic and paraneoplastic cases of RS₃PE, which suggests the importance of investigating novel serum tumor markers.

Previous studies have found two angiogenesis cytokines, namely vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-3, were involved in the pathogenesis of RS₃PE along with malignancy [5–8]. But later findings indicated that elevated levels of VEGF were also characteristics of infections and organizing pneumonia in RS₃PE [9, 10]. MMP-3 was elevated in RS₃PE patients with solid malignancy [11], but it was also an indicator for active arthritis [12]. It still

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remains elusive whether there is a specific biomarker for identifying arthritis with malignancy.

Since angiogenesis plays an important role in the pathogenesis and progression of cancer, we simultaneously evaluated the serum levels of 12 angiogenesis cytokines in paraneoplastic $RS_3PE$, comparing with idiopathic $RS_3PE$, osteoarthritis (OA), and elderly-onset rheumatoid arthritis (EORA) in the current study. We aimed to discover some novel markers for predicting malignancy in $RS_3PE$.

## Methods

### Patients enrolled

A single-center cohort study was performed in the Department of Rheumatology, Peking University People's Hospital. Fifty-one patients diagnosed with $RS_3PE$ syndrome were consecutively enrolled from September 2007 to May 2019, fulfilling the following criteria: (1) bilateral pitting edema of dorsum of hands and/or feet, (2) abrupt onset of polyarthritis, (3) age > 50 years, and (4) seronegative for rheumatoid factor (RF) [13]. As disease controls, 15 patients with OA and 14 patients with EORA were also enrolled, with sex- and age-matched. All the participants in disease control groups were excluded from malignancy.

### Study design and data collection

Patients with $RS_3PE$ were followed up for 5 years or monitored up to February 29, 2021, if they enrolled after February 28, 2016. The primary clinical outcome was the occurrence of malignancy. The baseline clinical and laboratory characteristics, coexistence of malignancy, and response to treatment were obtained from the medical records. If no follow-up data was available in our center, we contacted the family members to acquire the physical status (especially the occurrence of malignancy) confirmed by regular medical examination reports.

### Measurement of angiogenesis cytokines

The serum samples were collected from 45 $RS_3PE$ patients and all disease controls at baseline and stored at −80℃ in polypropylene microfuge tubes without thawing before the test. Serum levels of VEGF-A, VEGF-C, VEGF-D, FMS-like tyrosine kinase 1 (Flt-1), Tie-2, placental growth factor (PIGF), and basic fibroblast growth factor (bFGF) were measured via electrochemiluminescent immunoassay by V-PLEX Plus Angiogenesis Panel 1 Human Kit (Meso Scale Discovery). Serum levels of MMP-1, MMP-3, MMP-7, mesothelin, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) were determined with Luminex Human Magnetic Assay (5-Plex) LXSAHM-05 (R&D).

### Statistical analysis

Data analyses were performed using SPSS 23.0 for Windows. Continuous data with the normal distribution were expressed as the mean ± standard, and differences between groups were analyzed by one-way ANOVA. Continuous data with skewed distribution were expressed as median (P25, P75), and differences between groups were analyzed by Kruskal-Wallis test. Dichotomous variables were reported as frequency (percentages), and differences between groups were compared using the chi-square test (or Fisher's exact test when appropriate). The cut-off value of bFGF in $RS_3PE$ patients with malignancy was determined by receiver operating characteristic (ROC) methods. Univariate and multivariate logistic regression analyses were adopted to identify risk factors of malignancy. The variables assessed in the univariate regression analysis were entered as independent variables in multivariate logistic regression analysis when $P$ value <0.1. Two-sided $P < 0.05$ was considered statistically significant. The $P$ value was adjusted by Bonferroni correction in multiple tests.

