Association of Circulating Vascular Endothelial Growth Factor Levels With Autoimmune Diseases: A Systematic Review and Meta-Analysis

Haoting Zhan1,2†, Haolong Li1,2†, Chenxi Liu1,2, Linlin Cheng1,2, Songxin Yan1,2 and Yongzhe Li1,2*

1 Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, 2 Department, State Key Laboratory of Complex, Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

Background: Autoimmune diseases (ADs) are characterized by immune-mediated tissue damage, in which angiogenesis is a prominent pathogenic mechanism. Vascular endothelial growth factor (VEGF), an angiogenesis modulator, is significantly elevated in several ADs including rheumatoid arthritis (RA), systemic sclerosis (SSc), and systemic lupus erythematosus (SLE). We determined whether circulating VEGF levels were associated with ADs based on pooled evidence.

Methods: The analyses included 165 studies from the PubMed, EMBASE, Cochrane Library, and Web of Science databases and fulfilled the study criteria. Comparisons of circulating VEGF levels between patients with ADs and healthy controls were performed by determining pooled standard mean differences (SMDs) with 95% confidence intervals (CIs) in a random-effect model using STATA 16.0. Subgroup, sensitivity, and meta-regression analyses were performed to determine heterogeneity and to test robustness.

Results: Compared with healthy subjects, circulating VEGF levels were significantly higher in patients with SLE (SMD 0.84, 95% CI 0.25–1.44, P = 0.0056), RA (SMD 1.48, 95% CI 0.82–2.15, P <0.0001), SSc (SMD 0.56, 95% CI 0.36–0.75, P <0.0001), Behcet’s disease (SMD 1.65, 95% CI 0.88–2.41, P <0.0001), Kawasaki disease (SMD 2.41, 95% CI 0.10–4.72, P = 0.0406), ankylosing spondylitis (SMD 0.78, 95% CI 0.23–1.33, P = 0.0052), inflammatory bowel disease (SMD 0.57, 95% CI 0.43–0.71, P <0.0001), psoriasis (SMD 0.98, 95% CI 0.62–1.34, P <0.0001), and Graves’ disease (SMD 0.69, 95% CI 0.20–1.19, P = 0.0056). Circulating VEGF levels correlated with disease activity and hematological parameters in ADs.

Conclusion: Circulating VEGF levels were associated with ADs and could predict disease manifestations, severity and activity in patients with ADs.
INTRODUCTION

Angiogenesis, a hallmark of inflammatory activation, is an integral part of pathogenic processes including endothelial cell proliferation and migration and subsequent neovascularization and remodeling in autoimmune diseases (ADs). Synovial pannus initiates the invasion of cartilage and subchondral bone to perpetuate rheumatoid arthritis (RA) (1, 2), whereas ankylosing spondylitis (AS) is characterized by increased vascularity and vascular lesions (3). Vascular endothelial dysfunction and injury are considered as the primum movens triggering Kawasaki disease (KD), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), Behçet’s disease (BD), systemic sclerosis (SSc), and psoriasis (PsA) (4–9). Therefore, early detection of vascular involvement is pivotal in AD diagnosis.

Vascular endothelial growth factor (VEGF)-A, generally known as VEGF, is a crucial regulator of endothelial dysfunction, capillary permeability, and angiogenesis. For example, serum VEGF level and intrathyroid microvessel density were reported to be increased patients with Graves’ disease (GD) compared to healthy control (HC) subjects (10). Increased serum VEGF and significant difference in diffused and limited SSc suggest VEGF as a potential surrogate indicator of capillary damage (11). Strong VEGF expression in synovial fluid and serum of patients with RA was shown to lead to synovial neovascularization and destruction in cartilage and bones (12, 13). VEGF was reported to be overexpressed in the skin and peripheral blood of patients with PsA (14). Serum VEGF levels were shown to be elevated and to correlate with disease activity and severity in PsA, SLE, BD, IBD, KD, and AS (14–19). These findings suggest VEGF as a potential pathogenic factor with promising diagnostic value in ADs. However, no clinical guidelines currently recommend serum VEGF evaluation in routine care and counseling of patients with ADs, and intensive studies are warranted to identify the clinical implications of the findings regarding VEGF’s role in ADs to date and to resolve contradictory results (20–24).

Given the inconsistency among these findings and lower statistic power of the studies, we performed a systematic review and meta-analysis to generate independent results and recognize the source of heterogeneity. In the present study, we aimed to determine whether circulating VEGF was a causative factor in ADs.

MATERIALS AND METHODS

Literature Search

The present systematic review with meta-analysis was performed according to the PRISMA guidelines (PROSPERO registration number, CRD42021227843). Two authors (HTZ and HLL) independently searched the PubMed, Embase, Cochrane Library, and the Web of Science databases for studies published until October 14. The detailed search strategies are provided in the online Supplemental Materials. Reference lists were manually retrieved.

Eligibility Criteria

Without restrictions on time, language, ethnicity, and geographical region, studies satisfying the following criteria were included: (1) case-control or cohort studies on the association between circulating VEGF and ADs including SLE, RA, SSc, BD, KD, AS, IBD, PsA, and GD; (2) HCs without ADs (2); available data on circulating VEGF levels (serum or plasma); (3) sufficient data on VEGF levels for both HCs and patients with ADs to evaluate standard mean differences (SMDs) with 95% confidence intervals (CIs). Studies based on animal and cellular models, those comprising HCs with insufficient data; and editorial letters with insufficient data were excluded.

Data Extraction and Quality Assessment

Two independent investigators (HTZ and HLL) individually screened the literature and extracted and evaluated the data. Any discrepancies were resolved by consensus or by a third opinion (YZL). Study number, name of the first author, publication year, country, study type, sample type, inclusion and exclusion criteria, demographic features, aggregated number of subjects and circulating VEGF levels in patients with ADs and HCs, diagnostic criteria, type of VEGF assay, and treatment history and strategy were extracted into pre-designed charts. For meta-analysis, continuous variables were translated from medians (interquartile range [IQR] or range) to means ± standard deviation (25). Newcastle–Ottawa quality assessment scale was used to evaluate study quality. Further details of the pooled studies were obtained by directly contacting the authors if warranted.

