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META-ANALYSIS

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Vascular endothelial growth factor in inflammatory bowel disease: A systematic review and meta-analysis

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Abstract

Aim: Vascular endothelial growth factor (VEGF) is linked to inflammation and angiogenesis, indicating a possible role in inflammatory bowel disease (IBD) and its main clinical manifestations, Crohn's disease (CD) and ulcerative colitis (UC). This systematic review and meta-analysis investigated studies assessing circulating VEGF concentrations in IBD patients and healthy controls, considering the effect of IBD type, sample type and geographical location.

Methods: A systematic search identified 18 studies (28 group comparators) investigating 1741 IBD patients and 1291 controls. Data were extracted and analysed using standardized mean differences (SMD) with 95% confidence intervals (CI).

Results: VEGF concentrations were significantly higher in IBD patients (SMD = .71, 95% CI .38 to 1.04; $p < .001$). UC patients showed higher VEGF concentrations than CD patients. Serum samples indicated significant VEGF elevations, unlike plasma samples. Significant VEGF increases were observed in studies conducted in Western Europe and Asia, but not in Eastern Europe. No significant differences were found between active and inactive disease.

Conclusions: VEGF concentrations are elevated in IBD patients, with variations by disease type, sample type and geography. However, VEGF is not a reliable marker of disease activity. Future research should standardize methods and explore regional influences to enhance VEGF's clinical utility as a biomarker of IBD.

KEYWORDS

biomarkers, Crohn's disease, inflammatory bowel disease, ulcerative colitis, vascular endothelial growth factor

1 | INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic relapsing–remitting condition characterized by inflammation of the gastrointestinal tract.[1] IBD affects millions of individuals worldwide, with increasing prevalence in both developed and developing countries.[2,3] The pathogenesis of IBD is multifactorial, involving genetic susceptibility, environmental triggers, dysregulated immune responses and alterations in the gut microbiota.[4,5] Despite advancements in understanding these mechanisms, the precise aetiology of IBD remains elusive, and there is a need for reliable biomarkers to aid in diagnosis, monitoring disease activity and predicting therapeutic responses.

Vascular endothelial growth factor (VEGF) is a pivotal mediator of angiogenesis, playing a critical role in both physiological and pathological processes.[6,7] VEGF promotes the formation of new blood vessels and increases vascular permeability, which are essential in tissue repair and regeneration.[8,9] However, in the context of chronic inflammatory diseases such as IBD, these processes can contribute to disease pathology by sustaining and exacerbating inflammation.[10,11] Elevated concentrations of VEGF have been observed in various inflammatory conditions, suggesting its potential involvement in the inflammatory cascades of IBD.[12]

Previous studies have reported increased VEGF concentrations in IBD patients compared to healthy controls, implicating VEGF in the disease's inflammatory processes.[13] However, the findings across studies have been inconsistent, with variations in VEGF concentrations reported depending on the type of IBD, ulcerative colitis (UC) or Chron's disease (CD), disease activity, sample type and geographical location of the study. The pathophysiological role of VEGF in UC and CD appears to be related to their distinct inflammatory patterns. In UC, where inflammation is restricted to the mucosal layer, VEGF might contribute more directly to ongoing mucosal damage and repair. In contrast, CD involves transmural inflammation, potentially leading to a more complex interaction between VEGF-mediated angiogenesis and fibrosis, which could explain the observed variability in VEGF levels between these two conditions.[14,15] These discrepancies highlight the need for a comprehensive synthesis of the existing evidence to clarify the relationship between VEGF concentrations and IBD.

This meta-analysis seeks to bridge these gaps by providing a systematic and detailed evaluation of VEGF concentrations in IBD patients. We address several key aspects that have been largely unexplored, including variations in VEGF levels between UC and CD, the influence of disease activity, differences in biomarker detection based on sample type, and potential geographical variability. Our work aims not only to summarize the existing evidence but also to provide a more nuanced understanding of how these factors may contribute to the inconsistent results observed across studies.

2 | METHODS

2.1 | Literature search

A systematic literature search was conducted on the following databases: PubMed, Web of Science and Scopus, from each database's inception up to 15 July 2024. The literature search strategy used a combination of keywords, as follows: ('Crohn's disease' OR 'ulcerative colitis' OR 'Inflammatory bowel disease' OR 'IBD') AND ('VEGF' OR 'Vascular endothelial growth factor'). Abstracts were screened by two independent reviewers, and full texts were reviewed if the studies were found relevant. The overall initial concordance rate between the two reviewers was 98.5%. Any remaining discrepancies were resolved by consulting with a third reviewer.

