• Meta-Analysis •

Association between findings in nailfold capillaroscopy and diabetic retinopathy: a systematic review and Meta-analysis

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Abstract

● **AIM:** To systematically evaluate the association between nailfold capillaroscopic findings and diabetic retinopathy (DR) and compare findings in diabetic patients with and without DR.

● **METHODS:** PubMed, Web of Science, and Embase databases were searched from inception to February 2024. The quality of the included studies was evaluated using a National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross Sectional Studies. Meta-analysis was conducted to compare the findings of nailfold capillaroscopy between diabetic patients with or without DR. Subgroup analysis was employed to investigate the source of heterogeneity.

● **RESULTS:** Totally 12 studies with 1349 diabetic patients were included, of which 628 had DR. The overall quality of included studies was acceptable. Patients with DR had increased arteriolar diameters [mean difference (MD): 2.68, 95% confidence interval (CI): 0.64-4.72] and a higher risk of developing nailfold capillaroscopic abnormalities, including bushy capillaries [odds ratio (OR): 2.82, 95%CI: 1.65-4.80], neoformation (OR: 4.61, 95%CI: 3.15-6.76), megacapillaries (OR: 8.37, 95%CI: 5.07-13.80), tortuosity (OR: 7.29, 95%CI: 2.76-19.22), microhemorrhages (OR: 6.16, 95%CI: 2.48-15.26), meandering capillaries (OR: 4.68, 95%CI: 1.05-20.80) and avascular areas (OR: 7.92, 95%CI: 2.68-23.38). The presence of tortuous capillary was more common in DR in India than in Turkey, while avascular area in the nailfolds was linked to DR only in India (OR: 11.28, 95%CI: 3.91-32.60). Among the nailfold capillaroscopic abnormalities, tortuosity, microhemorrhage, and meandering capillary showed no significant correlation with the severity of DR, except for avascular area (*P*=0.04).

● **CONCLUSION:** There are significant associations between nailfold capillaroscopic findings and the presence of DR, supporting its potential as a non-invasive technique for monitoring microvascular changes in diabetic patients. However, further research is needed to validate its utility as an early screening tool for microvascular complications in diabetes.

● **KEYWORDS:** diabetic retinopathy; diabetes mellitus; microvascular changes; nailfold capillaroscopy
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INTRODUCTION

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM), affecting approximately one-third of individuals living with diabetes, and remain the major cause of blindness in people of working age[1-2]. According to the presence of retinal neovascularization, it progresses through non-proliferative (NPDR) to proliferative (PDR) stages[3]. NPDR typically presents with milder symptoms, including the presence of microaneurysms, cotton-wool spots, intraretinal microvascular abnormalities, hard exudates and venous beading, whereas PDR represents a more advanced stage of retinal damage under conditions of hyperglycemia, characterized by neovascularization of the optic disc or elsewhere of the retina, pre-retinal and vitreous hemorrhage[3-4].

Epidemiologic studies have shown that DR caused an increase in age-standardized blindness prevalence between 1990 and 2020 globally[5]. As of 2020, about 103.12 million adults were estimated to have DR worldwide, and the number is

expected to reach 160.50 million by 2045[6]. The World Health Organization reported that at least 2.2 billion people suffer from near or distance vision impairments globally, with 3.9 million cases attributed to DR[7]. Alarmingly, an estimated half of those with diabetes remain undiagnosed, and oblivious to their potential risk of substantial vision loss and other serious complications, causing serious personal health burden[8-9].

Timely laser therapy and treatment methods such as intraocular injection of antivascular endothelial growth-factor agents are effective for preservation of sight in proliferative retinopathy[1-2,10]. Furthermore, DR is a sentinel indicator of diabetic heart disease, diabetic nephropathy, stroke and other cerebrovascular diseases[1,11-13]. Therefore, early detection and management of DR are crucial to diabetic patients. For diabetic patients, comprehensive and regular fundus examinations are difficult to universally implement due to their complex procedures and time-consuming nature[14].

Capillaries near the nailfold run parallel to the skin surface, making them readily visible compared to their perpendicular orientation elsewhere in the body[15]. Nailfold capillaroscopy is a convenient, noninvasive, safe, and useful tool for evaluating the changes in nailfold microvascular structure[16]. Its accuracy in diagnosing rheumatic conditions like systemic sclerosis has been validated[17-19]. The presence of alterations such as increased tortuosity, hyperlipidemia, neoformation, bushy capillary and megacapillary may serve as indicators of DR[16,20-23].