Data Analysis

STATA V.16.0 was used to perform the meta-analysis. SMDs with 95% CIs were used to estimate the pooled results and compare circulating VEGF levels between patients and HC groups. Random-effect model was used for analysis. Significant heterogeneity was ascertained based on a p value of ≤0.10 using the Cochrane Q test or an I^2 value of >50%. Subgroup, sensitivity, and meta-regression analyses were performed to identify the source of heterogeneity and to test robustness. Spearman correlation coefficients were transformed into Pearson’s r values, which were converted to Fisher’s z values to obtain approximately normal distributions. Ultimately, the summary Fisher’s z values were converted into summary r values. Summary r values of 0.8–1.0, 0.6–0.8, 0.4–0.6, and 0.2–0.4
indicated extreme, high, and moderate relevance and poor correlation, respectively (details provided in the online Supplemental Materials). Publication bias was assessed by Egger’s linear regression test and contour-enhanced funnel plots with collaborative meta-trim. A two-sided \( P < 0.05 \) was considered to indicate statistical significance.

**RESULTS**

**Search Results and Population Characteristics**

The literature search is summarized in Figure 1. After removing duplicate studies (\( n = 3,322 \)) and irrelevant publications (\( n = 8,673 \)), 298 articles were analyzed and the full texts of 273 articles were read. Thirty-two full-text articles were eliminated due to incomplete data or unrelated outcomes. Among 241 eligible studies meeting the inclusion criteria, 76 articles were excluded due to unextractable data, insufficient data on HCs, irrelevant VEGF sample type (urine/synovial fluid/tear fluid), or inappropriate disease control groups. Finally, 165 studies were included in the meta-analysis, with 28, 29, 40, 13, 8, 12, 16, 23, and six studies on SLE (20, 21, 26–51), RA (12, 22–24, 38, 43, 52–74), SSc (11, 38, 39, 64, 75–110), BD (111–123), KD (18, 124–130), AS (55, 73, 131–140), IBD (141–156), PsA (12, 14, 135, 136, 157–175) and GD (10, 176–180), respectively. The main study characteristics are summarized in Table 1 and Appendix 1. The studies were medium-to-high quality based on the Newcastle-Ottawa quality assessment scale scores (range, 4–9).

**Meta-Analysis of the Association Between Circulating VEGF and SLE**

Circulating VEGF levels were significantly higher in SLE than in HC (SMD 0.84, 95%CI 0.25–1.44, \( P = 0.0056 \)) (Figure 2A). Additionally, circulating VEGF was higher in active SLE than in inactive SLE (SMD 0.80, 95%CI 0.02–1.59, \( P = 0.0454 \)) (Figure 2B-i). Serum VEGF levels remained remarkable higher in active SLE.
### TABLE 1 | Population characteristics of the studies included in the meta-analysis.

| Year | Author          | Country  | Study type | SLE | Sample size | Female (%) | Age (years) | HC | Sample size | Female (%) | Age (years) |
|------|----------------|----------|------------|-----|-------------|------------|-------------|----|-------------|------------|-------------|
| 2015 | Barbulescu AL  | Romania  | case-control | SLE | 18          | 16 (88.88) | 45.00 ± 10.81 | 17 | 16 (94.11)  | range: 19-64 |
| 2019 | Barraclough M  | UK       | case-control | SLE | 36          | 34 (94)    | 40 ± 12.41  | 30 | 30 (100)    | 32 ± 14.44  |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 40 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
| 2015 | Ding Y         | China    | case-control | SLE | 41          | 30 (73.2)  | 11.1 ± 2.4  | 10 | 0  |            |            |
| 2009 | Elhelaly NS    | Egypt    | case-control | SLE | 23          | 21 (91.3)  | Range: 19-64 | 25 | 5 (25)      | 12 ± 3      |
| 2008 | Ciprandi G     | Italy    | case-control | SLE | 40          | 34 (100)   | 41.95 ± 8.3 | 40 | 33 (82.5)   | 43 ± 8.2    |
| 2014 | De Jesus GR    | Brazil   | case-control | SLE | 80          | 80 (100)   | 42.6 ± 9.1  | 80 | 80 (100)    | 40.1 ± 9.5  |
### TABLE 1 | Continued

| Year  | Author      | Country   | Study type | RA Sample size | RA Female (%) | RA Age (years) | RA | HC Sample size | HC Female (%) | HC Age (years) |
|-------|-------------|-----------|------------|----------------|---------------|----------------|----|----------------|---------------|----------------|
| 1998  | Kikuchi K   | Japan     | case-control | 11             | 10 (90.9)     | 51 ± 10.75     | 20 | 16 (80)       | 50 ± 12.5     |                |
| 2007  | Cho ML      | Korea     | case-control | 72             | 49.6 ± 1.3    | 54.3 ± 14.25   | 31 |               | 47.1 ± 2.1    |                |
| 2006  | Kurylczyn-Moskal A | Poland | case-control | 64             | 54 (84.4)     | 58.6 ± 12.6    | 32 |               | 52.7 ± 10.6   |                |
| 2004  | Kuwana M    | Japan     | case-control | 11             | 11 (100)      | 59.1 ± 12.0    | 11 | 11 (100)      | 52.7 ± 10.6   |                |
| 2010  | Milman N    | Canada    | case-control | 47             | 78.7          | 54.3 ± 14.25   | 30 | 28 (93.3)     | 34.03 ± 10.3  |                |
| 2018  | Misra S     | India     | case-control | 50             | 46 (92)       | 35.90 ± 18.607 | 20 |               | 25 ± 1        |                |
| 2016  | Novikov A   | Russia    | case-control | 74             | 59 (79.7)     | 35.90 ± 18.607 | 20 |               | 52.0 ± 2.5    |                |
| 2012  | Oranskiy SP | Russia    | case-control | 39             | 82.0          | 53.0 ± 2.75    | 20 |               | 52.0 ± 2.5    |                |
| 2010  | Ozgonenel L | Turkey    | case-control | 40             | 32 (80)       | 46 ± 12.59     | 38 | 18 (47.4)     | 44 ± 11.11    |                |
| 2009  | Young HR    | America   | case-control | 169            | 69.20         | 54.2 ± 11.8    | 92 | 63            | 53.2 ± 11.6   |                |
| 2016  | Rodriguez-Carrillo J | Spain | case-control | 212            | 175 (82.5)    | 54 ± 17.25     | 175| 102 (58.3)    | 51 ± 14.25    |                |
| 2016  | Smets P     | France    | case-control | 80:RA13        | 8 (61.5)      | 71 ± 7.97      | 37 | 24 (64.9)     | 73.35 ± 8.55  |                |
| 2004  | Strunk J    | Germany   | case-control | 16             | 16 (78.2)     | range: 38–79   | 41 | 38 (92.7)     | 56.09 ± 7.82  |                |
| 2010  | Ozgonenel L | Turkey    | case-control | 40             | 32 (80)       | 46 ± 12.59     | 38 | 18 (47.4)     | 44 ± 11.11    |                |
| 2001  | Sone H      | Japan     | case-control | 155            | 130 (83.9)    | range: 21–57   | 75 | 62 (82.7)     | 55.8 ± 15.4   |                |