2.2 | Data collection

The following inclusion criteria were used for the study: (i) assessment of VEGF level; (ii) case–control design where comparison has been done between individuals with and without IDB; (iii) a cohort of at least 10 patients with IBD; (iv) publications in English language; and (v) full-text availability. Exclusion criteria included: (i) case–control study designs and all others beyond case–control design; (ii) participants below the age of 18; (iii) studies conducted in an animal setup; (iv) duplicate studies or those that did not provide relevant information. Besides, all the references from each article selected were duly checked for viable articles. Independent extraction of key data from each article onto a spreadsheet for analysis was performed regarding the following: year of publication, lead author, study design, study location, sample type, size of IBD and control groups, type of IBD, VEGF levels and demographic details such as age and sex.

2.3 | Risk of Bias Assessment

The risk of bias was assessed using the JBI checklist for cross-sectional analytical studies,[16] whereas the certainty of evidence was assessed using GRADE.[17]

2.4 | Statistical Analysis

Standardized mean differences were computed to provide a measure of the overall effect size of the difference in VEGF levels between patients with IBD and controls and were presented by forest plots of continuous data. For statistical analysis, a *p*-value less than .05 was considered to be statistically significant, and it was given with a 95% confidence interval. The effect size was interpreted as small effect, SMD <.5; medium effect, SMD between .5 and .8; and large effect, SMD >.8.[16] Where necessary, medians and interquartile ranges were used to derive means and standard deviations using methods described by Wan et al.,[18] or individual plots were extracted using Graph Data Extractor software. The Q statistic was computed to examine the heterogeneity of SMDs across studies, setting the significance threshold at $p < .10$, and inconsistency was quantified by the I^2.[19,20] Especially, I^2 values were interpreted as follows: 0%–25%, no heterogeneity; 26%–50%, moderate heterogeneity; 51%–75%, substantial heterogeneity; and 76%–100%, considerable heterogeneity. If I^2 is 50% or more, statistical heterogeneity is assumed.[19] In cases of remarkable heterogeneity, a random-effects model was used. Further, sensitivity analysis was performed by excluding one study at a time to see the contribution of each single study toward the overall estimate of risk. Besides, checking publication bias by correlation of study size and effect size was done using Begg's adjusted rank correlation test and Egger's regression asymmetry test with a significance level of $p < .05$.[21,22] Publication bias, if necessary, was dealt with further by using the Duval and Tweedie 'trim and fill' method.[23]

All analyses were done in Stata 14 (Stata Corp., College Station, TX, USA). This study was reported according to the PRISMA guidelines for reporting systematic reviews and meta-analyses.[24] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024575078).

3 | RESULTS

3.1 | Systematic research and study characteristics

In the first search, 826 articles were identified. After duplicates and irrelevant studies were discarded, a final number of 734 records was reached, and these 92 articles were further screened on the basis of title and abstract. Of these, 25 were excluded as review articles, 21 were eliminated because they were commentaries, letters to the editor or book chapters; 18 were not in English; 6 were conducted in paediatric populations; and 4 did not contain a control group. Thus, 18 studies with 28 study groups were included in the final analysis (Figure 1)[25–42] (Table 1).

The included studies were published between 1998[25] and 2021.[42] Most were conducted in Europe, specifically 4 in Spain,[32,34,35,38] 3 in Poland,[33,36,37] 2 in Turkey,[40,42] 2 in Greece,[28,39] 2 in Germany,[25,26] 1 in Portugal,[30] 1 in Belgium[31] and 1 in Italy.[29] One other study was conducted in Japan,[27] and 1 in USA[41] (Table 1). The selected studies evaluated a total of 1741 IBD subjects (weighted average age 40.9) and 1291 healthy controls (weighted average age 39.9). The initial ranked as low level of the certainty of evidence was ranked as low (level 2), given the cross-sectional design of the selected studies.

3.2 | Risk of Bias

The risk of bias was low in 11 studies and moderate in the remaining seven (Table 2).

3.3 | Individual study results and synthesis

The forest plot for VEGF concentrations in IBD subjects and controls is depicted in Figure 2. Almost all studies[25–27,29,31–37,39–42] reported higher VEGF concentrations in IBD subjects than in controls (SMD = .71, 95% CI .38 to 1.04; $p < .001$), with 19 studies groups being statistically significant. However, six study groups reported lower VEGF concentrations in IBD patients compared to controls,[28,30] with only two of these results being statistically significant.[28] As substantial heterogeneity was observed between the studies ($I^2 = 93.4\%$, $p < .001$), random-effects models were used. The sensitivity analysis showed that the corresponding pooled SMDs were not substantially affected by the sequential removal of individual studies (effect size range .26–1.14) (Figure S1), although five studies[27,28,33] had a pronounced effect on the magnitude of the results. Furthermore, the funnel plot analysis showed that these same studies influenced the symmetry of the graph (Figure S2). Therefore, we assessed the effects of removing these studies on SMD and found that the effect size remained high, and the significance was unaffected (SMD = .63, 95% CI .44 to .82; $p < .001$). It should be noted that there was a significant reduction in heterogeneity between studies (15.6% less).