The aim of this article is to systematically review the studies about the association of nailfold capillaroscopy findings with DR, compare the findings of nailfold capillaroscopy in diabetic patients with and without DR, and to explore the potential of this technique as a diagnostic and monitoring tool for the early detection and management of DR.

MATERIALS AND METHODS

We performed a systematic review and Meta-analysis and reported its findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24]. The protocol has been registered on the International Prospective Register of Systematic Reviews PROSPERO (CRD42024535827).

Search Strategy Two reviewers conducted a meticulous and systematic search of the PubMed, Web of Science, and Embase, spanning from their inception to February 2024. The search strategy employed a combination of free text and index terms, aiming to capture a comprehensive set of relevant articles. A thorough review of the references from all eligible articles and pertinent reviews was conducted. Additionally, a forward citation search was performed using Google Scholar, further enhancing our ability to identify potentially relevant surveys.

Study Selection and Eligibility Criteria The inclusion criteria were as follows: 1) observational studies; 2) correctly collect data on nailfold capillaroscopic parameters in case and control patients; 3) DM patients with DR (NPDR, PDR or both) were selected as the case group and DM patients without DR as the control group; 4) the diagnosis of DR was confirmed by ophthalmological assessment including fundus (retinal) angiography and other examinations.

The exclusion criteria were as follows: 1) animal studies or *in vitro* experiments; 2) studies that did not report relevant outcome measures or secondary outcomes; 3) studies that were published in languages other than English.

Two review authors (Yan Q and Chen SS) independently screened titles and abstracts, and full-text articles, to determine eligibility. Discrepancies were resolved through discussion.

Data Extraction and Quality Assessment Data extraction was performed independently by two reviewers (Yan Q and Chen SS). We retrieved information regarding the studies, the participants' baseline characteristics and nailfold capillaroscopic outcomes, including capillary density, loop width, megacapillaries, combination of dilated capillaries, hemorrhages, and so on. Disagreements between two reviewers were resolved by adjudication with senior adviser (Wu HQ).

The included articles underwent quality appraisal by authors Yan Q and Chen SS individually, using a standardized scoring sheet consisting 15 questions, more specifically the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross Sectional Studies[25]. All included studies were assessed, and each question was assigned 1 point if it was answered yes, -1 point if answered no, and 0 point if answered as not reported, resulting in a total score ranging from -15 to 15 points. The study was considered good quality if the total score ≥9 points, fair quality if ≥4 points but <9 points, poor quality <4 points. Two reviewers (Yan Q and Chen SS) convened to reach consensus on the scores through discussion and discrepancies were resolved by adjudication with senior adviser (Wu HQ).

Statistical Analysis This Meta-analysis was conducted using the RevMan software (version 5.4.1.) and Stata (version 14.0.). Mean difference (MD) and 95% confidence interval (CI) were calculated for continuous outcomes, whereas odds ratio (OR) and 95%CI were calculated for dichotomous outcomes. Statistical heterogeneity among the studies was evaluated by Q test. Heterogeneity was quantitatively estimated based on I^2 which ranged from 0 to 100%. When $P>0.1$ and $I^2<50\%$, a fixed effect model was used, and if $P\leq0.1$ and $I^2\geq50\%$, which suggests significant heterogeneity, a random effect model was used. Subgroup analysis were performed to explore the possible reasons of heterogeneity. A $P<0.05$ was considered statistically significant.

RESULTS

Search Results, Study Characteristics and Quality

Assessment The systematic search identified 223 records in PubMed, 321 in Web of Science, 674 in Embase, and 4 in searching reference list and Google Scholar. Primary electronic database searching identified 770 records after the removal of duplicates, and of which 713 records were excluded after screening their titles and the abstracts. Full-text review was performed on 57 records, resulting in the retention of 12 original studies eligible for qualitative analysis (Figure 1)[16,20-23,26-32]. Two studies[23,29] were excluded in the Meta-analysis due to their inconsistent definitions in the scoring criteria of the nailfold capillaroscopy.