| Year  | Author      | Country   | Study type | SSc Sample size | SSc Female (%) | SSc Age (years) | RA Sample size | RA Female (%) | RA Age (years) | HC Sample size | HC Female (%) | HC Age (years) |
|-------|-------------|-----------|------------|-----------------|----------------|----------------|----------------|---------------|----------------|----------------|---------------|----------------|
| 2012  | Bosello SL  | Italy     | case-control | 48             | 45 (81.8)      | 40.6 ± 13      | 55 | 30            | 38 ± 6        |                |
| 2017  | Chora I     | Italy     | case-control | 55             | 49 (89.0)      | 64 ± 11        | 55 | 51 (92.7)     | 52 ± 10.25    |                |
| 2013  | De Lauretis A | UK       | case-control | 74             | 59 (79.7)      | 51.4 ± 12.1    | 20 | 7 (35)        | 32.7 ± 6.3    |                |
| 2017  | Delle Sedie A | Italy   | case-control | 41             | 40 (97.6)      | 56 ± 15        | 31 | 25 (80.6)     | 50 ± 16       |                |
| 2011  | Distler JHW | Germany   | case-control | 40             | 34 (85)        | 46 ± 14.5      | 66 | 44 (66.7)     | 39 ± 13.75    |                |
| 2002  | Distler O   | Italy     | case-control | 43             | 35 (81.4)      | 61 ± 13.75     | 21 | 16 (76.2)     | 55 ± 16.75    |                |
| 2012  | Dunne JV    | Ireland   | case-control | 40             | 35 (87.5)      | 45.5 ± 9.5     | 40 |               |               |                |
| 2005  | Dziankowska-Bartkowiak B | Poland | case-control | 34             | 26 (76.5)      | 48 ± 13.5      | 20 | 19 (95.0)     | 46 ± 9.75     |                |
| 2006  | Dziankowska-Bartkowiak B | Poland | case-control | 28             | 22 (78.6)      | 47.5 ± 13      | 20 | 15 (75)       | 46 ± 9.75     |                |
| 2013  | Farouk HM   | Egypt     | case-control | 26             | 21 (84)        | 40.3 ± 5.86    | 20 | 17 (85)       | 38.9 ± 3.8    |                |
| 2014  | Glokowska-Mrowka E | Poland | case-control | 66             | 60 (90)        | 53 ± 13.25     | 21 | 18 (85.7)     | 52 ± 10.25    |                |
| 2018  | Gigante A   | Italy     | case-control | 15             | 15 (100)       | 41 ± 10.835    | 10 |               | 39 ± 10.484   |                |

(Continued)
| Year | Author | Country | Study type | Sample size | SSc | Sample size | HC |
|------|--------|---------|------------|-------------|-----|-------------|----|
| 2008 | Hummers LK (93) | America | case-control | 113 | 88.90 | 53.0 ± 12.2 | 27 | 63 | 57.5 ± 2.8 |
| 2017 | Ibrahim SE (94) | Egypt | case-control | 35 | 33 (94.2) | 30.43 ± 4.53 | 20 | 16 (80) | 50 ± 12.5 |
| 2018 | Kawashiri S (95) | Japan | case-control | 60 | 56 (93.3) | 64 ± 6.67 | 25 |
| 1998 | Kikuchi K (38) | Japan | case-control | 40 | 37 (92.5) | 53 ± 16.25 | 0 |
| 2004 | Kuryliszyn-Moskal A (96) | Poland | case-control | 31 | 31 (100) | 55.2 ± 10.4 | 100 |
| 2013 | Koca SS (39) | Turkey | case-control | 37 | 32 (86.5) | 45.7 ± 13.6 | 40 |
| 2019 | Michalska-Jakubus M (98) | Poland | case-control | 47 | 47 (100) | 58.43 ± 11.01 | 27 | 27 (100) | 52.37 ± 8.87 |
| 2010 | Minier T (99) | Hungary | case-control | 131 | 90.80 | 55.9 ± 11.3 | 30 |
| 2012 | Morgel E (100) | Poland | case-control | 30 | 28 (60.7) | 54 ± 10.3 | 20 |
| 2009 | Papaioannou AI (101) | Greece | case-control | 40 | 33 (82.5) | 56.75 ± 12.5 | 13 |
| 2015 | Reiseter S (102) | Norway | cohort | 298 | 243 (82) | 56.0 ± 13.8 | 100 |
| 2001 | Satou S (103) | Japan | case-control | 32 | 29 (90.6) | 47 ± 18 | 20 |
| 2010 | Ricceri V (104) | Italy | case-control | 65 | 63 (96.9) | 57.3 ± 15.25 | 16 |
| 2017 | Saranya C (105) | India | case-control | 55 | median | 57.4 ± 10.3 | 30 |
| 2016 | Shenavandeh S (106) | Iran | case-control | 44 | 40 (90.9) | 40.7 ± 12.8 | 44 | 41 (93.2) | 39.4 ± 11.76 |
| 2003 | Cekmen M (112) | Turkey | case-control | 39 | 18 (46.2) | 38.1 ± 10.4 | 13 |
| 2012 | Ganeb SS (115) | Egypt | case-control | 70 | 27 (38.6) | 32.8 ± 3.63 | 20 |
| 2019 | Gheita TA (116) | Egypt | case-control | 40 | 16 (40) | 37.6 ± 8.7 | 25 | 20 (90) | 59.4 ± 9.9 |
| 2011 | Ibrahim SE (117) | Egypt | case-control | 40 | 8 (20) | 40.35 ± 7.34 | 40 | 9 (22.5) | 37.3 ± 7.06 |
| 2009 | Ozdamar Y (119) | Turkey | case-control | 30 | 20 | 32.6 ± 9.14 | 70 | 29 (104.4) | 32.81 ± 3.89 |