3.4 | Publication Bias

Egger's regression test and visual funnel plot asymmetry were used to check for publication bias. The *p*-values

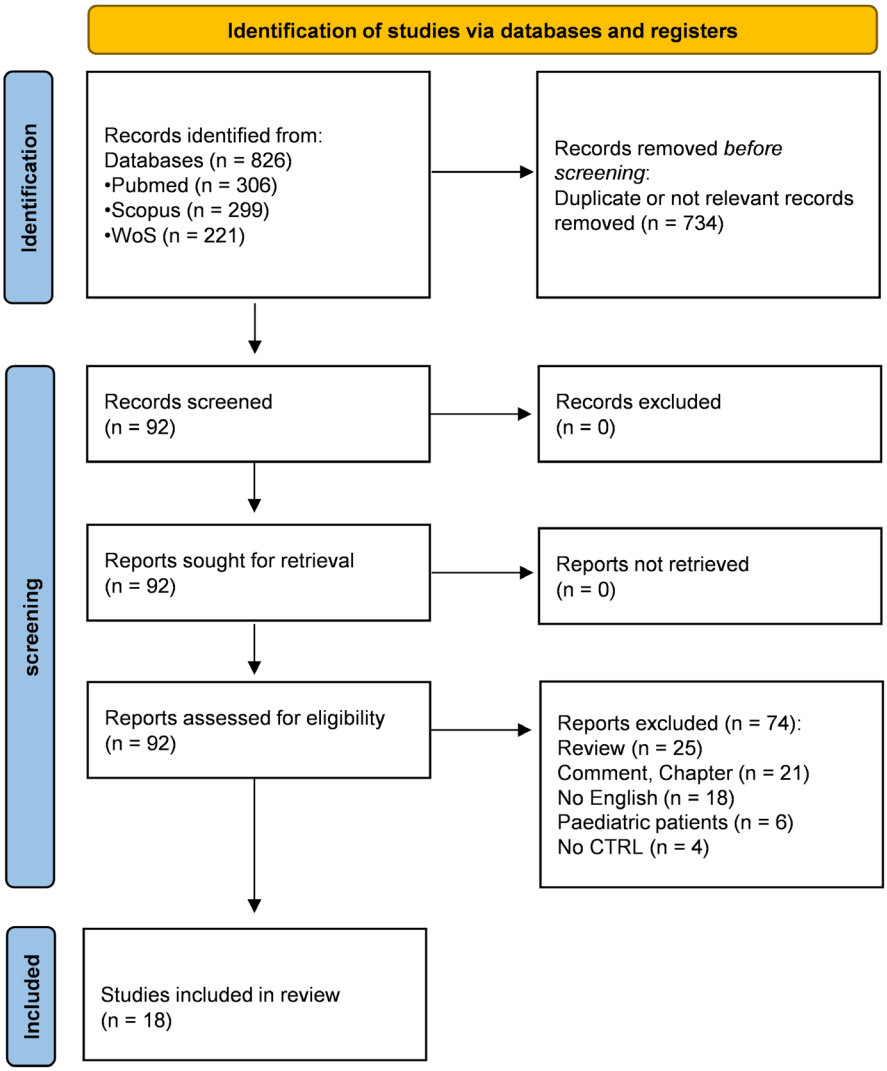

FIGURE 1 PRISMA 2020 flow diagram.

obtained from Begg's and Egger's tests were 0.039 and 0.178, respectively; therefore, using Begg's test, there was publication bias. To account for this bias, the trim-and-fill method was applied, imputing six missing studies on the left side of the plot to symmetrize the plot funnel (Figure S3). Although attenuated, the adjusted SMD remained significant, 0.47 (95% CI 0.27 to 0.66; $p < .001$).

3.5 | Meta-Regression and Sub-Group Analysis

Using univariate meta-regression analysis, non significant associations were observed with sample size ($t = -.54$, $p = .593$), year of publication ($t = -.25$, $p = .801$) and sex ($t = -.76$, $p = .455$). In contrast, age showed a significant correlation with effect size ($t = 2.29$, $p = .032$) (Figure S4).

In the subgroup analysis, the SMD pool was statistically significant in studies that examined patients with UC (SMD = .92, 95% CI .38 to 1.47, $p < .001$; $I^2 = 93.7\%$, $p < .001$) but not with CD (SMD = .45, 95% CI −.13 to 1.04, $p = .129$; $I^2 = 94.9\%$, $p < .001$) (Figure 3).

In addition to this analysis, we also evaluated the subgroups based on sample type. We observed a statistically significant pooled SMD in studies using serum samples (SMD = .97, 95% CI .69 to 1.25; $p < .001$), but not plasma (SMD = −1.49, 95% CI −3.73 to .76; $p = .194$, Figure 4). Moreover, the overall comparison between serum and plasma revealed a significant difference between groups ($p = .001$).