## Results

### Clinical and laboratory features of RS₃PE patients

The clinical and laboratory features of overall $RS_3PE$ patients were shown in Table 1. Forty-eight patients (94.1%) were available with follow-up data, and a total of 26 patients (54.1%) completed a 5-year follow-up, and the follow-up time for the remaining 22 patients ranged from 1 month to 54 months. During the study period, eight of them (16.7%) were diagnosed with malignant tumors. Twenty-eight patients (54%) were male, and the average age at onset was 73.24±9.23 years. Pitting edema was seen in the hands of 45 patients (88.2%) and in the feet of 27 patients (52.9%). Weight loss was seen in 19 patients (37.3%). Patients had an elevated level of C-reactive protein (CRP) (43.9 [22.8, 82.0] mg/dL) and erythrocyte sedimentation rate (ESR) (55.37±34.12 mm/h). All patients had a normal level of carcinoembryonic antigen (<4.7 ng/mL). Eight patients (17.4%) had an elevated level of neuroenolase (>16.3ng/mL), 3 patients (5.8%) had an elevated level of cytokeratin 19 fragment (>3.3ng/mL), 2 patients (3.9%) had an elevated level of carbohydrate antigen 19-9 (>39U/mL), and only one patient (1.9%) had an elevated level of alpha-fetoprotein (>7ng/mL). Antinuclear antibody (ANA) was positive (≥1:80) in 6/51 (11.8%), and anti-Ro-52 was positive in 5/51 (9.8%). The median of

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**Table 1** Characteristics of RS$_3$PE patients with or without malignancy

|  | Overall (*n* = 51) | RS$_3$PE with malignancy (*n* = 8) | RS$_3$PE without malignancy (*n* = 40) | *P* |
|---|---|---|---|---|
| Age (years) | 73.39±9.18 | 75.00±11.07 | 73.50±8.51 | 0.667 |
| Age of onset (years) | 73.24±9.23 | 74.5±11.30 | 73.4±8.53 | 0.754 |
| Gender (M/F) | 28/23 | 5/3 | 21/19 | 0.710 |
| Pitting edema of hands (*n*, %) | 45 (88.2) | 7 (87.5) | 35 (87.5) | 1 |
| Bilateral (*n*, %) | 42 (93.3) | 5 (71.4) | 34 (97.1) | 0.067 |
| Weight loss (*n*, %) | 18 (35.3) | 5 (62.5) | 12 (30) | 0.112 |
| CEA > 4.7 ng/mL | 0[a] | / | / | / |
| AFP > 7ng/mL | 1 (2.6)[a] | 1 (14.3)[c] | 0[b] | 0.152 |
| CA19-9 > 39U/mL | 2 (5.1)[a] | 0[c] | 2 (5.1)[b] | 1 |
| CYFRA21-1 >3.3 ng/mL | 3 (6.5)[a] | 1 (14.3)[c] | 2 (5.1)[b] | 0.398 |
| NSE >16.3 ng/mL | 8 (17.4)[a] | 2 (28.6)[c] | 6 (18.2)[b] | 0.587 |
| C reactive protein (mg/L) | 43.9 (22.8, 82.0) | 35.9 (12.0, 91.0) | 45.7 (26.4, 84.9) | 0.674 |
| Erythrocyte sedimentation rate (mm/h) | 55.37±34.12 | 48.88±29.00 | 56.85±35.81 | 0.558 |
| Immunoglobulin A (g/L) | 3.05 (1.62, 3.73) | 2.71 (1.18, 3.66) | 3.13 (1.62, 4.04) | 0.734 |
| Immunoglobulin G (g/L) | 12.42±4.74 | 12.56±5.24 | 12.32±4.81 | 0.900 |
| Immunoglobulin M (g/L) | 0.71 (0.50, 1.09) | 0.68 (0.50, 1.39) | 0.71 (0.47, 1.12) | 0.968 |
| Complement 3 (g/L) | 1.04 (0.87, 1.28) | 1.03 (0.79, 1.16) | 1.05 (0.88, 1.29) | 0.422 |
| Complement 4 (g/L) | 0.23±0.09 | 0.25±0.04 | 0.24±0/09 | 0.722 |
| ANA≥1:80 (*n*, %) | 6 (11.8) | 0 | 6 (15) | 0.571 |
| Anti-Ro-52 (*n*, %) | 5 (9.8) | 1 (12.5) | 4 (10) | 1 |
| Initial prednisolone dose | 15 (15, 30) | 15 (10, 30) | 15 (15, 27.5) | 0.946 |
| Fast response to prednisolone (*n*, %) | 44 (89.8) | 3 (42.8)[d] | 38 (97.4) | **0.001**[*] |

Values displayed as *n* (%), mean ±standard deviation, or median (P25, P75) according to their features of the distribution

*Note*: *RS$_3$PE* remitting seronegative symmetrical synovitis with pitting edema, *ANA* anti-nuclear antibody, *CEA* carcinoembryonic antigen, *AFP* alpha-fetoprotein, *CA19-9* carbohydrate antigen 19-9, *CYFRA21-1* cytokeratin 19 fragment, *NSE* neuroenolase

[*] *P*<0.05, a significant difference between RS$_3$PE patients with and without malignancy

[a] Five patients did not have the data of serum tumor markers

[b] Two patients did not have the data of serum tumor markers

[c] One patient did not have the data of serum tumor markers

[d] One patient did not receive glucocorticoids

the initial prednisolone dose was 15 mg/day, and 44/51 (89.8%) showed a good response to prednisolone.