| Year | Author | Country | Study type | Sample size | BD | Sample size | HC |
|------|--------|---------|------------|-------------|----|-------------|----|
| 2018 | Arica DA (111) | Turkey | case-control | 45 | 22 (48.9) | 36.7 ± 10.3 | 28 |
| 2003 | Cekmen M (112) | Turkey | case-control | 39 | 18 (46.2) | 38.1 ± 10.4 | 15 | 7 (46.7) | 39.2 ± 9.3 |
| 2013 | Eldin AB (113) | Egypt | case-control | 30 | 6 (20) | 30.6 ± 9.36 | 20 | 4 (20) | 26.9 ± 8.38 |
| 2003 | Erdem F (114) | Turkey | case-control | 33 | 16 (48.5) | 33.2 ± 10.4 | 30 | 9 (30) | 34.0 ± 11.1 |
| 2012 | Ganeb SS (115) | Egypt | case-control | 70 | 27 (38.6) | 32.8 ± 3.63 | 70 | 29 (104.4) | 32.81 ± 3.89 |
| 2019 | Gheta TA (116) | Egypt | case-control | 96 | active 59 | 34.9 ± 10.1 | 60 | 9 (25) | 36.7 ± 12.6 |
| 2011 | Ibrahim SE (117) | Egypt | case-control | 40 | active 40 | 37.6 ± 8.7 | 40 | 18 (45) | 38.8 ± 7.9 |
| 2017 | Kul A (118) | Turkey | case-control | 16 | active | 33 ± 6 | |
| 2009 | Ozdamar Y (119) | Turkey | case-control | 7 (35) | active | 33 ± 6 | |

| Year | Author | Country | Study type | Sample size | KD | Sample size | HC |
|------|--------|---------|------------|-------------|----|-------------|----|
| 2011 | Breunis WB (120) | Netherlands | case-control | 21 | early101 | 35.8 ± 8.6 | 21 |
| 2001 | Hamamichi Y (125) | Japan | case-control | 55 | 18 (32.7) | 40 ± 10 | 31 | 12 (38.7) | 40 ± 13 |
| 2006 | Shaker O (122) | Egypt | case-control | 30 | 20 | 32.6 ± 9.14 | 15 | 20 | 30.13 ± 12.32 |
| 2013 | Yalincig A (123) | Turkey | case-control | 65 | 32 (49) | 40.3 ± 9.8 | 21 | 11 (48) | 38.5 ± 9.3 |

(Continued)
TABLE 1 | Continued

| Year | Author | Country | Study type | Sample size | Female (%) | Age (years) | Sample size | Female (%) | Age (years) |
|------|--------|---------|------------|-------------|------------|-------------|-------------|------------|-------------|
| 1998 | Maeno N (126) | Japan | case-control | convalescent 30 | 4.8 ± 0.7 | 10 (45.5) | 2.2 ± 1.4 | healthy 19 | 9 (47.7) | 1.4 ± 1.4 |
|      |        |         |            | acute 20 | 1.5 ± 1.15 | 10 (50) | 2.5 ± 1.325 | febrile 22 | 10 (45.5) | 1.3 ± 1.4 |
|      |        |         |            | subacute 13 | 1.9 ± 1.4 | 5 (38.5) |             |            |             |             |
|      |        |         |            | convalescent 15 | 1.79 ± 2.375 | 8 (53.3) |             |            |             |             |
| 1999 | Ohno T (19) | Japan | case-control | acute 66 | 1.3 ± 1.15 | 24 (36.4) |             |            |             |             |
|      |        |         |            | acute phase | 31 |             |            |             |             |             |
|      |        |         |            | convalescent phase31 | 1.93 ± 2.75 |             |            |             |             |
| 2002 | Takuro Ohno (127) | Japan | case-control | acute phase | 41 | 14 (34.1) | 1.83 ± 2.17 |             |            |             |
|      |        |         |            | convalescent phase | 41 |             |            |             |             |             |
| 2019 | Su Y (128) | China | case-control | acute phase | 31 | 24 (36.4) | 2.55 ± 1.72 | healthy 60 | 28 (46.7) | 2.19 ± 2.22 |
|      |        |         |            | febrile | 18 | 9 (47.7) | 4.25 ± 1.75 | febrile 40 | 20 (50) | 2.84 ± 1.63 |
| 2009 | Ueno K (129) | Japan | case-control | acute | 80 | 37 (46.25) | 2.1 ± 1.8 |             |            |             |
| 2016 | Zeng H (130) | China | case-control | acute | 52 | 37 (46.25) | 2.1 ± 1.8 |             |            |             |

(Continued)
| Year  | Author       | Country       | Study type | Sample size | IBD          | HC         |
|-------|--------------|---------------|------------|-------------|--------------|------------|
|       |              |               |            |             | Female (%)  | Age (years) | Female (%)  | Age (years) |
| 2011  | Pousa ID     | Spain         | case-control | CD 145      | 84 (57.9)   | 33 ± 14.5  | 69 (51.3)   | 32 ± 9.75   |
| 2004  | Magro F      | Portugal      | case-control | CD 145      | 84 (57.9)   | 33 ± 14.5  | 69 (51.3)   | 32 ± 9.75   |
|       |              |               |            | UC 73       | 43 (58.9)   | 35 ± 11.75 | 50 (40.3)   | 33 ± 11.15  |
| 1997  | Schurer-Maly CC | Switzerland  | case-control | CD 24       | 46          | 46 ± 12    | 30 (60)     | 43 ± 14     |
|       |              |               |            | CD 70       | 39 (55.7)   | 42 ± 13    | 20 (40)     | 43 ± 14     |
| 2020  | deZoeten EF  | America       | case-control | UC 23       | 5/18 (27.8) | 12.7 ± 12  | 17 (78.9)   | 12.7 ± 16.5 |
| 2007  | Wiercinska-Drapalo A | Poland    | case-control | UC 33       | 13 (39.4)   | 43 ± 12.75 | 20 (75)     | 38 ± 6      |