Twelve studies were published between 1992 and 2024, of which 5 studies were from India, 2 from Turkey, and the rest were distributed across East Asia, Europe and North Africa. All included articles were designed as cross-sectional studies and involved 1349 diabetes patients. Among them, 628 cases (46.6%) were diagnosed with DR. Six studies reported the results of nailfold capillary endoscopy examination for NPDR and PDR, with 185 cases diagnosed with PDR and 255 cases diagnosed with NPDR[16,20-21,26,28,32]. Most of the included studies were focused on patients with type 2 diabetes mellitus (T2DM). In the studies providing corresponding data, the average age of the patients with DR was 57.32±10.35y, and the average course of disease was 10.83±6.26y. In comparison, in the patients without DR, the average age is 55.86±10.90y, and the duration of the disease is 5.95±4.55y, indicating that DR patients were older and had a longer disease course than non-DR patients. Tables 1 and 2 contain the important demographic characteristics of the 12 included studies.

Of the 12 included studies, 4 scored 10 points and 2 scored 9 as good quality, 4 scored 8, 1 scored 5 and 1 scored 4 as fair quality.

Pooled Analysis of Included Studies

Quantitative assessment Two studies with 60 participants assessed arteriolar diameters when evaluating nailfold capillaroscopy[27,32]. Arteriolar diameters were increased in patients with DR compared to patients without DR (MD: 2.68, 95%CI: 0.64-4.72; Figure 2).

No significant statistical differences were observed in the length (P=0.09), width (P=0.95), density (P=0.22), and venular diameters of capillaries (P=0.11) in the nailfolds between individuals with and without DR.

Qualitative assessment Compared with patients without DR, patients with DR had a higher risk of developing bushy capillaries in the nailfolds (OR: 2.82, 95%CI: 1.65-4.80; Figure 3A), as did neoformation (OR: 4.61, 95%CI: 3.15-6.76; Figure 3B), megacapillary (OR: 8.37, 95%CI: 5.07-13.80; Figure 3C), tortuous capillaries (OR: 7.29, 95%CI: 2.76-19.22; Figure 3D), microhemorrhages (OR: 6.16, 95%CI: 2.48-15.26; Figure 3E), meandering capillaries (OR: 4.68, 95%CI: 1.05-20.80; Figure 3F), and avascular areas (OR: 7.92, 95%CI: 2.68-23.38; Figure 3G). Substantial heterogeneity was observed among studies investigating tortuous capillaries (I^2=86%), microhemorrhages (I^2=79%), meandering capillaries (I^2=80%), and avascular areas (I^2=64%) in patients with DR compared to those without DR.

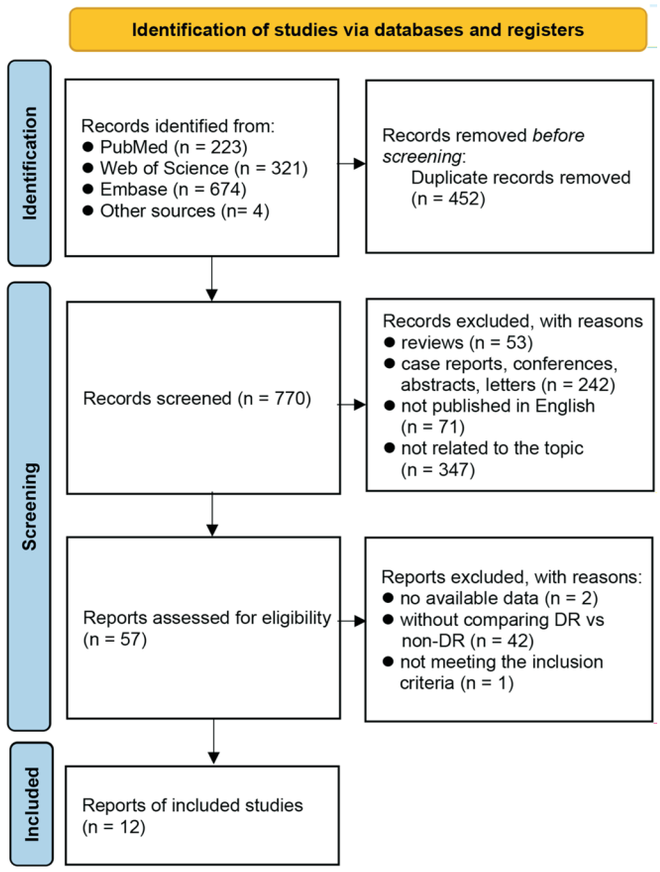

Figure 1 Flowchart of the study selection process DR: Diabetic retinopathy.

