Ghasemi *et al. BMC Ophthalmology* (2024) 24:483
https://doi.org/10.1186/s12886-024-03751-9

BMC Ophthalmology

SYSTEMATIC REVIEW

Open Access

Characteristics of optical coherence tomography in patients with iron deficiency anemia : a systematic review and meta-analysis

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Abstract

Objective The primary objective of this systematic review and meta-analysis was to assess the association between iron deficiency anemia (IDA) and retinal changes via optical coherence tomography (OCT).

Methods The search was conducted in MEDLINE, Scopus, Embase, Web of Science, and Google Scholar until February 1, 2024. Two independent researchers included the articles based on the inclusion and exclusion criteria. Data regarding the study design, patient characteristics, number of patients with and without IDA, mean and SD of the retinal nerve fiber layer (RNFL), C/D ratio, foveal avascular zone (FAZ) area and perimeter, foveal density and superficial and deep capillary plexus (SCP and DCP) vascular density (VD) were collected. STATA version 17.0 was used to compute pooled measures of the standardized mean difference. I2 and chi-square tests were used to assess heterogeneity between studies.

Results We found 1378 nonduplicate studies, 35 of which were potentially relevant. 19 articles met the inclusion criteria and were included in the review. The meta-analysis confirmed that there was a statistically significant association between IDA and RNFL thickness reduction (SMD = -0.76, 95% CI: -1.09 to -0.44 ; p-value = 0.001, I2 = 86.88%), FAZ area (SMD =-0.35, 95% CI: -0.67 to -0.02; p value = 0.04, I2 = 59.76%) and SCP VD (SMD = -1.12, 95% CI: -1.85 to -0.39; p-value = 0.001, I2 = 83.15%). The associations between IDA and the C/D ratio (SMD = 0.07, 95% CI: -0.13 to 0.28; p value = 0.49, I2 = 0.0%) and DCP VD (SMD = -0.30, 95% CI: -0.89 to 0.29; ,p-value = 0.32 ,I2 = 77.20%) were not significant. There was no considerable publication bias.

Conclusion The results of this meta-analysis demonstrated that, compared with healthy controls, individuals with IDA presented a thinner RNFL, a smaller FAZ, and lower SCP and DCP vascular densities. However, further studies are needed to reach more conclusive results.

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Keywords Iron deficiency anemia, IDA, Optical coherence tomography, OCT, Meta-analysis

Introduction

Anemia is a significant global health issue. In 2021, the primary cause of anemia was iron deficiency anemia (IDA), accounting for 66.2% of all anemia cases. This condition affected a total of 825 million women and 444 million men worldwide [1, 2]. The etiological parameters contributing to the development of IDA include inadequate dietary iron intake or situations that lead to bleeding and reduced iron absorption [3].

In IDA, there is a decrease in the concentration of hemoglobin (Hb), resulting in a diminished capacity to carry oxygen to tissues. The retina and choroid are highly metabolically active tissues in the body, and require a significant amount of nutrients and oxygen to sustain their visual function. As a result, these tissues possess a highly concentrated and intricate system of blood vessels [4]. Therefore, maintaining the physical and functional integrity of the retina, requires a consistent supply of oxygen [5].

Owing to hypoxia caused by IDA, numerous processes lead to neuronal death. A reduction in normal perfusion and oxygen saturation is known to harm retinal ganglion cells [6, 7].

Additionally, iron is essential for the proper functioning of oligodendrocytes, which are crucial for the process of myelination [8]. Compared with other brain cells, oligodendrocytes have been shown to contain greater amounts of iron-containing enzymes [9]. Thus, Anemia is considered a substantial contributor to the advancement or emergence of ocular neuropathies because of its impact on blood vessels and nerves.

Reduced thickness of the retinal nerve fiber layer (RNFL) has been documented in some conditions, such as diabetic retinopathy, glaucoma, retinal vascular occlusion, and retinopathy of prematurity [10–12]. Also in people who have IDA anemia, RNFL thickness may be decreased [13, 14]. Therefore, the reduced thickness of the retinal nerve fiber layer (RNFL) can be crucial in the diagnosis and monitoring of some illnesses [15].

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) are noninvasive imaging techniques that have facilitated a deeper understanding of the diseases influencing retinal nerve fiber thickness and the retinal blood supply. These approaches can be useful for evaluating and monitoring systemic disorders that impact retinal tissue and blood supply [16–21].

To the best of our knowledge, there are currently no systematic reviews and meta-analyses that address the associations between IDA and retinal tissue and blood vessel density changes.

Therefore, the present study conducted a meta-analysis of existing studies to assess the association between IDA and retinal changes via OCT and OCT-A.

Method

Search strategy

This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard [22]. The selection of keywords was conducted by three strategies: MeSH terms, Emtree terms, and expert consultation. We performed a comprehensive search of the PubMed/MEDLINE, Scopus, the Web of Science (WOS), Google Scholar, and Embase databases to identify relevant publications published from the beginning until February 1, 2024. The search strategy for all databases can be found in Supplementary Table 1.

To find additional documents in the grey literature, such as conference abstracts, Scopus was used. A manual search of the reference lists of included studies was performed to identify further documents.

The study protocol has been registered in PROSPERO with a code of CRD42024510236.