Furthermore, it was possible to stratify the results based on geographical differences. This stratification revealed statistically significant differences in VEGF concentrations between IBD patients and controls in studies conducted in Western Europe (SMD = .75, 95% CI .50 to .99; $p < .001$) and Asia (SMD = 4.27, 95% CI 3.33 to 5.20; $p < .001$). In contrast, the difference was not statistically significant in Eastern Europe (SMD = .02, 95% CI −.98 to 1.03; $p = .961$). The heterogeneity was slightly lower for Western Europe ($I^2 = 82.2\%$, $p < .001$) compared to Eastern

TABLE 1 Summary of the studies included in the meta-analysis reporting VEGF concentrations in IBD patients and controls.

	Control			IBD				
First Author, Year, Country	*n*	Age (Mean Years)	VEGF (Mean ± SD)	*n*	Age (Mean Years)	VEGF (Mean ± SD)	Disease	Unit
Griga T et al. (a) 1998, Germany	9	31.5	148 ± 110.9	31	33.1	494.8 ± 237.3	CD	pg/mL
Griga T et al. (b) 1998, Germany	9	31.5	148 ± 110.9	15	34.5	453.8 ± 236.6	UC	pg/mL
Griga T et al. (a) 1999, Germany	10	29.3	216.4 ± 137.7	8	34.8	430.3 ± 251	CD	pg/mL
Griga T et al. (b) 1999, Germany	10	29.3	216.4 ± 137.7	19	46.6	1198.8 ± 772.4	UC	pg/mL
Kanazawa S et al. (a) 2001, Japan	20	60	196.6 ± 59.2	11	38.5	740 ± 182.3	CD	pg/mL
Kanazawa S et al. (b) 2001, Japan	20	60	196.6 ± 59.2	11	56.5	659.8 ± 181	UC	pg/mL
Kapsoritakis A et al. (a) 2003, Greece	23	38	275 ± 74	44	NR	268 ± 49	CD	pg/mL
Kapsoritakis A et al. (b) 2003, Greece	23	38	275 ± 74	50	NR	262 ± 30	UC	pg/mL
Kapsoritakis A et al. (c) 2003, Greece	23	38	40 ± 1.9	44	NR	32 ± 1.3	CD	pg/mL
Kapsoritakis A et al. (d) 2003, Greece	23	38	40 ± 1.9	50	NR	35 ± 2.6	UC	pg/mL
Di Sabatino A et al. 2004, Italy	22	38.3	180 ± 173.5	25	37.8	639 ± 709.8	CD	pg/mL
Magro F et al. (a) 2004, Portugal	115	32	139.8 ± 256.7	145	33	114.7 ± 261.2	CD	pg/mL
Magro F et al. (b) 2004, Portugal	115	32	139.8 ± 256.7	73	35	108.9 ± 336.1	UC	pg/mL
Ferrante M et al. (a) 2006, Belgium	263	28	118.6 ± 95.1	549	38	210 ± 163.5	CD	pg/mL
Ferrante M et al. (b) 2006, Belgium	263	28	118.6 ± 95.1	234	41.3	197.6 ± 142.4	UC	pg/mL
Pousa ID et al. 2007, Spain	30	43	335 ± 118	30	44	494 ± 247	CD	pg/mL
Wiercinska-Drapalo A et al. 2007, Poland	20	36.6	110.9 ± 15.7	33	47.3	326.4 ± 58.1	UC	pg/mL
Pousa ID et al. 2008, Spain	30	43	335 ± 118	70	42	489 ± 271	CD	pg/mL
Frysz-Naglak D et al. (a) 2011, Poland	15	47	39.7 ± 31.2	33	43.6	86.78 ± 52.9	UC	pg/mL
Frysz-Naglak D et al. (b) 2011, Poland	15	47	42.6 ± 1.8	33	43.6	43.4 ± 2.9	UC	pg/mL
Pousa ID et al. 2011, Spain	26	46	312 ± 85	13	46	496 ± 213	UC	pg/mL
Marlicz W et al. 2012, Poland	25	38	78 ± 88	25	39	167.4 ± 104.4	IBD	pg/mL
Algaba A et al. 2014, Spain	40	43	395.5 ± 256.4	37	36	511.5 ± 255.6	IBD	pg/mL
Kopanakis N et al. 2014, Greece	40	50	464.6 ± 283.1	40	44	1158.5 ± 845.4	IBD	pg/mL
Aksoy EK et al. 2018, Turkey	15	41.4	236.1 ± 40.6	39	46.1	511.9 ± 377.5	IBD	pg/mL
deZoeten EF et al. 2020, USA	19	56.9	99 ± 210.63	20	44.5	276.4 ± 302.6	UC	pg/mL
Samanci SN et al. (a) 2021, Turkey	34	37	18.3 ± 14.8	28	37	31.2 ± 22	CD	mg/mL
Samanci SN et al. (b) 2021, Turkey	34	37	18.3 ± 14.8	31	41	25.6 ± 16	UC	mg/mL

Note: VEGF concentration has reported as pg/mL or mg/mL.