There was no statistically significant difference in the presence of bizarre capillaries (P=0.10), capillary ectasia (P=0.14), cross-linked capillaries (P=0.18), bleeding areas (P=0.92) and receding capillaries (P=0.28) between patients with and without DR.

Subgroup Analysis Subgroup analysis was carried out for studies with substantial heterogeneity according to region and DR severity.

The presence of tortuous capillaries in the nailfolds was associated with DR both in Turkey (OR: 2.38, 95%CI: 1.11-5.10) and in India (OR: 15.58, 95%CI: 4.72-51.41; Figure 4A). The test for subgroup differences suggested that the presence of tortuous capillaries was more common in DR in India than in Turkey (P=0.009). Avascular area in the nailfolds was linked to DR in India (OR: 11.28, 95%CI: 3.91-32.60), while there was no significant difference between patients with and without DR in Turkey (OR: 1.24, 95%CI: 0.02-76.30; Figure 4B).

The patients with NPDR had a higher risk to develop tortuous capillaries in the nailfolds (OR: 7.35, 95%CI: 1.83-29.53;

Table 1 Demographical characteristics of patients with DR *vs* patients without DR

mean±SD

Study ID	Type	Site of assessment	Location	Sample size (male)		Age		HbA1c (%)		Diabetes years	
				DR (+)	DR (-)	DR (+)	DR (-)	DR (+)	DR (-)	DR (+)	DR (-)
Uyar, 2016[16]	T2DM	8 fingers (excluding the thumbs)	Türkiye	93 (45)	123 (45)	60.89±8.21	58.92±8.506	8.7	7.2	14, 0-40 (median, min-max)	4, 0-25 (median, min-max)
Mohanty, 2021[26]	T1DM+T2DM	NR	India	125	125	NR	NR	NR	NR	11.53±4.28	5.5±3.2
Bakirci, 2019[22]	T2DM	8 fingers (except thumbs)	Türkiye	44 (21)	20 (11)	61.4±7.4	56.6±9.2	9.0±1.9	8.6±2.2	14.6±6.4	8.0±5.4
Abd El-Khalik, 2022[20]	T2DM	10 or 8 fingers	Egypt	26	36	>18		9.72±1.94	8.65±2.1	13±5.61	8±4.65
Gasser, 1992[27]	TIDM	NR	Switzerland	13	12	45.0±11.9	52.2±15.7	6.9±0.8	7.1±1.3	23.6±9.6	15.8±9.8
Raina, 2023[23]	T2DM	All 8 fingernails (excluding the thumb)	India	54	46	55.63±8.7	NR	NR	NR	NR	NR
Ahmad, 2023[21]	T2DM	Each proximal nailfold	India	118 (77)	144 (87)	56±12	53±12	9.4±2.2	7.3±1.7	6.9±4.4	5±3.8
Okabe, 2024[28]	T2DM	Fourth finger on the left hand	Japan	53 (30)	30 (20)	57.89±8.36	58.0±9.4	7.69±1.67	7.04±0.98	NR	NR
Kuryliszyn-Moskal, 2017[29]	T1DM	NR	Poland	45	61	NR	NR	NR	NR	NR	NR
Jakhar, 2020[30]	T2DM	All 10 fingernails	India	15	81	>18	NR	NR	NR	NR	NR
Bohania, 2022[31]	T1DM+T2DM	4 fingers (index and middle fingers of both hands)	India	17	33	49.5±10.6	NR	8.46±1.05	7.44±1	10.06±5.32	4.76±3.19
Chang, 1997[32]	NR	The left hand, the fourth finger	Taiwan, China	25 (13)	10 (4)	55.6	51	NR	NR	15.1	4.2

DM: Diabetes mellitus; DR (+): Patient with diabetic retinopathy; DR (-): Patient without diabetic retinopathy; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; NR: Not report.

Figure 5A). The patients with PDR were more likely to have microhemorrhage in their nailfolds (OR: 21.60, 95%CI: 1.20-388.15; Figure 5B). The risk of meandering capillaries in the nailfolds was not significantly different between patients with NPDR and those without DR (OR: 3.91, 95%CI: 0.16-93.59), nor between patients with PDR and those without DR (OR: 8.60, 95%CI: 1.00-73.97; Figure 5C). The presence of avascular areas in the nailfolds was associated with both NPDR (OR: 7.50, 95%CI: 1.95-28.80) and PDR (OR: 62.31, 95%CI: 14.67-264.63; Figure 5D), and people with PDR had a higher likelihood of developing avascular areas in their nailfolds than those with NPDR (P=0.04).