Eligibility criteria and screening methods

We adopted the PECO criteria to set up the inclusion and exclusion criteria, as well as the research questions, for the study. People of various races, ages, and genders made up the population (P) in the included articles. In addition, they should have evaluated the association between iron deficiency anemia (IDA) as the exposure(E) and the findings of OCT or OCT-A as the outcome(O). The studies were considered eligible if the control group consisted of people without iron deficient anemia(C).

Studies with no control group, no evaluation of OCT or OCT-A data, case reports, case series, clinical trials, literature reviews, book chapters, letters, editorials, or protocols were excluded.

The search was conducted by M.G, while the screening processes were independently carried out by S.Z. and S.K. The selection processes were also independently handled by M.G. and A.G. If there were any discrepancies between the two authors, they were resolved either through discussion or with the guidance of an expert reviewer (H.N.).

Data extraction and risk of bias assessment

Both authors (M.G. and A.G.) independently collected data, which included the first author's name, publication year, study design, country, study population (that is, women or children), specific eye assessed (right, not reported, or both), mean age and standard deviation (SD), and the percentage of males in the study.

The mean and standard deviation (SD) of the following OCT and OCTA parameters were obtained: the cup to disc ratio (C/D ratio), average retinal nerve fiber layer thickness (RNFLT), superior, inferior, nasal, and temporal sections; vessel density of the superficial and deep capillary plexuses; foveal avascular zone area and perimeter; and foveal vessel density.

Table 1 provides a concise overview of the data extraction sheet. In cases where it was not possible to extract data from an article, the corresponding author was contacted.

Both authors (M.G. and A.G.) separately evaluated the risk of bias using the Joanna Briggs Institute critical appraisal tool for cross-sectional and case-control studies (JBI checklist).

The authors' differences were resolved through discussion or, if needed, by receiving guidance from an expert reviewer (H.N.).

Statistical analysis

Stata 17.0 (StataCorp LLC, College Station, TX, USA) was used for the statistical analyses. We computed a standardised mean difference (SMD) along with a 95% confidence interval (95% CI) for each sample. Subsequently, we combined these values to get an overall effect size. For meta-analysis to be conducted, a minimum of three relevant studies were needed.

Random-effects model (restricted maximum-likelihood method) was selected due to methodological heterogeneities between research, including population and methodology variations.

We assessed the heterogeneity among studies by use the I2 statistic and the Q test. Higgins et al. propose a categorization for I^2 values as follows: 0 to 25% (mild heterogeneity), 25 to 50% (moderate heterogeneity), 50 to 75% (severe heterogeneity), and 75 to 100% (extremely severe heterogeneity) [23].

We conducted subgroup analyses based on the study population (limited to women, limited to children, or not specified), the assessed eye (right eye, both eyes, or not reported), the quality of the study (high quality vs. low to moderate quality) and the OCT/OCTA device which had been used. Furthermore, we used meta-regression to identify potential sources of heterogeneity based on the mean age of participants and the males to females ratio.

We assessed publication bias via funnel plots, Egger's tests, and the trim and fill approach [24].

As a component of our sensitivity analysis, we utilized the one-out-remove technique, which involves systematically eliminating one study at a time and assessing its relative influence on the overall estimate.

Results

Study characteristics

Figure 1 displays the study flowchart. After eliminating duplicate entries from 1567 publications, 1378 titles and abstracts were carefully evaluated. Subsequently, 35 articles that showed probable relevance were chosen for a detailed examination of their full texts, according to the defined inclusion and exclusion criteria. In total, 18 cross-sectional studies [13, 14, 25–40] and 1 case-control study published between 2013 and 2024 [41].

Using forward and backward citation tracking of the included studies, no new articles were found. Table 1 provides a concise overview of the key features of the studies that were included.

The studies were done entirely in Asia.

16 studies were evaluated for optical coherence tomography (OCT) findings, while 4 studies were assessed for optical coherence tomography angiography (OCT-A) findings.

Only six research focused only on pregnant women, whereas four studies exclusively focused on children.

The studies included in the meta-analysis had a quality score ranging from 2 to 8 out of 8.(Table 3).

A total of 833 individuals with IDA and 894 individuals without IDA were included in these studies. The mean age of the patients was 30.55±7.45 years, and 31.25% of them were male.

Association between iron deficiency anemia (IDA) and retinal nerve fiber layer thickness (RNFLT)

The average retinal nerve fiber layer thickness (RNFLT) and iron deficiency anemia (IDA) were found to be significantly correlated when pooled standardized mean differences (SMDs) were compared (SMD = -0.76, 95% CI: -1.09 to -0.44 ; p-value=0.001, I2=86.88%). In patients with IDA and without IDA, the mean and standard deviation of average RNFLT were, respectively, 98.454±8.99 µm and 105.44±11.41 µm, respectively (WMD = -6.99 µm, 95% CI: -10.35 to -3.64; p-value=0.001, I2=92.56%). Figure 2 displays the results of the meta-analysis.

supplementary Fig. 1 demonstrates the association between iron deficiency anemia and the retinal nerve fiber layer thickness (RNFLT) by differentiating it into four regions: superior, inferior, nasal, and temporal. The most significant reduction in the Retinal Nerve Fiber Layer Thickness (RNFLT) was observed in the inferior region, whereas the smallest reduction was observed in the superior region.