| Year  | Author       | Country       | Study type | Sample size | PsA          | HC         |
|-------|--------------|---------------|------------|-------------|--------------|------------|
|       |              |               |            |             | Female (%)  | Age (years) | Female (%)  | Age (years) |
| 2009  | Ablin JN     | Israel        | case-control | skin10      | 4 (40)       | 48.6 ± 18.6 | 16 (75)     | 41.69 ± 9.71 |
| 2007  | Akman A      | Turkey        | case-control | arthritis22 | 10 (45.5)    | 47.18 ± 8.15  | 20 (75)     | 34.6 ± 14.5   |
| 2010  | Anderson KS  | Sweden        | case-control | plaque(PV)14 | 4 (28.6)    | 47 ± 10.75  | 14          | 43 ± 14.75   |
| 2001  | Ballara S    | UK            | cohort      | arthritis13 | 62          | 46 ± 17.04  | 31 (65)     | 49 ± 12.59   |
| 2016  | Batycka-Baran A | Poland    | case-control | arthritis24 | 37.5        | 48.29 ± 9.05 | 36          | 41.35 ± 15.23 |
| 2012  | Batycka-Baran A | Poland    | case-control | plaque-type psoriasis | 41.3 | 42.16 ± 15.42 | 31          | 48.4         |
| 2016  | Capkin AA    | Turkey        | case-control | chronic plaque 15 | 16 (33.3) | 48.6 ± 12.5 | 48          | 21 (41.7)    | 52.3 ± 8.4   |
| 1999  | Bhushan M    | UK            | case-control | chronic plaque 15 | 6 (30) | 45 ± 13.75  | 13          | 7 (53.8)     | 43 ± 14.75   |
| 2002  | Creamer D    | UK            | case-control | severe 11 moderate 11 arthritis 10 non-arthritis 12 chronic plaque 59 mild 24 moderate 20 severe 15 arthritis 28 active 14 inactive 14 arthritis 28 active 14 inactive 14 arthritis 28 active 14 inactive 14 | 16 (27.1) | 49.1 ± 2.1 | 20          | 4.3 ± 4.3    |
| 2010  | Fisiak I     | Poland        | case-control | skin10      | 10 (35.7)   | 48.6 ± 18.6 | 9 (22.2)    | 56 ± 9      |
| 2007  | Fink AM      | Austria       | case-control | plaque(PV)58 | 23 (39.7) | 41.7 ± 12.0 | 58 (51.7) | 41.4 ± 12.1  |
| 2012  | Kaur S       | Estonia       | case-control | plaque(PV)58 | 22 (37.9) | 30.17 ± 10.71 | 22 (100) | 29.36 ± 8.83 |
| 2014  | Méki AR      | Saudi Arabia  | case-control | plaque(PV)58 | 16 (29.6) | 41.26 ± 11.83 | 54 (100) | 41.22 ± 11.77 |
| 2002  | Nielsen HU   | Denmark       | cohort      | plaque(PV)16 | 9 (56.25) | 24–70 years | 13          | 40 (40)     |
| 2008  | Nofal A      | Egypt         | case-control | plaque(PV)30 | 11 (37) | 42 ± 12.2   | 10          | 4 (40)      | 38.5 ± 11.6 |
| 2015  | Przepiera-Bedzak H | Poland | case-control | plaque(PV)69 | 39 (56.5) | 52.0 ± 12.0 | 29 (65.5) | 48.2 ± 13.5 |
| 2016  | Przepiera-Bedzak H | Poland | case-control | plaque(PV)76 | 43 (56.6) | 50.8 ± 12.7 | 30 (60)    | 43.5 ± 9.4  |
| 2013  | Przepiera-Bedzak H | Poland | case-control | plaque(PV)80 | 43 (53.8) | 50.1 ± 12.0 | 20 (60)    | 48.1 ± 14.0 |
| 2016  | Shahidi-Dadras M | Iran    | case-control | severe chronic plaque psoriasis 50 | 27 (45) | 38.35 ± 14.96 | 60          | 27 (45)     | 39.55 ± 15.24 |
| 2016  | Shahidi-Dadras M | Iran    | case-control | moderate-severe chronic plaque psoriasis 50 | 27 (46.6) | 37.5 ± 14.1 | 60 (25)    | 39.6 ± 15.2  |
TABLE 1 | Continued

| Year  | Author          | Country | Study type       | GD       | PSa         | HC       |
|-------|-----------------|---------|------------------|----------|-------------|----------|
|       |                 |         | Sample size | Female (%) | Age (years) | Sample size | Female (%) | Age (years) |
| 2009  | Takahashi H     | Japan   | case-control    | 122      | 41 (33.6)  | 47.5 ± 7.6 | 78        | 24 (30.8)  | 36.6 ± 12.25 |
| 2017  | Zheng YZ        | China   | case-control    | 74       | 74 (38.1)  | 39.5 ± 12.7 | 175       | 81 (46.3)  | 40.2 ± 7.58  |
| 1998  | Iitaka M        | Japan   | case-control    | 49       | 49 (79.6)  | 34.7 ± 11.9 | 55        | 29 (52.7)  | 46.36 ± 11.03 |
| 2016  | Rancier M       | Tunisia | case-control    | 21       | 21 (19.0)  | 44.84 ± 12.10 | 30        | 20 (66.7)  | 32.8 ± 10.8  |
| 2020  | Cheng CW        | China   | case-control    | 64       | 64 (96.3)  | 34.50 ± 13.45 | 14        | 100        | 44.1 ± 13.8  |
| 2009  | Figueroa-Vega N | Spain   | case-control    | 44       | 32 (72.7)  | 45.11 ± 15.20 | 22        | 14 (63.6)  | 43.47 ± 8.62 |
| 1998  | Takahashi H     | Japan   | plaque psoriasis | 122      | 9 (69.2)   | 46.42 ± 12.58 | 78        | 13 (72.2)  | 48.77 ± 19.31 |
| 2014  | Kajdaniuk D     | Poland  | case-control    | 49       | 12 (75)    | 37 ± 9     | 37        | 26 (70.3)  | 35.7 ± 11.2  |
| 2016  | Rancier M       | Tunisia | case-control    | 21       | 4 (19.0)   | 44.84 ± 12.10 | 55        | 29 (52.7)  | 46.36 ± 11.03 |

SLE, systemic lupus erythematosus; LN, lupus nephritis; HC, healthy control; RA, rheumatoid arthritis; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease; RD, Behcet’s disease; DDR, healthy control; KD, Kawasaki disease; HC, healthy control. AS, ankylosing spondylitis; HC, healthy control; IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; HC, healthy control; PsA, psoriasis; PV, psoriasis vulgaris; HC, healthy control; Gr, Graves’ disease; Oph, ophthalmopathy; HC, healthy control.

SLE than in inactive SLE (SMD 0.51, 95% CI 0.33–0.70, P < 0.0001) (Figure 2B-ii), whereas serum VEGF levels were significantly higher in SLE with renal involvement than that without renal involvement (SMD 1.43, 95% CI 0.58–2.28, P = 0.0010) (Figure 2C). Due to the observed heterogeneity, the sample types were stratified (serum versus plasma); the heterogeneity in serum VEGF levels in active and inactive SLE disappeared after removing studies using plasma (before, I² = 94.04%, P = 0.0002; after, I² = 0.00%, P = 0.3178).

The subgroup analysis indicated significantly higher serum (SMD 0.64, 95% CI 0.37–0.91, P < 0.0001) and plasma (SMD 1.56, 95% CI 0.49–2.63, P = 0.0040) VEGF levels in SLE (Figure 2D-i). Significantly higher circulating VEGF levels were present in small (n ≤50) (SMD 0.39, 95% CI 0.07–0.72, P = 0.0170) studies (Figure 2D-ii).

Meta-regression analysis adjusted for age and percentage of female patients demonstrated age (P = 0.0030) but not sex (P = 0.9700) had a significant effect.