Sensitivity Analysis Sensitivity analysis was conducted by sequentially deleting each study and calculating the results based on the remaining studies. The findings remained consistent in the sensitivity analysis of studies examining the link between neoformation, megacapillaries, tortuosity, microhemorrhage, avascular area, and DR after removing any individual study. However, the study by Uyar *et al*[16] had an influence on the results regarding the relationship between bushy capillary and DR, while the studies by Ahmad *et al*[21] and Jakhar *et al*[30] separately exerted an influence on the correlation between meandering capillary and DR.

DISCUSSION

The pathogenesis underlying DR is still under investigation. Previous studies have shown that microvascular mural cells (pericytes) loss in the vascular bed of the retina is one of the earliest hallmarks of DR[33-34]. Pericytes can support and stabilise the microvasculature, and are present in all vascular beds[33-34]. The density of pericytes is very high in the retina with an endothelial cell to pericyte ratio of 3:1[34]. Thus, the loss of pericyte in the nailfold capillary might lead to capillary instability, increasing abnormal nailfold capillary morphology[35]. DR and finger crossing capillaries are likely to be caused by the same pathological pathway in DM[36]. In addition, hyperglycemia triggered a variety of metabolic pathways in diabetes, including the polyol and hexosamine pathways, diacylglycerol synthesis by protein kinase C, the production of free radicals and advanced glycation end products, inflammatory mechanisms, oxidative stress and circRNA, which competes with miRNA, affecting mRNA in retinal and renal endothelial cells, driving DR pathogenesis[14,35,37-38].

About 5%-10% diabetic patients progress to the sight-threatening stages of PDR and diabetic macular edema[39]. However, it is a chronic, progressive disease that develops in stages. It is rarely detected in the first few years after diabetes onset, and the incidence rises to 50% by 10th year, and to 90% by 25th year of diabetes[40]. Therefore, early diagnosis and control of DR are crucial.

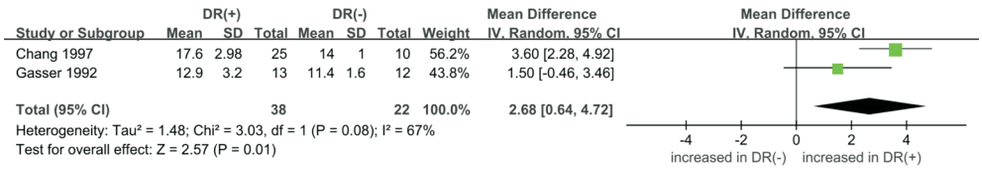

Figure 2 Forest plot of studies exploring arteriolar diameters (μm) in patients with DR *vs* patients without DR DR: Diabetic retinopathy; DR (+): Patient with DR; DR (-): Patient without DR; SD: Standard deviation; IV: Inverse variance; CI: Confidence interval.