Association between iron deficiency anemia (IDA) and the cup to disc ratio (C/D ratio)

The results indicated that there was no significant association between iron deficiency anemia (IDA) and

Table 1 Characteristics of included studies

First author	Year	Design	Location	OCT/OCT-A Device	Population	Patients(n)			Which eye was assessed?	Age [a]	Male (%)	Total quality score
						IDA	control	Total				
Wu	2024	nested case control	China	ZEISS	pregnant women	99	184	283	Not reported	32.37(5.44)	0	6/10
Joshi	2023	cross-sectional	India	Optovue	Not specified	58	58	116	Both	NR	NR	5/8
Gupta	2023	cross-sectional	India	Nidek	Not specified	50	50	100	Both	38.08(11.83)	31.19	7/8
Samant	2022	cross-sectional	India	Topcon	Not specified	25	25	50	Right	40.44(14.06)	32	5/8
Koca	2022	cross-sectional	Turkey	Optovue	Not specified	33	33	66	Right	NR	NR	3/8
El-Gamal	2022	cross-sectional	Egypt	Topcon	Not specified	30	30	60	Both	23.83(9.06)	36.7	8/8
Ugurlu	2021	cross-sectional	turkey	Nidek	women only	40	40	80	Right	30.4(12.9)	0	5/8
Hamed	2021	cross-sectional	Egypt	Topcon	children	16	16	32	Not reported	NR	NR	5/8
Duzgun	2022	cross-sectional	Turkey	Optovue	Not specified	40	35	75	Right	37.71(7.44)	NR	6/8
Kocer	2020	cross-sectional	Turkey	Optovue	Not specified	40	46	86	Right	NR	NR	6/8
Kumari	2020	cross-sectional	India	ZEISS	women only	59	44	103	Right	NR	0	5/8
Korkmaz	2020	cross-sectional	Turkey	Optovue	children	33	29	62	Not reported	12.22(4.48)	37.5	7/8
Jaiswal	2018	cross-sectional	India	ZEISS	Not specified	80	80	160	Both	29.79(0.97)	14	5/8
Coskun	2018	cross-sectional	Turkey	ZEISS	women only	35	35	70	Right	37.85(11.06)	0	6/8
Acir	2015	cross-sectional	Turkey	ZEISS	Not specified	73	68	141	Both	NR	NR	5/8
Cikmazkara	2016	cross-sectional	Turkey	ZEISS	women only	102	49	151	Right	NR	NR	2/8
Akdogan	2014	cross-sectional	Turkey	ZEISS	women only	40	40	80	Not reported	NR	0	6/8
Aksoy	2014	cross-sectional	Turkey	Heidelberg	children	22	59	81	Right	9.14(2.53)	37	5/8
Türkyılmaz	2013	cross-sectional	Turkey	ZEISS	children	40	40	80	Not reported	NR	NR	5/8

IDA: iron deficiency anemia, NR: not reported, OCT: optical coherence tomography, OCT-A: OCT angiography

a: presented as the mean(SD)