Meta-analysis of the Association Between Circulating VEGF and RA
Circulating VEGF levels were significantly higher in RA than in HC (SMD 1.48, 95% CI 0.82–2.15, P < 0.0001) (Figure 3A). Overall heterogeneity was apparent.

The subgroup analysis indicated significantly higher VEGF levels in serum (SMD 1.49, 95% CI 1.09–1.88, P < 0.0001) but not plasma (P = 0.0820) in RA (Figure 3B-i). Higher circulating VEGF levels were present in small (n ≤50) (SMD 1.58, 95% CI 1.10–2.05, P < 0.0001) and large (n >50) (SMD 1.03, 95% CI 0.47–1.60, P < 0.0001) studies on RA (Figure 3B-ii).

Meta-regression analysis adjusted for age and female sex demonstrated neither age (P = 0.4090) nor sex (P = 0.7570) had a significant effect.

Meta-analysis of the Association Between Circulating VEGF and SSc
Circulating VEGF levels were significantly higher in SSc than in HC (SMD 0.56, 95% CI 0.36–0.75, P < 0.0001) (Figure 4A). The comparison of serum VEGF levels between limited and diffused SSc did not reach statistical significance (P = 0.2735) (Figure 4B).

The subgroup analysis performed due to the obvious overall heterogeneity (I² = 98.35%, P < 0.0001) revealed significantly higher VEGF levels in serum (SMD 0.48, 95% CI 0.28–0.67, P < 0.0001) and plasma (SMD 0.86, 95% CI 0.49–1.24, P < 0.0001) samples of patients with SSc (Figure 4C-i). Elevated circulating VEGF levels were observed in small (n ≤50) (SMD 0.57, 95% CI 0.33–0.81, P < 0.0001) and large (n >50) (SMD 0.52, 95% CI 0.28–0.75, P < 0.0001) studies on SSc (Figure 4C-ii).

Meta-regression analysis adjusted for age and female sex demonstrated neither age (P = 0.2740) nor sex (P = 0.7020) had a significant effect.

Meta-analysis of the Association Between Circulating VEGF and BD
Circulating VEGF levels were significantly higher in BD than in HC (SMD 1.65, 95% CI 0.88–2.41, P < 0.0001) (Figure 5A) as
well as in active BD than in inactive BD (SMD 0.91, 95% CI 0.26–1.55, \(P = 0.0064\)) (Figure 5B). Heterogeneity was present.

The subgroup analysis revealed significantly elevated serum VEGF levels (SMD 1.60, 95% CI 0.85–2.34, \(P <0.0001\)) (Figure 5C-i), specifically in small (n ≤50) (SMD 1.86, 95% CI 1.15–2.57, \(P <0.0001\)) and not in large (n >50) studies (\(P = 0.1200\)) (Figure 5C-ii).

Meta-regression analysis adjusted for age and female sex demonstrated neither age (\(P = 0.2700\)) nor sex (\(P = 0.0720\)) had a significant effect.

**Meta-Analysis of the Association Between Circulating VEGF and KD**

Circulating VEGF levels were elevated in KD than in HC (SMD 2.41, 95% CI 0.10–4.72, \(P = 0.0406\)) (Figure S1A) and febrile controls (SMD 1.08, 95% CI 0.02–2.14, \(P = 0.0452\)) (Figure S1B). The comparison of serum VEGF levels between acute and convalescent KD revealed no statistical significance (\(P = 0.0831\)) (Figure S1C). Heterogeneity was prominent.

The subgroup analysis indicated serum VEGF levels were higher in KD than in HC (SMD 2.26, 95% CI 0.10–4.42, \(P = 0.0100\)) (Figure S1D-i). Increased circulating VEGF levels were found in small (n ≤50) (SMD 1.36, 95% CI 0.45–2.27, \(P = 0.0030\)) and large (n >50) studies (SMD 3.19, 95% CI 1.01–5.38, \(P = 0.0040\)) (Figure S1D-ii). Meta-regression analysis adjusted for age and female sex demonstrated female sex (\(P = 0.0100\)) but not age (\(P = 0.1280\)) had a significant effect.

**Meta-Analysis of the Association Between Circulating VEGF and AS**

Circulating VEGF levels were significantly elevated in AS than in HC (SMD 0.78, 95% CI 0.23–1.33, \(P = 0.0052\)) (Figure S2A). The overall heterogeneity was apparent (\(I^2 = 95.68\%), \(P <0.0001\)).
FIGURE 3 | Forest plot of RA associated with the circulating VEGF. (A) RA vs. HC, forest plot; (B) Subgroup analysis: (i) Serum vs. Plasma (a for serum and b for plasma); (ii) Sample size n≤50 vs. n>50 (a for n≤50 and b for n>50).

FIGURE 4 | Forest plot of SSc associated with the circulating VEGF. (A) SSc vs. HC, forest plot; (B) Limited SSc vs. Diffused SSc, forest plot; (C) Subgroup analysis: (i) Serum vs. Plasma (a for serum and b for plasma); (ii) Sample size n≤50 vs. n>50 (a for n≤50 and b for n>50).
The subgroup analysis revealed significantly higher serum VEGF levels in AS than in HC (SMD 0.60, 95% CI 0.36–0.84, \( P < 0.0001 \)) \((\text{Figure S2B-i})\). Significantly elevated circulating VEGF levels were found in small \((n \leq 50)\) (SMD 1.66, 95% CI 0.35–2.98, \( P = 0.0130 \)) and large \((n >50)\) studies (SMD 0.55, 95% CI 0.29–0.80, \( P < 0.0001 \)) on AS \((\text{Figure S2B-ii})\).

Meta-regression analysis adjusted for age and female sex demonstrated neither age (\( P = 0.8040 \)) nor sex (\( P = 0.8500 \)) had a significant effect.

**Meta-Analysis of the Association Between Circulating VEGF and IBD**

Serum VEGF levels were significantly higher in IBD than in HC (SMD 0.57, 95% CI 0.43–0.71, \( P < 0.0001 \)) \((\text{Figure S3A})\). The overall heterogeneity was extremely low \((I^2 = 3.12\%, \ P < 0.0001)\). Meta-regression analysis adjusted for age or females demonstrated insignificantly increased circulating VEGF levels were present in small \((n \leq 50)\) (SMD 0.86, 95% CI 0.32–1.40, \( P = 0.0020 \)) but not in large \((n >50)\) studies \((P = 0.0600)\) \((\text{Figure S3C-i})\). Moreover, serum VEGF levels were significantly higher in active CD than in inactive CD (SMD 0.53, 95% CI 0.09–0.96, \( P = 0.0176 \)) \((\text{Figure S3C-ii})\). Meta-regression analysis adjusted for age and female sex demonstrated age \((P = 0.0120)\) and sex \((P = 0.0010)\) had significant effects.