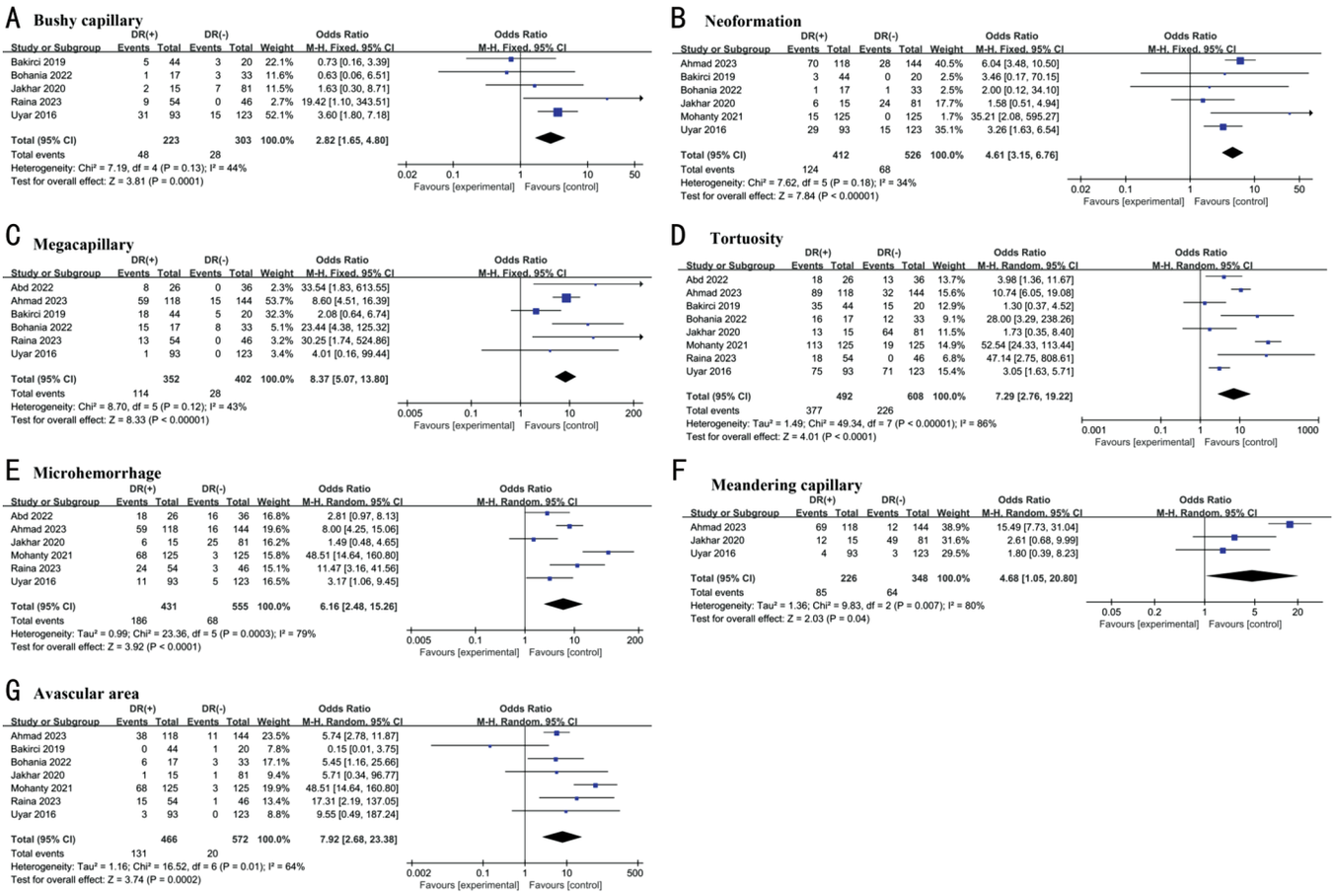

Figure 3 Forest plot of all studies exploring the odds ratio for bushy capillary (A), neoformation (B), megacapillary (C), tortuosity (D), microhemorrhage (E), meandering capillary (F) and avascular area (G) in patients with DR *vs* without DR DR: Diabetic retinopathy; DR (+): Patient with DR; DR (-): Patient without DR; M-H: Mantel-Haenszel; CI: Confidence interval.

Table 2 Demographical characteristics of patients with NPDR *vs* patients with PDR mean±SD

Study ID	Sample size (male)		Age		HbA1c (%)		Diabetes years	
	PDR	NPDR	PDR	NPDR	PDR	NPDR	PDR	NPDR
Uyar, 2016[16]	62	31	60.89±8.21		8.7		NR	NR
Mohanty, 2021[26]	59	66	NR	NR	NR	NR	12.8±4.8	10.4±3.4
Abd El-Khalik, 2022[20]	4	22	>18		NR	NR	NR	NR
Ahmad, 2023[21]	16	102	56±12		9.4±2.2		6.9±4.4	
Okabe, 2024[28]	29 (16)	24 (14)	56.4±9.0	59.7±7.3	7.73±1.84	7.65±1.47	NR	NR
Chang, 1997[32]	15 (9)	10 (4)	56	55	NR	NR	16.1	13.6

NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HbA1c: Hemoglobin A1c; SD: Standard deviation.