Abbreviations: CD, Crohn's Disease; NR, not reported; UC, Ulcerative Colitis;

Europe ($I^2 = 97.8\%$) (Figure 5). When comparing VEGF concentrations between regions, we found that the difference between Western Europe and Eastern Europe was not statistically significant ($p = .258$), indicating similar VEGF concentrations in these regions. In contrast, the difference between Asia and Western Europe was highly significant ($p < .001$), with studies from Asia showing much higher VEGF concentrations. Additionally, there was a statistically significant difference between Asia and Eastern Europe ($p = .043$), further emphasizing the elevated VEGF concentrations in the Asian studies compared to those from Eastern Europe.

Finally, we were able to evaluate the differences in VEGF concentrations between active and inactive CD, as well as between active and inactive UC. However, no statistically significant differences were reported in these comparisons ($p = .467$, $p = .853$, respectively).

3.6 | Certainty of evidence

The overall level of the certainty of evidence remained low (level 2) after considering the low-moderate risk of bias in all studies (no change), the high but partially explainable

TABLE 2 Assessment of the risk of bias using the Joanna Briggs Institute critical appraisal checklist.

Study	Were the inclusion criteria clearly defined?	Were the subjects and the setting described in detail?	Was the exposure measured in a reliable way?	Were standard criteria used to assess the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a reliable way?	Was appropriate statistical analysis used?	Risk of bias
Griga T et al. 1998	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Griga T et al. 1999	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Kanazawa S et al. 2001	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Kapsoritakis A et al. 2003	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Di Sabatino A et al. 2004	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Magro F et al. 2004	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Ferrante M et al. 2006	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Pousa ID et al. 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Wiercinska-Drapalo A et al. 2007	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Pousa ID et al. 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Frysz-Naglak D et al. 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Pousa ID et al. 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Marlicz W et al. 2012	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Algaba A et al. 2014	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Kopanakis N et al. 2014	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Aksoy EK et al. 2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
deZoeten EF et al. 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low
Samanci SN et al. 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Low

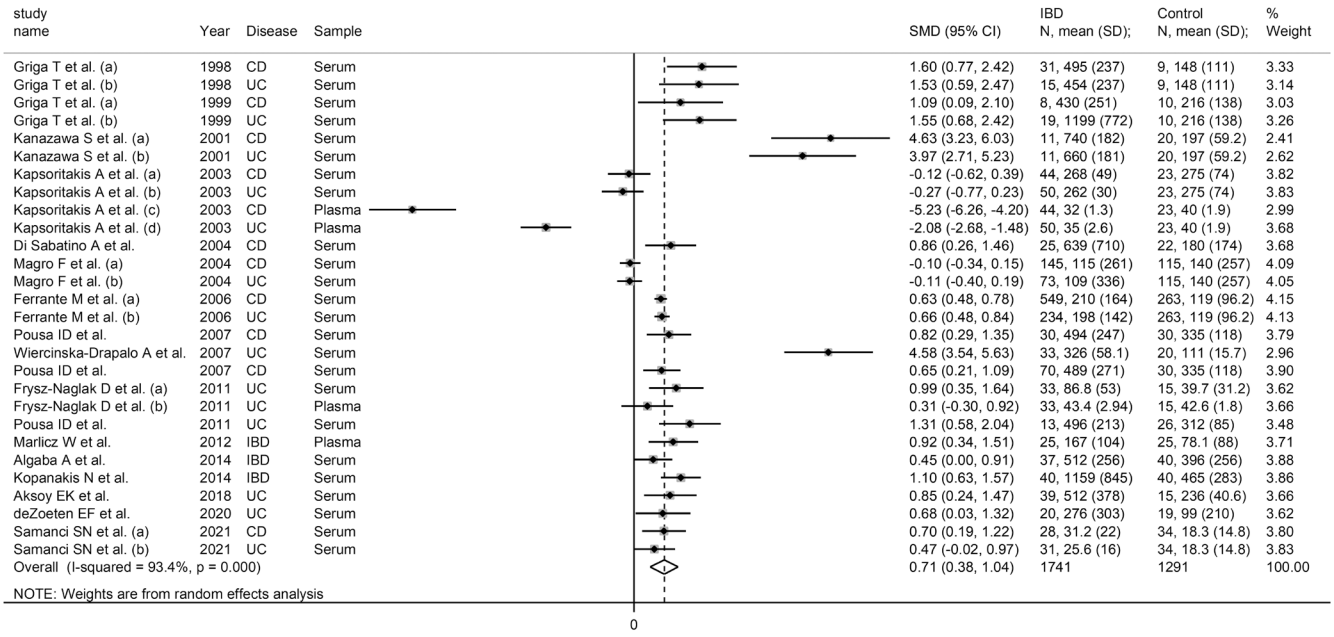

FIGURE 2 Forest plot depicting studies examining VEGF concentrations in patients with IBD compared to controls.