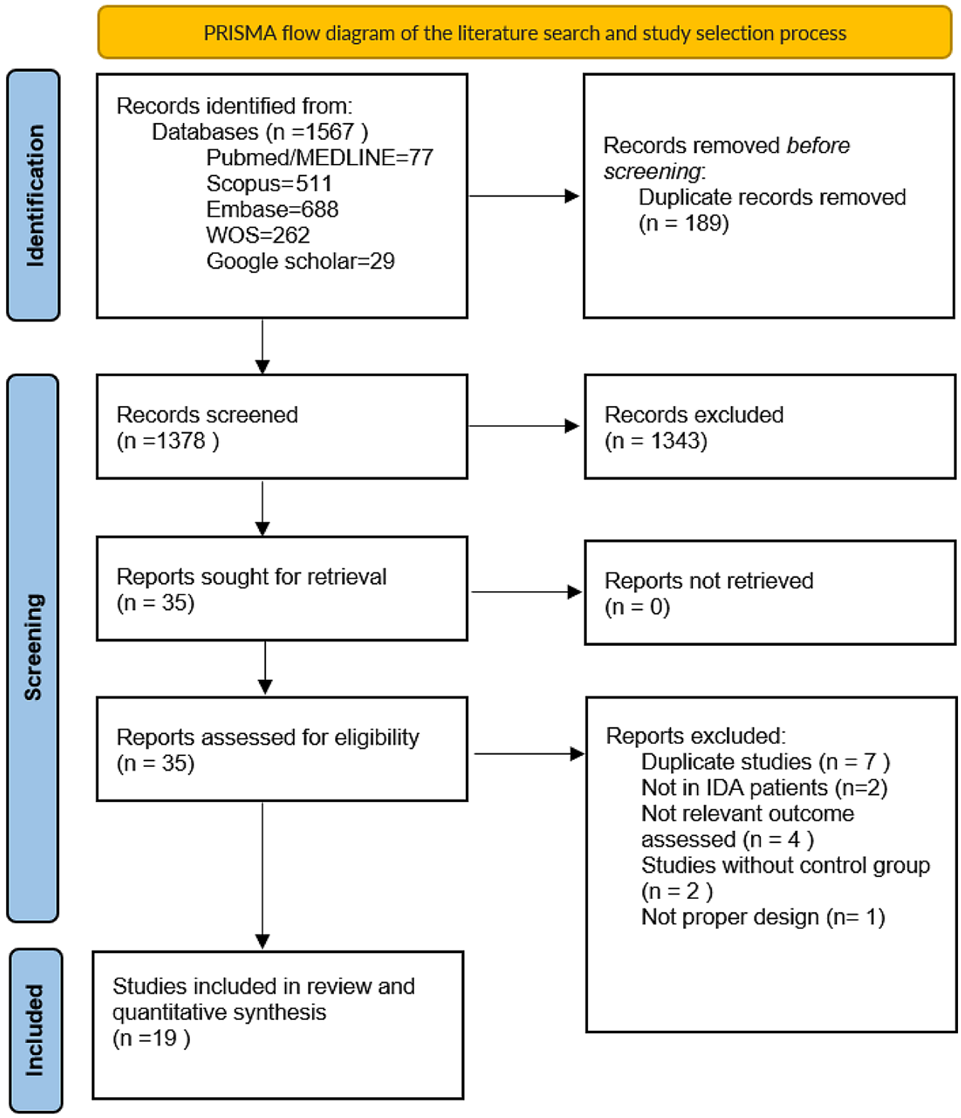

Fig. 1 PRISMA flow diagram of the literature search and study selection process

cup to disc ratio (SMD=0.07, 95% CI: -0.13 to 0.28; p value=0.49, I2=0.0%).

The C/D ratios for patients with and without IDA had respective means and standard deviations of 0.393±0.0325 and 0.385±0.0307 (WMD=0.008, 95% CI: -0.025 to 0.042; p-value=0.628, I2=0.02%). The meta-analysis's findings are presented in Fig. 2.

Association between iron deficiency anemia (IDA) and foveal avascular zone (FAZ) parameters

The available data regarding foveal avascular zone (FAZ) parameters in the included studies were the FAZ area, FAZ perimeter, and foveal vessel density in the SCP. We perform a meta-analysis on these items.

A weak negative association was observed between IDA and both the FAZ area (SMD =-0.35, 95% CI: -0.67 to -0.02; p value=0.04, I2=59.76%) and the FAZ perimeter (SMD = -0.34, 95% CI: -0.65 to -0.03; p value=0.03, I2=55.98%). Additionally, there was a negative association between IDA and foveal VD (SMD = -0.73, 95% CI: -1.28 to -0.18; p value=0.01, I2=72.66%). The results of the meta-analysis are displayed in Fig. 3.

Association between iron deficiency anemia (IDA) and vascular density (VD)

Our results demonstrated that IDA patients have significantly lower whole image vascular density in the superficial capillary plexus (SCP) than controls (SMD = -1.12, 95% CI: -1.85 to -0.39; p-value=0.001, I2=83.15%). Similar findings were observed in the deep capillary plexus (DCP), however the difference was not statistically significant (SMD = -0.30, 95% CI: -0.89 to 0.29; ,p-value=0.32 ,I2=77.20%). The results of the meta-analysis are shown in Fig. 4.