**Meta-Analysis of the Association Between Circulating VEGF and PsA**

Circulating VEGF levels were significantly higher in PsA (SMD 0.98, 95% CI 0.62–1.34, \( P < 0.0001)\) \((\text{Figure S4A})\), in psoriatic arthritis (SMD 0.72, 95% CI 0.12–1.32, \( P = 0.0192)\) \((\text{Figure S4B})\), and psoriasis with skin involvement (SMD 1.26, 95% CI 0.65–1.86, \( P = 0.0001)\) than in HC \((\text{Figure S4C})\). Heterogeneity was observed in the analyses.

The subgroup analysis indicated significantly higher serum VEGF levels in CD (SMD 0.62, 95% CI 0.10–1.15, \( P = 0.0200 \) and SMD 0.78, 95% CI 0.33–1.22, \( P = 0.0010 \)) \((\text{Figure S3D-ii})\). Significantly increased serum VEGF levels were present in small \((n \leq 50)\) (SMD 0.86, 95% CI 0.32–1.40, \( P = 0.0020 \)) but not in large \((n >50)\) studies \((P = 0.0600)\) \((\text{Figure S3D-iii})\). Moreover, serum VEGF levels were significantly higher in active CD than in inactive CD (SMD 0.53, 95% CI 0.09–0.96, \( P = 0.0176)\) \((\text{Figure S3C-ii})\). Meta-regression analysis adjusted for age and female sex demonstrated age \((P = 0.0120)\) and sex \((P = 0.0010)\) had significant effects.

**FIGURE 5** | Forest plot of BD associated with the circulating VEGF. (A) BD vs. HC, forest plot; (B) Active BD vs. Inactive BD, forest plot; (C) Subgroup analysis: (i) Serum vs. Plasma (a for serum and b for plasma); (ii) Sample size n<50 vs. n>50 (a for n≤50 and b for n>50).
Meta-Analysis of the Association Between Circulating VEGF and GD

Circulating VEGF levels were significantly higher in GD than in HC (SMD 0.69, 95% CI 0.20–1.19, P = 0.0056), with considerable heterogeneity (Figure S5A). Circulating VEGF levels were higher in active than in inactive Graves’ ophthalmopathy (GO) (SMD 0.80, 95% CI 0.29–1.30, P = 0.0019), without any heterogeneity (I² = 0.00%, P = 0.7548) (Figure S5B).

Serum (SMD 0.77, 95% CI 0.27–1.28, P = 0.0020) but not plasma (P = 0.3880) VEGF levels were significantly higher in GD than in HC (Figure S5C). Meta-regression analysis adjusted for age and female sex demonstrated the significant effect of age (P = 0.0070) but not sex (P = 0.2420).

Correlation Analyses Between Circulating VEGF and AD Clinical Features

We explored the potential correlation of VEGF in clinical implications and hematological indicators of ADs. For SLE (Figure S6), the summary Fisher’s z showed a positive, moderate correlation between circulating VEGF level and disease activity (SLEDAI/SLAM, ES 0.55, 95% CI 0.29–0.81, P < 0.0001; summary r = 0.50), erythrocyte sedimentation rate (ESR; ES 0.40, 95% CI 0.18–0.63, P = 0.0004; summary r = 0.38). A negative, poor correlation was found for C3 (ES −0.45, 95% CI −0.81 to −0.08, P = 0.0162, summary r = −0.42). There was no correlation between circulating VEGF level and platelet count (P = 0.1163).

In RA (Figure S7), there was a positive, weak correlation between circulating VEGF and disease activity (DAS-28; ES 0.33, 95% CI 0.22–0.44, P < 0.0001, summary r = 0.32), ESR (ES 0.35, 95% CI 0.18–0.51, P < 0.0001; summary r = 0.34) as well as C-reactive protein (CRP; ES 0.38, 95% CI 0.24–0.52, P < 0.0001; summary r = 0.36).

In SSc (Figure S8), there was a positive, moderate relationship between circulating VEGF level and pulmonary artery pressure (ES 0.62, 95% CI 0.37–0.87, P < 0.0001; summary r = 0.55) and Medical Research Council dyspnea score (ES 0.65, 95% CI 0.08–1.22, P = 0.0246; summary r = 0.57). There was no relationship between circulating VEGF level and modified Ronan skin score (P = 0.3100).

In BD (Figure S9), summary correlation coefficients indicated a significant, positive, and strong correlation with disease activity based on Behcet’s disease current activity form score (ES 1.22, 95% CI 0.03–2.41, P = 0.0446, summary r = 0.84) and moderate correlation with ESR (ES 0.47, 95% CI 0.11–0.82, P = 0.0108, summary r = 0.44).

In AS (Figure S10), circulating VEGF level was poorly correlated with disease activity (BASDAI/BASMI; ES 0.35, 95% CI 0.09–0.60, P = 0.0080; summary r = 0.34), ESR (ES 0.26, 95% CI 0.17–0.36, P < 0.0001; summary r = 0.25), and CRP (ES 0.24, 95% CI 0.14–0.35, P < 0.0001; summary r = 0.24).

In IBD (Figure S11), circulating VEGF level exhibited a positive, poor correlation with Crohn’s disease activity index (CDAI; ES 0.34, 95% CI 0.10–0.57, P = 0.0053, summary r = 0.33), medium correlation with UC activity index (UDDAI; ES 0.57, 95% CI 0.29–0.86, P = 0.0001; summary r = 0.52), strong correlation with ESR (ES 0.87, 95% CI 0.63–1.12, P < 0.0001; summary r = 0.70), and weak correlation with platelet count (ES 0.32, 95% CI 0.16–0.49, P = 0.0001; summary r 0.31).

In PsA (Figure S12), circulating VEGF level was positively correlated with psoriasis area and severity index score (ES 1.12, 95% CI 0.64–1.60, P < 0.0001; summary r = 0.81) and had a positive, moderate correlation with disease duration (ES 0.51, 95% CI 0.32–0.69, P < 0.0001; summary r = 0.47).