## Comparison between RS$_3$PE patients with and without malignancy

The detailed clinical profiles of the eight RS$_3$PE patients with malignancy were displayed in Table 2. The prevalence of malignancy was 16.7% (8/48), six were hematological tumors, and 2 were solid tumors. The time from the onset of arthritis to confirmation of malignancy was from 2 months to 3 years. In these 6 patients with hematological tumors, 4 patients were diagnosed within 6 months from arthritis onset, and 3 patients showed poor response to low-dose prednisolone. Both patients with solid tumors were diagnosed 2 years after arthritis onset, and one of them (50%) was resistant to low-dose prednisolone.

We next compared the clinical and laboratory features between patients with or without malignancy (Table 1). Better response to prednisolone was found in patients without malignancy (*n*=38/40, 97.4%) than patients with malignancy (*n*=3/7, 42.8%). However, significant differences were not seen in demographic figures (age and gender), clinical features (patterns of edema and weight loss), and laboratory features (CRP, ESR, immunoglobulin, complement, and tumor markers).

## Serum levels of angiogenesis cytokines among RS$_3$PE with/ without malignancy, OA, and EORA

Twelve angiogenesis cytokines were measured, and the results were demonstrated in Table 3. Serum levels of bFGF were exclusively higher in RS$_3$PE patients with malignancy [14.21 (7.52, 23.18) ng/mL] than RS$_3$PE patients without malignancy [4.32 (2.88, 7.42) ng/mL],

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**Table 2** Detailed clinical profiles of RS₃PE patients with malignancy

| No. | Age/sex | Type of malignancy | Time from arthritis onset to malignancy confirmation | Signs | ESR (mm/h) | CRP (mg/L) | bFGF (ng/mL) | Initial pred. (mg/day) | Response to pred. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 85/M | Acute myeloid leukemia -M2 | 6 months | Unilateral hands | 29 | 16.9 | 25.04 | 0 | / |
| 2 | 75/F | Multiple myeloma (IgA, λ) | 2 years | Bilateral hands | 61.2 | 70 | 24.35 | 15 | poor |
| 3 | 80/M | Diffuse large B cell lymphoma | 2 months | Bilateral hands | 86 | 45.9 | 10.2 | 40 | poor |
| 4 | 53/M | Plasma cell leukemia | 8 months | Unilateral hands | 19 | 177.3 | 42.48 | 30 | poor |
| 5 | 85/F | Rectal carcinoma | 3 years | No hands | 44 | 10.4 | 17.58 | 30 | poor |
| 6 | 66/F | Multiple myeloma | 3months | Bilateral hands | 71 | 26.11 | 10.94 | 15 | good |
| 7 | 83/M | Non-Hodgkin lymphoma | 2 months | Bilateral hands | 67 | 101 | 5.57 | 15 | good |
| 8 | 73/M | Lung carcinoma | 2 years | bilateral hands | 5 | 9.39 | 6.63 | 7.5 | good |

*RS₃PE* remitting seronegative symmetrical synovitis with pitting edema, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Pred.* prednisolone