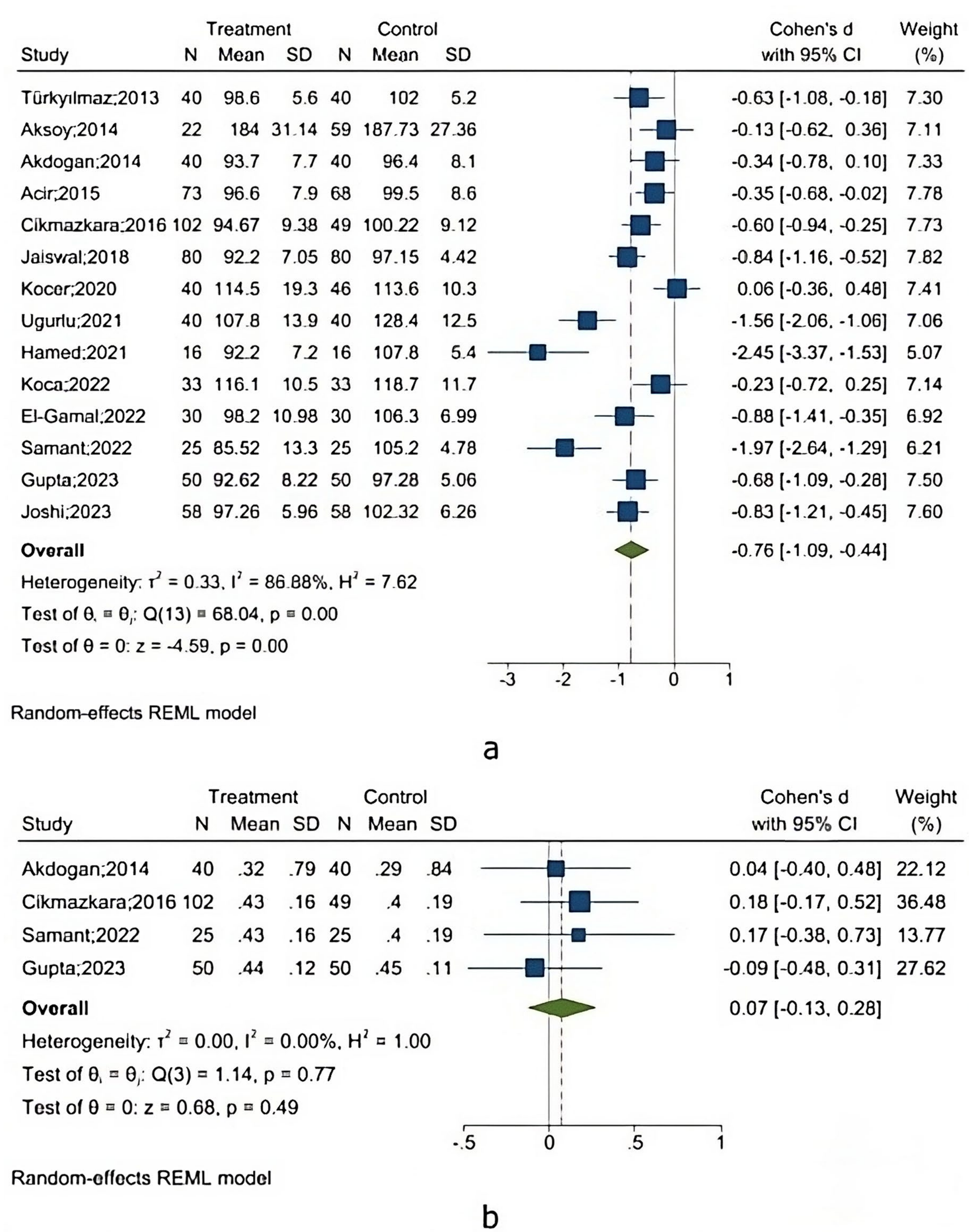

Fig. 2 Forest plot (random-effects model) depicting: (**a**) the association of iron deficiency anemia(IDA) and average retinal nerve fiber layer thickness(RNFLT), (**b**) the association of iron deficiency anemia(IDA) and cup to disc(C/D) ratio

Subgroup analysis and meta-regression

All the results of the subgroup analyses are shown in Table 2. The subgroup analysis by study population revealed no significant difference between strata (p-value=0.814, Supplementary Fig. 2a, SMD = -0.82, 95% CI: -1.47 to -0.17 for studies consisted only women, SMD = -0.98, 95% CI: -2.01 to 0.04 for studies consisted

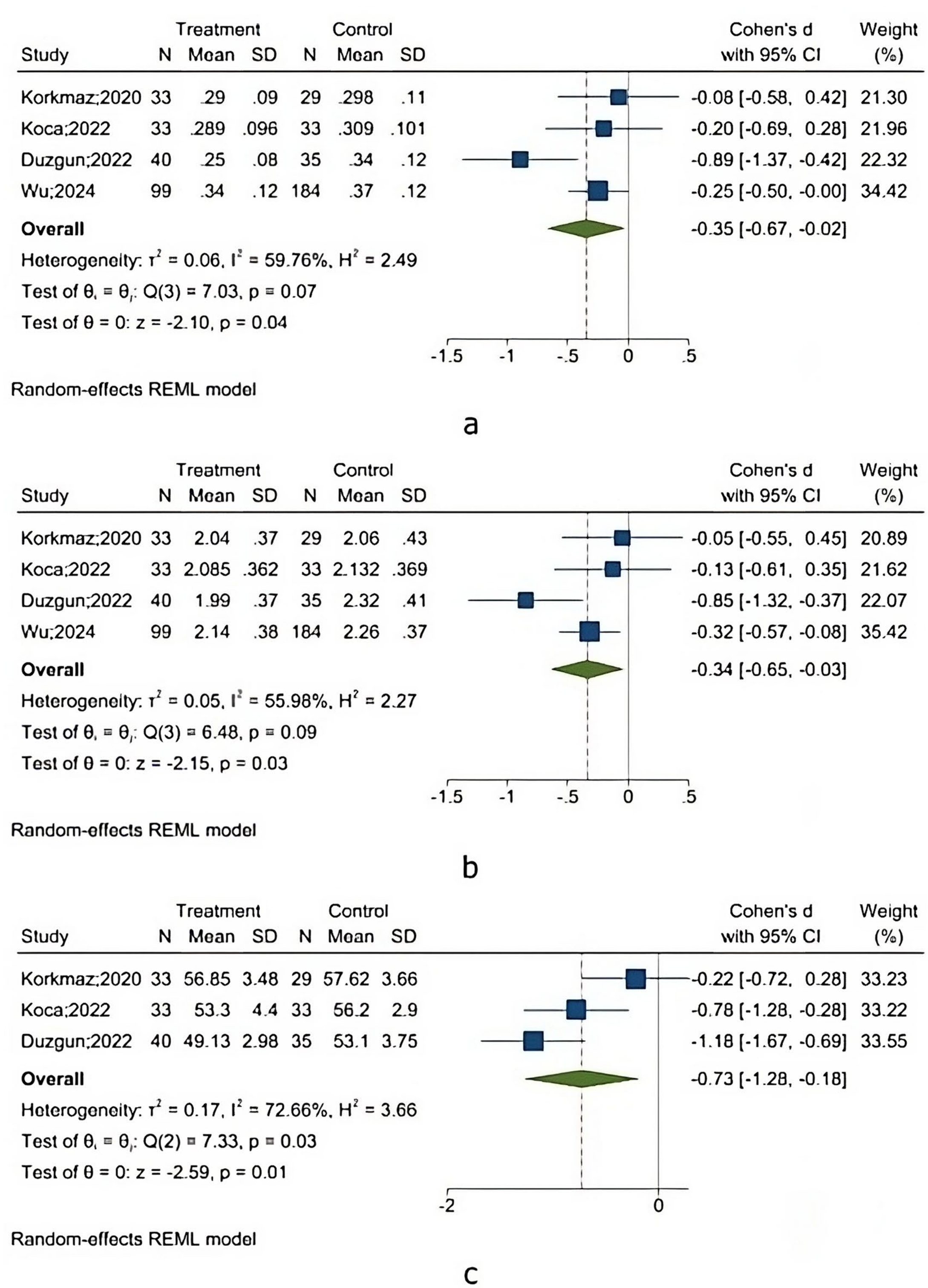

Fig. 3 Forest plot (random-effects model) depicting the association of iron deficiency anemia(IDA) and foveal avascular zone(FAZ) parameters in superficial capillary plexus(SCP): (**a**) FAZ area, (**b**) FAZ perimeter, (**c**) foveal density

only children and SMD = -0.67, 95% CI: -1.00 to -0.34 for studies with no specified population).