Sensitivity Analysis and Publication Bias

The sensitivity analysis revealed the stability of pooled results (data not shown). For SLE, RA, SSc, KD, and AS, the contour-enhanced funnel plots revealed no publication bias (Figure S13), the meta-trim practice demonstrated that all imputed studies fell into the significant region. In contrast, Egger’s test suggested publication bias for SLE, RA, and KD (P < 0.0001 for all) as well as for AS (P = 0.0001). However, there was consistency in publication bias for SSc by Egger’s test (P = 0.1413). This remind us to be cautious with using Egger’s test to determine publication bias in small number of studies (<20). There was no publication bias with PsA and GD (P = 0.4874 and P = 0.5419, respectively), in contrast to that observed with BD (P = 0.0006). The imputed studies on IBD fell into the non-significant region, and Egger’s test also represented evidence of it (P = 0.0017) in UC; the existence of publication bias was proven by Egger’s test (P = 0.0113) in CD.

DISCUSSION

In the current meta-analysis, we found a close relationship between circulating VEGF level and ADs. First, our analyses revealed significantly increased circulating VEGF levels in SLE, RA, SSc, BD, KD, AS, IBD, PsA, and GD. Additionally, we showed that serum VEGF could distinguish active from inactive SLE and renal from non-renal SLE; it could also discriminate between active and inactive CD. Likewise, circulating VEGF had a strong ability to differentiate active from inactive BD and GO. Serum VEGF exhibited its dipartite boundedness in limited/diffused cutaneous SSc, active/inactive UC, and acute/convalescent KD. Furthermore, we demonstrated the correlation of circulating VEGF levels with metrics of disease activity and severity (SLEDAI/SLAM, DAS-28, MRC dyspnea score, modified Ronan skin score, BD current activity form score, BASDAI/BASMI, CDAI, UDDAI, psoriasis area and severity index) as well as with hematological parameters (ESR, CRP, platelet count, pulmonary artery pressure). Overall, these results indicate that circulating VEGF reflects pathogenesis and should be considered as a potent hematological marker for diagnosis and disease progression in ADs.

Structural and functional abnormalities in neovascularization may lead to damage in chronic inflammatory diseases. Consecutive angiogenesis and immune-mediated vascular endothelial cell injury and dysfunction as well as persistent inflammation play important pathological roles in SLE (20), whereas expansion and invasion of synovial vessels facilitate inflammation and erosive joint destruction in RA (12). Early generalized microvascular endothelial damage leading to immune activation and defective...
angiogenesis are significant events in cumulative systemic fibrosis and microangiopathy in SSc (76). Additionally, BD is characterized by systemic vasculitis, inflammatory infiltrates, subsequent vascular lesions, and neovascularization (113, 115), whereas subendothelial edema and fenestrated endothelium constitute acute systemic vasculitis observed in KD (181). Structural changes in vascular endothelium due to inflammation and hypoxia stimulate angiogenesis to permeate vascular and mediate tissue repair in IBD (6). Finally, early psoriatic skin plaque formation is triggered by inappropriate expansion and vascular alterations, pronounced permeability, and endothelial cell proliferation (162). Therefore, angiogenesis and angiopathy are considered as major pathogenic events predisposing to ADs.

VEGF, an increasingly recognized proangiogenic inducer of endothelial proliferation and microvascular hyperpermeability, may reverse the tide of inducers against inhibitors and promote angiogenesis (182). Despite the unclear role of angiogenesis in AS and GD, higher-than-normal VEGF levels support its role in bone and enchondral ossification in AS (183) and increased microvessel density in GD (184). Over the past decades, numerous studies have reported increased VEGF levels in ADs, beyond its well-known role in tumorigenesis. In the present study, our meta-analysis reveals differences in circulating VEGF levels between patients with ADs and HC subjects, providing further evidence for its utility in determining disease activity and severity in ADs.

In the present meta-analysis, there were variations in circulating VEGF levels due to differences in sample collection methods and demographic characteristics across the studies, requiring adjustment for the interpretation of the final laboratory results. Serum VEGF levels are 7–10 times higher than plasma VEGF levels in RA (60). Serum VEGF is a combination of efflux from platelets, neutrophils during coagulation, and circulating VEGF, which rarely occurs in vivo; in contrast, plasma VEGF directly reflects circulating VEGF in the absence of coagulation in vivo. In support of this difference, the present meta-analysis also revealed that the removal of plasma samples from the analysis led to the disappearance of heterogeneity in serum VEGF levels in active and inactive SLE. Plasma samples with citrate anticoagulants had the lowest VEGF levels, reflecting that that reservation of platelets VEGF releasing is effective and that different anticoagulation procedures should be considered in evaluating variations in VEGF levels across studies. Higher plasma VEGF levels in female patients compared with male patients, increasing VEGF levels with age in adults, and decreasing VEGF levels with age in children illustrate the contributory roles of sex and age to discrepancy (185). The cohort size in specific studies might also impact the mean and standard deviation. Therefore, we addressed these variables in subgroup and meta-regression analyses. The subgroup analyses explored the source of heterogeneity in serum VEGF levels for only studies on active and inactive SLE (before, $I^2 = 94.04\%$, $P = 0.0002$; after, $I^2 = 0.00\%$, $P = 0.3178$). We also observed apparent associations of circulating VEGF levels with age and female sex in SLE and CD, with sex in KD, and with age in GD.

There are several limitations in the present meta-analysis. First, although subgroup and meta-regression analyses were performed to explore heterogeneity, much of it remains to be explained and reported. Second, the funnel plots indicated publication bias in studies on BD and IBD, including UC as well as CD, which might have led to the overestimation of pooled SMDs. Third, data could not be fully retrieved, which might have resulted in missing values in meta-regression and the omission of covariates in tests assessing heterogeneity. Availability of complete data on patient inclusion and exclusion criteria, ethnicity, AD treatment details, and exact timing and method of VEGF measurement would greatly reduce the bias in our analyses. Although the existing heterogeneity could be partially explained by age, sex, sample type, and sample size of the individual studies, an exact conclusion could not be drawn due to the lacking explanation for the remaining heterogeneity. Further studies using more comprehensive data should be performed to elucidate the association of circulating VEGF levels with ADs.

In conclusion, our meta-analysis unveiled a close association between circulating VEGF levels and ADs including disease activity and severity as well as clinical hematological manifestations. Serum VEGF is a reliable marker that can distinguish active from inactive in SLE and GO and can potentially differentiate IBD from HC. Early and regular measurement of circulating VEGF levels may be considered as a noninvasive method to monitor vascular involvement and activity in ADs. Future studies should focus on the prognostic and diagnostic utility of circulating VEGF, its role in pathogenesis, and the utility of VEGF-targeted therapeutic strategies in ADs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YL conceived and designed the research. HZ and HL extracted data and conducted quality assessment. CL, LC, SY, HL, and HZ analyzed the data. HZ and HL wrote the paper. All authors are accountable for all aspects of the study, and attest to the accuracy and integrity of the results. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.674343/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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