**Table 3** Comparison of angiogenesis cytokines among RS₃PE with/without malignancy, OA, and EORA

| | RS₃PE with malignancy (n = 8) | RS₃PE without malignancy (n = 38) | OA (n = 15) | EORA (n = 14) | F/t | P |
|---|---|---|---|---|---|---|
| Flt-1 (ng/mL) | 7.38±2.64 | 6.14±2.25 | 5.96±1.53 | 5.59±1.67 | 1.321 | 0.275 |
| PlGF (ng/mL) | 6.14 (4.436, 6.58) | 5.99 (4.45, 7.29) | 5.61(4.74, 6.6) | 4.81 (4.48, 7.15) | 0.745 | 0.863 |
| Tie-2 (ng/mL) | 8.99±2.34 | 9.92±2.89 | 11.26±2.72 | 8.47±2.41 | **2.816** | **0.045** |
| VEGF (ng/mL) | 168.41 (90.86, 327.61) | 83.15 (50.34, 200.11) | 156.24 (117.94, 239.03) | 71.68 (40.74, 234.95) | 4.144 | 0.246 |
| VEGF-C (ng/mL) | 3.76 (1.69, 7.58) | 4.75 (3.72, 9.79) | 6.57 (5.45, 7.82) | 5.31 (3.87, 6.46) | 3.281 | 0.350 |
| VEGF-D (ng/mL) | 18.40 (14.86, 30.31) | 31.92 (26.88, 46.75) | 26.43 (23.64, 36.74) | 24.98 (17.56, 34.74) | **10.433** | **0.015** |
| bFGF (ng/mL) | 14.21 (7.52, 23.18) | 4.32 (2.88, 7.42)▲ | 3.23 (1.96, 5.59)▲ | 3.20 (2.20, 5.30)▲ | **15.861** | **0.001** |
| MMP-3 (ng/mL) | 24.74 (17.96, 51.67) | 36.08 (19.01, 54.34) | 22.03 (14.84, 25.57) | 33.31 (15.86, 41.44) | 5.346 | 0.148 |
| MMP-1 (ng/mL) | 4.98 (3.80, 7.50) | 3.93 (1.94, 7.73) | 2.90 (1.72, 4.50) | 5.80 (3.37, 10.73) | 5.472 | 0.140 |
| MMP-7 (ng/mL) | 2.11 (1.55, 5.02) | 2.86 (1.99, 3.40) | 2.68 (1.64, 4.16) | 3.06 (2.02, 5.03) | 0.864 | 0.834 |
| TRAIL (pg/mL) | 82.28 (57.26, 121.38) | 93.86 (75.98, 140.34) | 98.56 (84.51, 114.28) | 89.96 (61.04, 124.94) | 2.324 | 0.508 |
| Mesothelin (ng/mL) | 25.65 (17.81, 34.84) | 24.10 (17.89, 30.54) | 27.20 (15.40, 30.27) | 21.96 (18.94, 28.50) | 0.688 | 0.876 |

*Note:* ▲Significance comparing with RS₃PEpatients with malignancy, adjusted $P<0.05$. *RS₃PE* remitting seronegative symmetrical synovitis with pitting edema, *Flt-1* Fms-like tyrosine kinase 1, *VEGF* vascular endothelial growth factor, *PlGF* placental growth factor, *bFGF* basic fibroblast growth factor, *MMP* matrix metalloproteinase, *TRAIL* tumor necrosis factor-related apoptosis-inducing ligand

OA [3.23 (1.96, 5.59) ng/mL], and EORA [3.20 (2.20, 5.30) ng/mL]. However, there were no significant differences in serum levels of VEGF-A, VEGF-C, VEGF-D, Flt-1, Tie-2, PlGF, MMP-1, MMP-3, MMP-7, mesothelin, and TRAIL among different groups. Figure 1 showed the ROC curve of bFGF with an AUC value of 0.817, and the optimal cut-off value was 10ng/mL; the sensitivity was 75% and the specificity was 89.5%.

### Risk factors for malignancy in RS₃PE

As shown in Table 4, the results of univariate logistics models found that bilateral pitting edema of the hands (OR=0.074, 95%CI (0.006–0.968), $P=0.047$) and good response to prednisolone (OR=0.039, 95%CI (0.005–0.311), $P=0.002$) were negatively associated with malignancy in RS₃PE, and elevation of bFGF (>10ng/ml) (OR=14.084, 95%CI (2.421–83.332), $P=0.003$) was positively associated with malignancy in RS₃PE. Then, the multivariate logistic models showed elevation of bFGF was a unique risk factor for malignancy (OR=14.667, 95%CI (2.029–106.038), $P=0.008$).