There were also no significant differences between studies with low risk of bias (ROB) compared to high to moderate ROB (p-value = 0.902, Figure S2b).

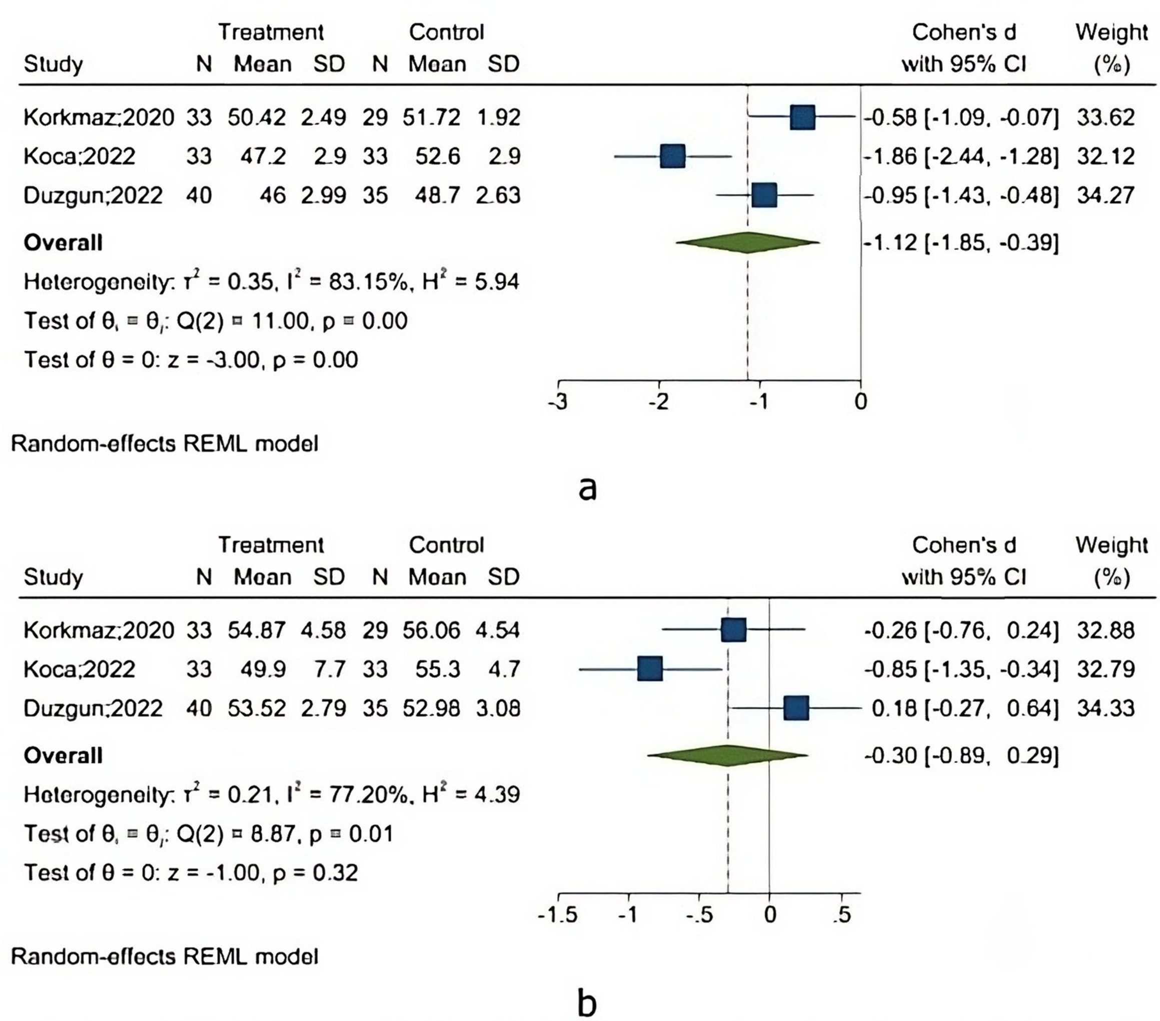

Fig. 4 Forest plot (random-effects model) depicting the association of iron deficiency anmeia(IDA) and vascular denisty : (**a**) superficial capillary plexus(SCP), (**b**) deep capillary plexus(DCP)

Studies that reported right eye retinal nerve fiber layer thickness (RNFLT) did not differ significantly from those reported mean RNFLT of both eyes (p-value=0.754, Figure S2c).

Subgroup analysis by OCT/OCTA devices revealed a significant difference between them (p-value=0.03, Figure S2d). Moreover, the statistical heterogeneity in the ZEISS subgroup was considerably decreased compared with all study I2 (30.78 vs. 86.88, respectively). For other objectives, subgroup analyses were not feasible due to the small number of studies.