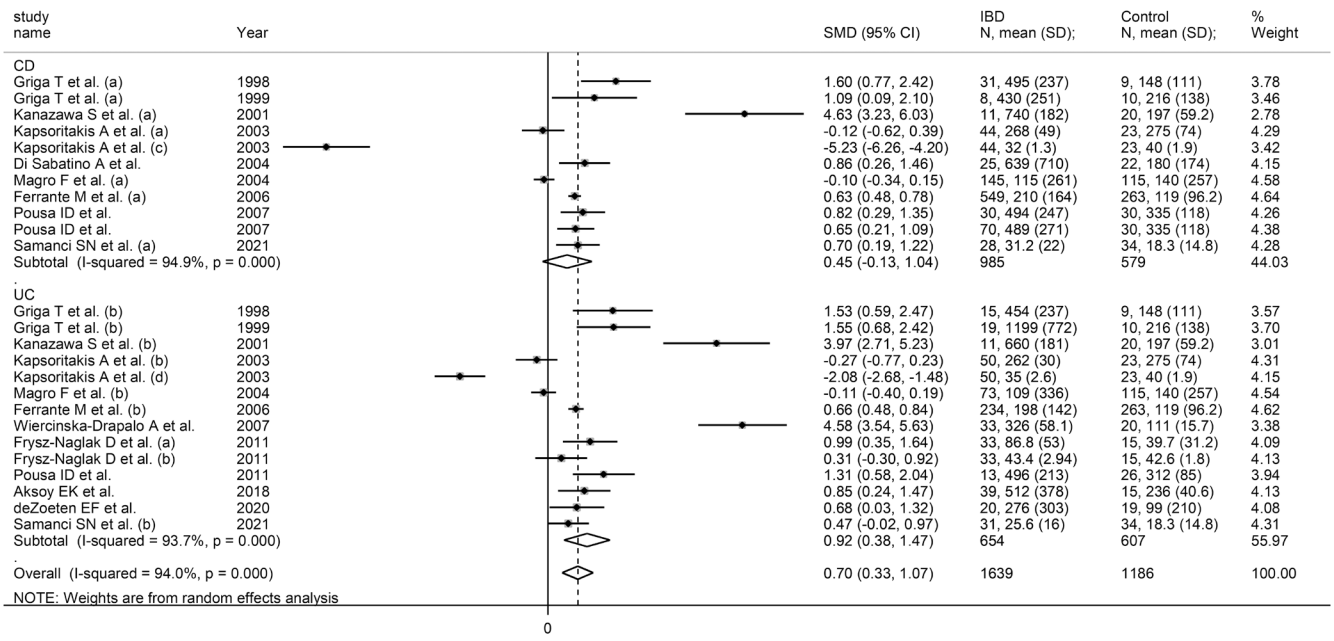

FIGURE 3 Forest plots of studies examining VEGF concentrations in IBD and controls according to the IBD subtypes (CD or UC).

heterogeneity (no change), the lack of indirectness (no change), the moderate effect size (SMD = .71, no change) and the presence of publication bias which was addressed with the 'trim and fill' procedure (no change).

4 | DISCUSSION

This meta-analysis aimed to elucidate the relationship between VEGF concentrations and IBD, CD and UC. Our findings indicate a general trend of elevated VEGF concentrations in IBD patients compared to controls, suggesting a potential role for VEGF in the pathophysiology of IBD. VEGF is a critical mediator of angiogenesis and increased vascular permeability, both of which are fundamental processes in inflammation and tissue repair.[43,44] Its elevated concentrations in IBD patients may reflect the heightened inflammatory activity and tissue remodelling characteristic of these diseases.[45,46] The substantial heterogeneity observed across studies