### Discussion

In the present study, we reviewed the clinical and laboratory features and simultaneously analyzed multiple angiogenesis cytokines in RS₃PE patients with malignancy. We found elevation of bFGF might be a useful predictor for malignancy in RS₃PE.
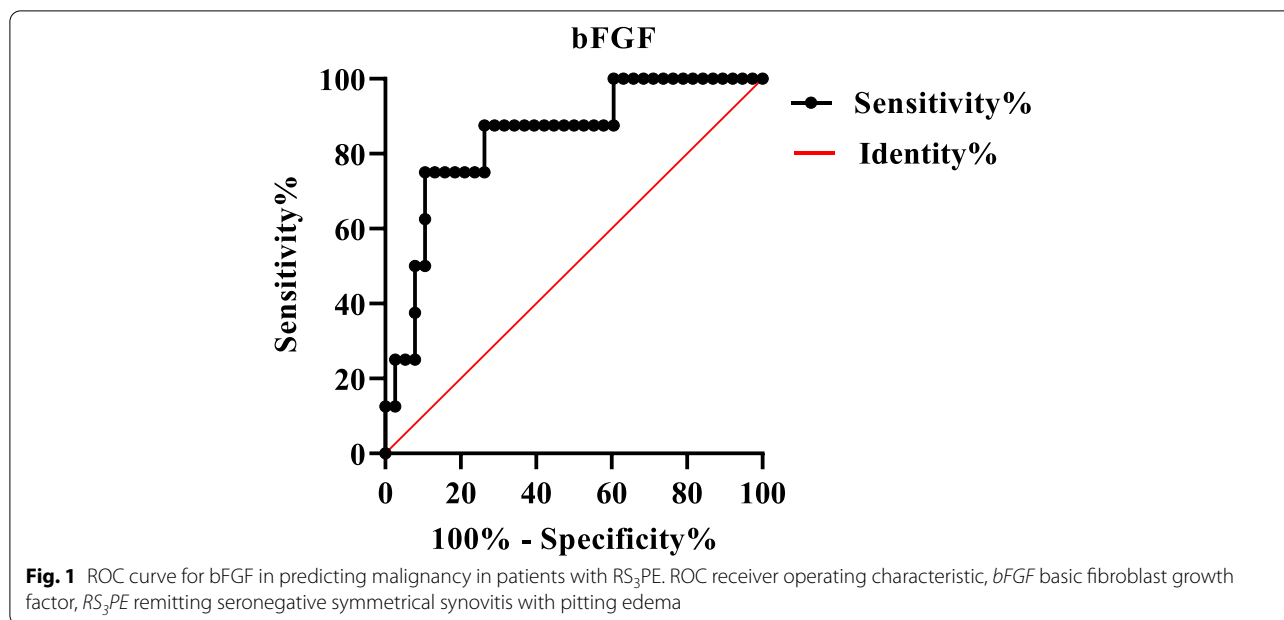
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**Fig. 1** ROC curve for bFGF in predicting malignancy in patients with RS$_3$PE. ROC receiver operating characteristic, *bFGF* basic fibroblast growth factor, *RS$_3$PE* remitting seronegative symmetrical synovitis with pitting edema

**Table 4** Risk factors for malignancy in RS3PE by logistic models

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | *B* | OR (95%CI) | *P* | *B* | OR (95%CI) | *P* |
| Male | 0.411 | 1.508 (0.317–7.177) | 0.606 | | | |
| Bilateral pitting edema of hands | −2.61 | 0.074 (0.006–0.968) | **0.047** | −1.255 | 0.285 (0.035–2.320) | 0.068 |
| Good response to prednisolone | −3.232 | 0.039 (0.005–0.311) | **0.002** | −1.967 | 0.140 (0.017–1.182) | 0.071 |
| bFGF>10ng/ml | 2.651 | 14.084 (2.421–83.332) | **0.003** | 2.686 | 14.667 (2.029–106.038) | **0.008** |

*RS$_3$PE* remitting seronegative symmetrical synovitis with pitting edema, *bFGF* basic fibroblast growth factor

Increased associated malignancy in RS$_3$PE has been reported since 1985, including hematological malignancies and solid tumors [2, 14–16], and the average malignancy rate was estimated to 20% [2], which is similar to our study. Although hematological malignancies were the primary tumors in our study and most of them were diagnosed within the first 6 months, both two associated solid tumors were confirmed during the follow-up. Besides, a French study of six men with RS$_3$PE demonstrated that all solid malignancy was discovered during a 5-year follow-up [17]. These findings indicate that solid tumors might be relatively insidious in RS$_3$PE-related malignancies, reminding rheumatologists the importance of tumor screening during the follow-up.