Table 3 and supplementary Fig. 6 present the meta-regression results for the role of mean age and male to female ratios. Among all of the conducted meta-regressions, only the male-to-female ratio in association between IDA with FAZ perimeter and FD in SCP resulted in a considerable reduction in residual I2 (0.00 residual I2 for both).

Risk of bias assessment

Table 4A and 4B summarizes the results of the JBI checklist for cross-sectional and case-control studies. In cross sectional studies the total quality score of the included articles varied from 3 to 8. Two studies had a low risk of bias, twelve had a moderate risk, and one had a high risk of bias. The association between iron deficiency anemia and RNFLT doesn't differ significantly among high to moderate and low-quality studies, as previously mentioned. All investigations used a valid and reliable method for RNFLT assessment.

Publication bias

Egger's tests, funnel plots, and the trim and fill method were used to evaluate the publication bias (Fig. 5). Since using a funnel plot is not appropriate when there are fewer than 10 studies are available, we opted to only utilize it for assessing the association between IDA and RNFLT [42]. For the association between IDA and

Table 2 Subgroup analyses for association between IDA and various outocmes

Potential fator		**No. of Studies**	**Subgroup analysis**			
			SMD(95% CI)	**I^2**	***p*-value***	**Interaction *p* value***
Association between Iron deficiency anemia (IDA) and average retinal nerve fiber layer thickness (RNFLT)						
Study Population	Women only	3	-0.82(-1.47 to -0.17)	85.7	0.001	**0.814**
	Children only	3	-0.98(-2.01 to 0.04)	89.3	0.000	
	Not specified	8	-0.67(-1.00 to -0.34)	79.3	0.000	
Study Quality	High to moderate	12	-0.75(-1.08 to -0.42)	83.3	0.000	**0.902**
	Low	2	-0.77(-1.03 to -0.52)	0.0	**0.547**	
which eye were assessed	Mean of both eyes	2	-0.59(-1.07 to -0.11)	76.6	0.039	**0.754**
	Right	7	-0.73(-1.22 to -0.23)	86.8	0.000	
	Not reported	5	-0.84(-1.27 to -0.41)	75.9	0.002	
OCT Device	ZEISS	5	-0.56(-0.76 to -0.36)	30.78	0.000	0.03
	Heidelberg	1	-0.13(-0.62 to 0.35)	-	**0.600**	
	Optovue	3	-0.34(-0.89 to 0.20)	78.11	**0.219**	
	Nidek	2	-1.10(-1.96 to -0.25)	85.98	0.011	
	Topcon	3	-0.74(-1.01 to -0.47)	81.26	0.000	
All studies	-	14	-0.76(-1.09 to -0.44)	86.88	0.000	-

OCT: optical cogerence tomography

*p-value for test of subgroup effect size.non-significant P-values are bold.

Table 3 Meta-regressions for different variables

Variable	**Meta-regression**			
	Coefficient (95% CI)	***p*-value**	**Residual I2**	**R2(%)**
Association between IDA and average RNFLT				
Mean age	-0.03 (-0.74 to 0.006)	0.13	79.57	33.66
Male to female ratio	0.005 (-0.011 to 0.023)	0.50	86.82	0.00
Association between IDA and vascular denisty in deep capillary plexus				
Mean age	-0.008 (-0.069 to 0.052)	0.790	88.20	0.00
Male to female ratio				
Association between IDA and vascular denisty in superficial capillary plexus				
Mean age	0.16 (-0.75 to 1.08)	0.263	77.94	74.08
Male to female ratio	0.019 (-983 to 983)	1.000	100	0.00
Association between IDA and FAZ area in superficial capillary plexus				
Mean age	-0.033 (-0.07 to 0.009)	0.129	72.36	47.10
Male to female ratio	-0.024 (-0.09 to 0.048)	0.51	96.78	0.00
Association between IDA and FAZ perimeter in superficial capillary plexus				
Mean age	-0.012 (-0.045 to 0.021)	0.473	70.08	0.00
Male to female ratio	0.004 (-0.009 to 0.017)	0.548	0.00	0.00
Association between IDA and foveal density in superficial capillary plexus				
Mean age	-0.011 (-0.043 to 0.021)	0.501	68.53	0.00
Male to female ratio	0.006(-0.006 to 0.019)	0.317	0.00	0.00

CI: confidence interval; IDA: iron deficiency anemia, RNFLT: retinal nerve fiber layer thickness, FAZ: foveal avascular zone

RNFLT, the funnel plot revealed some asymmetry, and the Egger test yielded significant results. However, the trim and fill method did not detect considerable publication bias. For all other objectives, the Egger's test was nonsignificant, and the trim and fill method did not indicate publication bias. The trim and fill findings are included in Supplementary Fig. 3, along with the p value for each objective egger test.

Sensitivity analysis

Following the use of the one-out, one-remove approach, no single study had a considerable impact on the pooled estimates (Supplementary Fig. 4).