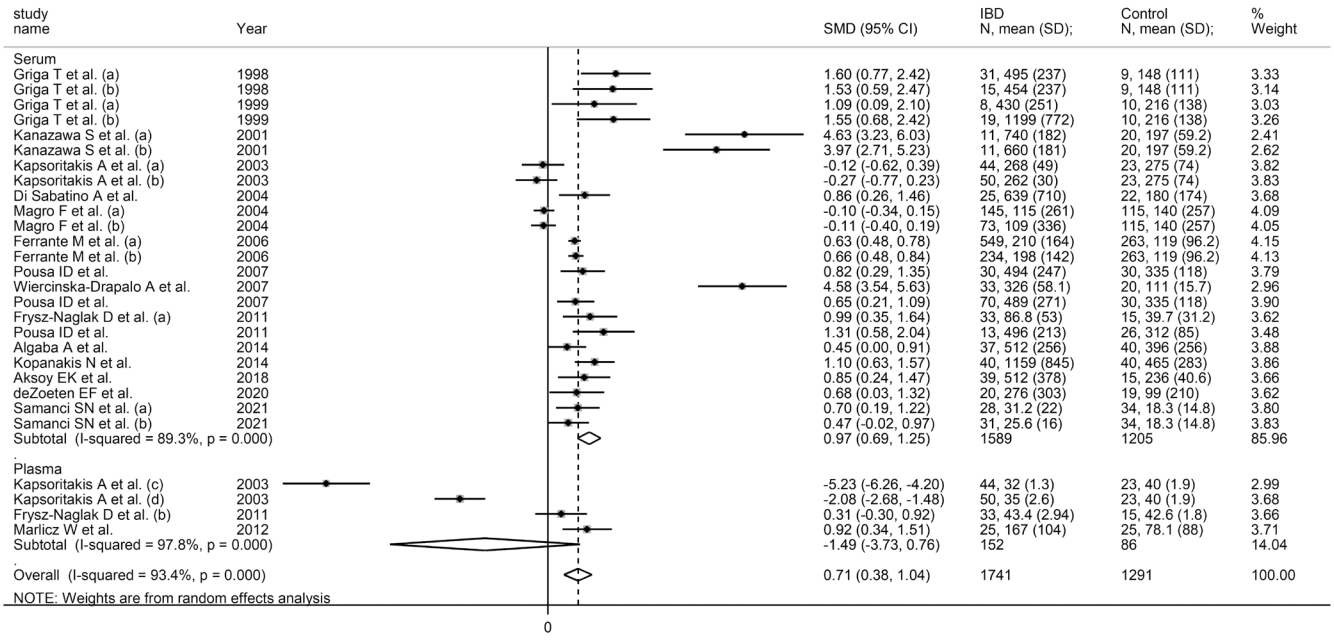

FIGURE 4 Forest of studies examining VEGF concentrations in IBD and controls according to sample type (serum or plasma).

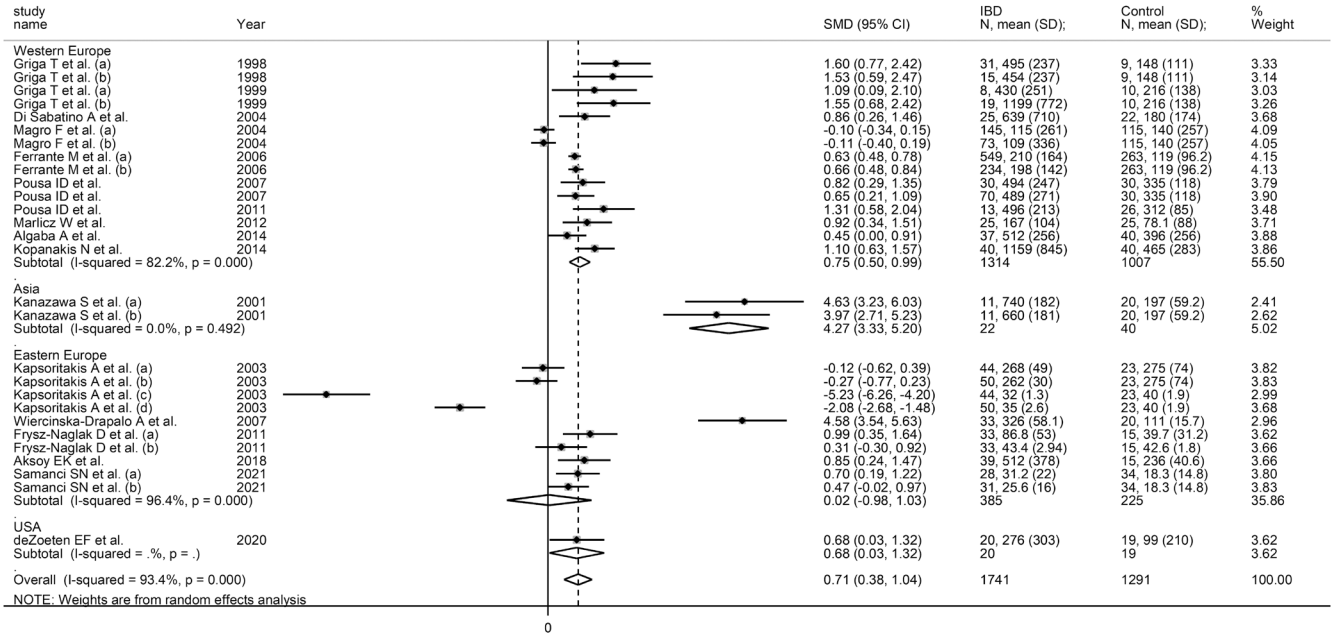

FIGURE 5 Forest of studies examining VEGF concentrations in IBDs and controls according to the geographic location of the study.