Poor response to low-dose prednisolone is associated with malignancies in RS$_3$PE in our study, and some reported cases of paraneoplastic RS$_3$PE are also revealed poor response to glucocorticoid [2, 18]. However, rapid response to glucocorticoid therapy is also found for some paraneoplastic RS$_3$PE, and there are no clinical variables

for predicting malignancy in RS$_3$PE [1, 3, 4, 19], which calls for more effective biomarkers.

Interestingly, our study discovered bFGF is the only angiogenesis cytokine which is elevated particularly in RS$_3$PE-associated malignancy, and further multiple logistic regressions revealed elevation of bFGF may serve as a marker for predicting malignancy in RS$_3$PE. bFGF, also known as fibroblast growth factor 2 (FGF-2), is one of the prototypes of the FGF family, which signals through FGF receptors (FGFRs) and promotes growth and differentiation of a broad spectrum of cell types, including dermal fibroblasts, keratinocytes, endothelial cells, and melanocytes [20–22]. In addition, bFGF also plays a critical role in promoting tumor angiogenesis and metastasis and has been shown to be involved in the invasion and progression of solid and hematological malignancies [21, 23–26].

Apart from tumor genesis, it has also been found that bFGF could stimulate osteoclastogenesis and promote bone absorption through binding to FGFRs, and is the only one of the bone-resorptive cytokines that

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are highly expressed in the synovial fluid of RA patients [27–29]. Thus, significantly higher serum bFGF in $RS_3PE$ may reflect the secretion of bFGF in situ of tumor tissues as well as synovium, suggesting that bFGF might play an important role in the pathogenesis of $RS_3PE$. Besides, the titers of bFGF were relatively lower in the $RS_3PE$-associated solid malignancy (confirmed after 2 years from arthritis onset) than $RS_3PE$-associated hematological malignancy (confirmed within 1 year from arthritis onset), which might partially due to the late onset of solid tumor.

Previous researches have pointed out that $RS_3PE$ might be a VEGF-associated disorder and elevated serum level of VEGF was also found in paraneoplastic $RS_3PE$ [6, 7]. However, a recent study has found serum VEGF is elevated in many elderly patients with different rheumatic diseases, indicating that VEGF may not be a marker for predicting malignancy [30]. Tomoki et al. reported high-serum MMP-3 is a characteristic of $RS_3PE$ patients with neoplasm. Nevertheless, serum levels of MMP-3 are relatively lower in our paraneoplastic $RS_3PE$ patients compared with non-paraneoplastic $RS_3PE$ patients. This difference might be partially due to different kinds of malignancy. All of the cancers in Tomoki et al.'s study are solid tumors, and they merely compared the difference of serum MMP-3 between patients with and without malignancy [11]. Most of our paraneoplastic $RS_3PE$ patents are hematological, and we utilized multiple logistic models to fully confirm the relationship between bFGF and malignancy.

## Limitations

Due to the rarity of $RS_3PE$, the number of associated malignant cases is relatively less at a single center; therefore, a prospective cohort or multi-center studies are needed to confirm the clinical significance of bFGF in further studies.

## Conclusion

Our study revealed the clinical significance of serum bFGF in $RS_3PE$; thus, bFGF might be associated with malignancy in $RS_3PE$. Further research might verify our findings by multi-center studies and explore the prognostic value for angiogenesis cytokines.

## Abbreviations

bFGF: Basic fibroblast growth factor; EORA: Elderly-onset rheumatoid arthritis; Flt-1: FMS-like tyrosine kinase 1; MMP: Matrix metalloproteinase; OA: Osteoarthritis; PIGF: Placental growth factor; RF: Rheumatoid factor; ROC: Receiver operating characteristic; $RS_3PE$: Remitting seronegative symmetrical synovitis with pitting edema; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; VEGF: Vascular endothelial growth factor.

## Authors' contributions
YG: data interpretation and analysis, manuscript drafting, review, and editing. HY: methodology, review, and editing. JC, YC, and XL: clinical data collecting and follow-up of the paticipants. YS and YW: laboratory analysis. The authors read and approved the final manuscript.

## Availability of data and materials
Dr. Hua Ye and Dr. Yuzhou Gan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

## Declarations

### Ethics approval and consent to participate
The study was approved by the ethics committee of Peking University People's Hospital (2020PHB060) and the study complied with the Declaration of Helsinki guidelines. All the participants were given written informed consent.

### Consent for publication
Not applicable

### Competing interests
The authors declare that they have no competing interests.

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