This is the first systematic review and Meta-analysis of studies evaluating endothelial and microvascular function in DM individuals with and without DR. The main findings suggested that increased arteriolar capillary diameters and various qualitative nailfold capillaroscopic abnormalities including bushy capillaries, neoformation, and megacapillaries, tortuosity, microhemorrhages, meandering capillaries, and avascular areas, were more common in diabetics with DR compared to diabetics without DR. Sensitivity analysis showed stability in most outcomes except for bushy capillaries and

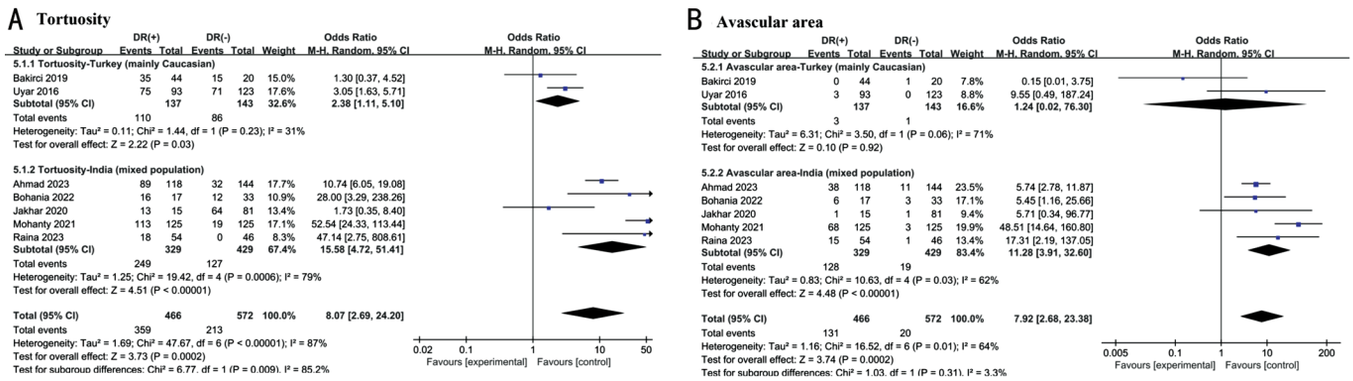

Figure 4 Forest plot of subgroups by race exploring the odds ratio for tortuosity (A) and avascular area (B) in patients with DR *vs* without DR
DR: Diabetic retinopathy; DR (+): Patient with DR; DR (-): Patient without DR; M-H: Mantel-Haenszel; CI: Confidence interval.