($I^2 = 93.4\%$) highlights the variability in VEGF concentrations, which could be attributed to differences in study design, sample types, geographical locations and patient demographics. While heterogeneity is a common issue in IBD biomarker studies, the large variability observed in this analysis suggests that specific subpopulations or environmental factors might play a more significant role than previously understood. This highlights the necessity for future research to consider such influences in study design. Similar heterogeneity has been noted in previous meta-analyses of inflammatory markers in IBD, indicating that such variability is not unique to VEGF but rather a common feature in IBD research.[47] The higher VEGF concentrations found in UC compared to CD may reflect differing inflammatory and angiogenic processes between these two conditions. UC is primarily characterized by continuous mucosal inflammation starting from the rectum, while CD often involves transmural inflammation and can affect any part of the gastrointestinal tract.[48–50] These pathological

differences could explain the variance in VEGF concentrations, as noted in the differential expression of other biomarkers such as CRP and IL-6 in these diseases. In UC, the mucosal inflammation is more localized and confined to the surface layer, which might lead to a stronger VEGF response directed toward mucosal healing and regeneration.[15] On the other hand, the transmural inflammation observed in CD involves deeper tissue layers, often resulting in fibrosis and strictures.[14] In this context, VEGF's role may shift from promoting vascular growth to contributing to fibrogenesis and tissue remodelling, which could explain the relatively lower levels of VEGF seen in CD. These observations suggest that VEGF may play distinct roles in these two disease states. One of the key findings of this meta-analysis is the lack of statistical significance in VEGF differences between active and inactive disease states. This suggests that, although VEGF is consistently elevated in IBD patients, it may not be a sensitive marker of disease activity or acute flares. This insight aligns with other research indicating that VEGF might be more reflective of chronic inflammation rather than short-term fluctuations in disease activity. Similar findings have been reported in other studies, where VEGF concentrations did not correlate with clinical disease activity indices but were elevated in patients with longstanding inflammation.[51] The significant geographical variations in VEGF concentrations, with notable increases in studies conducted in Western Europe and Asia but not in Eastern Europe, suggest that environmental, genetic or healthcare-related factors may influence VEGF concentrations. Studies have shown that dietary factors, microbiome composition and genetic predispositions vary significantly across regions and could impact inflammatory pathways and biomarker concentrations.[52] For instance, Western diets high in fat and sugar have been linked to increased inflammatory markers, including VEGF.[53] Additionally, genetic polymorphisms in VEGF-related genes could contribute to regional differences, as evidenced by the varied prevalence of certain VEGF gene variants in different populations.[54] These regional differences are particularly noteworthy, as they may point to localized risk factors or healthcare practices that influence the pathogenesis and progression of IBD. For clinicians and researchers, this underscores the importance of developing region-specific guidelines for the diagnosis and treatment of IBD, potentially leading to more personalized medical approaches. Furthermore, regional insights might direct future research toward understanding how VEGF expression and function are modulated by genetic or environmental factors in specific populations. These regional differences underscore the importance of context when interpreting biomarker data and highlight the need for region-specific clinical guidelines. Such guidelines would help tailor therapeutic approaches based on regional epidemiological data, potentially improving patient outcomes. Additionally, the differences in VEGF concentrations between serum and plasma samples emphasize the necessity of standardizing sample types in future studies to reduce variability and improve comparability. Given the significant discrepancies between serum and plasma-based VEGF measurements, future research should prioritize method standardization to ensure more reliable cross-study comparisons. Methodological considerations such as publication bias, which was addressed using the trim-and-fill method, further validate our findings, though the slight reduction in the pooled SMD post-adjustment suggests that some degree of bias was present. Despite this, the overall significance of the results remained, supporting the robustness of our conclusions. Publication bias is a common issue in meta-analyses, particularly in biomedical research, where studies with significant findings are more likely to be published. Addressing this bias is crucial for providing an accurate representation of the evidence base.

5 | CONCLUSION

In conclusion, this meta-analysis demonstrates elevated VEGF concentrations in IBD patients compared to controls, with significant regional and sample type variations. However, VEGF concentrations do not significantly differ between active and inactive disease states, questioning their utility as a biomarker for disease activity. These findings suggest that while VEGF plays a role in the inflammatory processes of IBD, it may not be a reliable marker for monitoring disease activity. Future research should focus on elucidating the mechanisms behind regional differences, standardizing methodologies to improve the reliability of VEGF as a biomarker and exploring its potential role in the context of other inflammatory pathways and biomarkers in IBD. Such efforts will enhance our understanding of VEGF's role in IBD and its potential utility in clinical practice.

AUTHOR CONTRIBUTIONS

Conceptualization: S.Z. and A.Z.; methodology: S.Z., A.A.M., B.D.L., P.P. and A.Z.; formal analysis: S.Z., A.A.M. and A.Z.; investigation and data curation: S.Z., A.A.M., B.D.L., A.Z., P.P. and C.C.; writing–original draft preparation: S.Z., A.Z. and A.A.M.; writing–review and editing: S.Z., A.A.M., B.D.L., P.P., C.C. and A.Z.;

supervision: A.A.M., P.P., C.C. and A.Z. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non financial interests to disclose.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article.

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