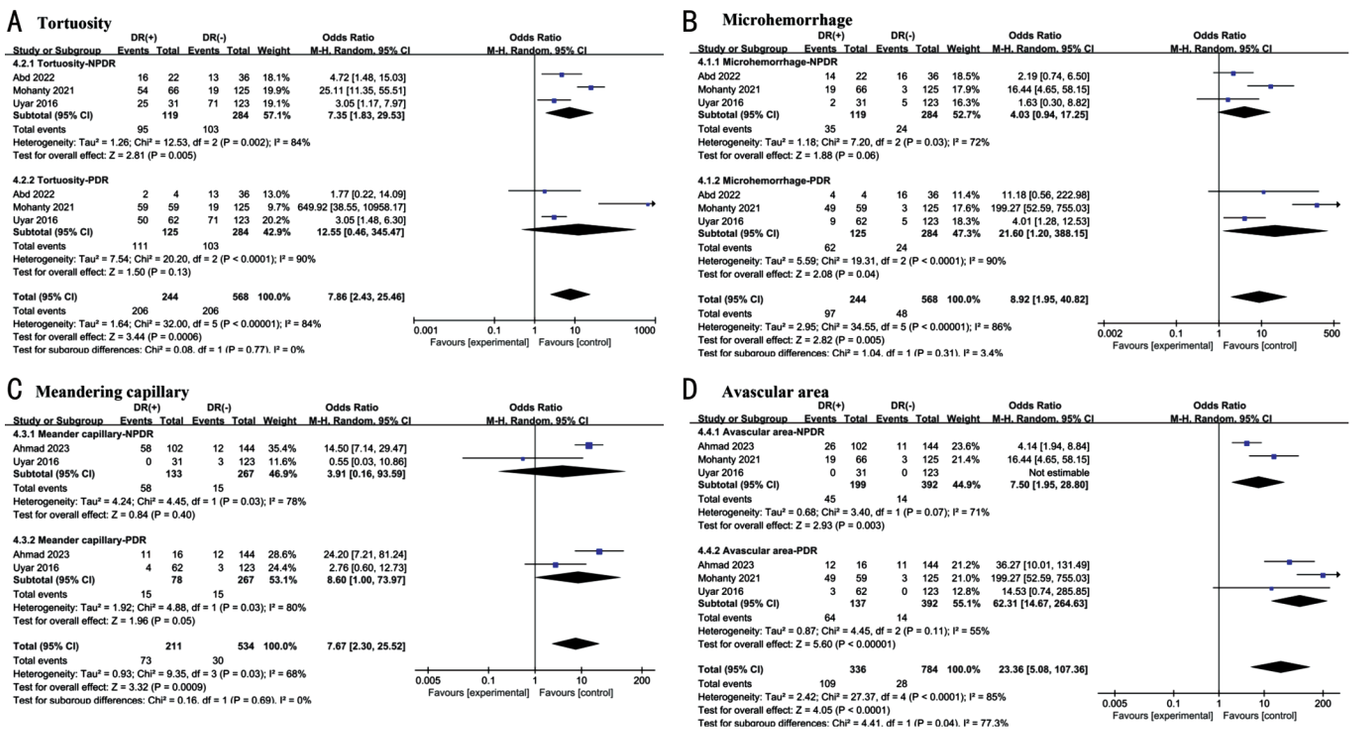

Figure 5 Forest plot of subgroups by DR severity exploring the odds ratio for tortuosity (A), microhemorrhage (B), meandering capillary (C) and avascular area (D) in patients with DR *vs* without DR DR: Diabetic retinopathy; DR (+): Patient with DR; DR (-): Patient without DR; M-H: Mantel-Haenszel; CI: Confidence interval.

meandering capillaries.

Subgroup analyses showed that region and severity of DR did not explain the heterogeneity; instead, the heterogeneity of the included studies may have arisen from several sources. A previous study noted that melanin's strong absorption of light in the visible spectrum can make capillaroscopy challenging in darkly pigmented skin[41]. Andrade *et al*[42] reported that non-white subjects had fewer capillaries than white subjects, likely due to poor general visibility in darker skin. Considering the difference in skin color between Indians and Turks, melanin will greatly interfere with the results of nailfold capillary endoscopy.

Almost no correlation was found between nailfold capillaroscopic findings and the severity of DR, in terms of tortuosity, microhemorrhage and meandering capillary, but PDR patients were more likely to have avascular areas in their nailfolds compared to NPDR patients.

While Barchetta *et al*[43] and Jakhar *et al*[30] suggested that nailfold capillaroscopic findings are unrelated to diabetes duration, more studies showed a positive correlation between nailfold capillaroscopic abnormalities and longer diabetes duration[20,29,31-32], particularly in patients with DR[16]. In addition to DR, capillaroscopic findings have also been linked to poor glycemic control and other diabetic complications such as nephropathy[16,20,26,31], suggesting that capillaroscopic changes may precede the clinical diagnosis of DR and other diabetic microvascular complications.

Some limitations existed in our study. First, limited research precludes detailed subgroup analysis and more precise

conclusions. Additionally, the definitions of nailfold capillaries employed in various studies are either not reported or show inconsistencies. The measurement tools used in each study varied significantly, originating from different manufacturers or models. Furthermore, all the studies included in our Meta-analysis were cross-sectional studies, which precludes the observation of the temporal evolution of DR and abnormal nailfold capillaries, resulting in weakly established causal relationships. Thus, our results should be interpreted cautiously and further validated in larger, high-quality studies. Lastly, according to the quality assessment standard of NIH, the quality of most included studies is acceptable, indicating a high degree of credibility of the Meta-analysis results. However, this evaluation tool fails to account for the varying importance of different indicators in assessing the quality of studies. Some indicators have a greater impact on the quality of studies, while others have less. It does not consider the weight of different items in the evaluation.

In summary, this Meta-analysis provides evidence of a significant association between nailfold capillaroscopic findings and the presence of DR. The observed microvascular alterations may reflect the pathophysiological mechanisms underlying DR, although further research is required to fully elucidate these mechanisms. Additionally, the potential utility of nailfold capillaroscopy as an early screening tool for microvascular complications in diabetes requires further validation. Nonetheless, our findings support the potential of nailfold capillaroscopy as a non-invasive technique for monitoring microvascular health in diabetic patients, which may have implications for early diagnosis and treatment of DR.

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