Discussion

This meta-analysis is the first study to investigate the relationship between IDA and the findings of OCT and OCTA. The findings of our study revealed a noteworthy association between IDA and the RNFLT. The RNFLT of patients with IDA showed a significant reduction in

Table 4 A. Detailed results of the risk of bias assessment of the included studies based on the JBI for cross-sectional studies

		items									
id	**study**	**Were the criteria for inclusion in the sample clearly defined?**	**Were the study subjects and the setting described in detail?**	**Was the exposure measured in a valid and reliable way?**	**Were objective, standard criteria used for measurement of the condition?**	**Were confounding factors identified?**	**Were strategies to deal with confounding factors stated?**	**Were the outcomes measured in a valid and reliable way?**	**Was appropriate statistical analysis used?**	**Overall score**	**ROB status**
1	Joshi 2023	Yes	No	Yes	Yes	UC	Yes	Yes	Yes	5/8	Moderate ROB
2	Gupta 2023	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7/8	Low ROB
3	Koca 2022	Yes	No	Yes	Yes	No	No	Yes	Yes	5/8	Moderate ROB
4	El-Gamal 2022	Yes	No	No	No	UC	No	Yes	Yes	3/8	High ROB
5	Duzgun 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low ROB
6	Samant 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6/8	Moderate ROB
7	Ugurlu 2021	UC	UC	Yes	Yes	UC	Yes	Yes	Yes	5/8	Moderate ROB
8	Hamed 2021	Yes	UC	Yes	Yes	UC	No	Yes	Yes	5/8	Moderate ROB
9	Kocer 2020	Yes	No	Yes	Yes	No	Yes	Yes	Yes	6/8	Moderate ROB
10	Korkmaz 2020	Yes	No	Yes	Yes	Yes	No	Yes	Yes	6/8	Moderate ROB
11	Kumari 2020	Yes	UC	Yes	Yes	UC	Yes	No	Yes	5/8	Moderate ROB
12	Jaiswal 2018	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7/8	Low ROB
13	Coskun 2018	Yes	No	Yes	Yes	UC	No	Yes	Yes	5/8	Moderate ROB
14	Acir 2015	Yes	No	Yes	Yes	No	Yes	Yes	Yes	6/8	Moderate ROB
15	Cikmazkara 2016	Yes	No	Yes	Yes	No	No	Yes	Yes	5/8	Moderate ROB
16	Akdogan 2014	Yes	No	Yes	Yes	No	Yes	Yes	Yes	6/8	Moderate ROB
17	Aksoy 2014	Yes	UC	Yes	Yes	No	No	Yes	Yes	5/8	Moderate ROB
18	Türkyılmaz 2013	Yes	UC	Yes	Yes	UC	No	Yes	Yes	5/8	Moderate ROB

ROB: risk of bias, UC: unclear,

Table 4 B. Detailed results of the risk of bias assessment of the included studies based on the JBI for case-control studies

id	study	items											
		Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	**Were cases and controls matched appropriately?**	**Were the same criteria used for identification of cases and controls?**	**Was exposure measured in a standard, valid and reliable way?**	**Was exposure measured in the same way for cases and controls?**	**Were confounding factors identified?**	**Were strategies to deal with confounding factors stated?**	**Were outcomes assessed in a standard, valid and reliable way for cases and controls?**	**Was the exposure period of interest long enough to be meaningful?**	**Was appropriate statistical analysis used?**	**Overall score**	**ROB status**
1	Wu 2024	Yes	NA	Yes	UC	Yes	UC	No	Yes	Yes	Yes	6/10	Moderate ROB

ROB: risk of bias, UC: unclear, NA: not applicable

comparison to individuals without the condition. The inferior region exhibited the greatest decline in retinal nerve fiber layer, whereas the superior region showed the least decrease. Furthermore, we found a considerable decrease in the area and perimeter of FAZ, foveal VD, and vascular density of the SCP and DCP in patients with IDA.

Most meta-analyses showed moderate to severe heterogeneity, rendering our results inconclusive. We attempted to address this issue by subgroup analysis and meta-regression on several variables. Among all the variables we have evaluated, OCT/OCTA device in association with IDA and average RNFLT, male to female ratio in association with IDA with FAZ perimeter and FD in SCP could explain the high heterogeneity observed in these items, along with a considerable reduced I2 and a step towards more conclusive findings. In addition, after subgroup analysis based on OCT/OCTA devices, we observed significant differences between subgroups. This emphasizes that interpretation of OCT/OCTA results is highly dependent on the device when analyzing findings.

IDA is a common global health concern, affecting individuals of all ages. It affects about 35% of the world's population, making it a significant public health concern [43]. Studies have highlighted the economic and human capital losses associated with IDA, further emphasizing its importance [44].

The differences in OCT and OCTA findings between individuals with IDA and healthy controls potentially offer a valuable tool for clinical monitoring. Additionally, these findings could have a substantial impact, as these pseudo-glaucomatous alterations may be mistakenly identified as glaucoma or other neuroophthalmological conditions [13].

The current meta-analysis study possesses several limitations that must be taken into account when interpreting the results. First, all of the studies included in the current meta-analysis were observational in nature. These studies are limited in nature and cannot account for all confounding factors, making it impossible to adequately prove causal correlations. The findings of this study should be validated through the cohorts. Second, clinical trials are necessary to determine whether these changes can be reversed through iron supplementation.

In addition, the included studies did not provide information regarding the duration and severity of anemia. We were unable to evaluate the differences between acute and chronic anemia, as well as mild and severe anemia. This can also be achieved through cohort studies.

Third, we were unable to conduct meta-analyses on FAZ parameters in the DCP due to insufficient data. The study was also limited by moderate to severe heterogeneity in most of the meta-analysis. While we tried to resolve this issue using subgroup analysis and meta-regression,

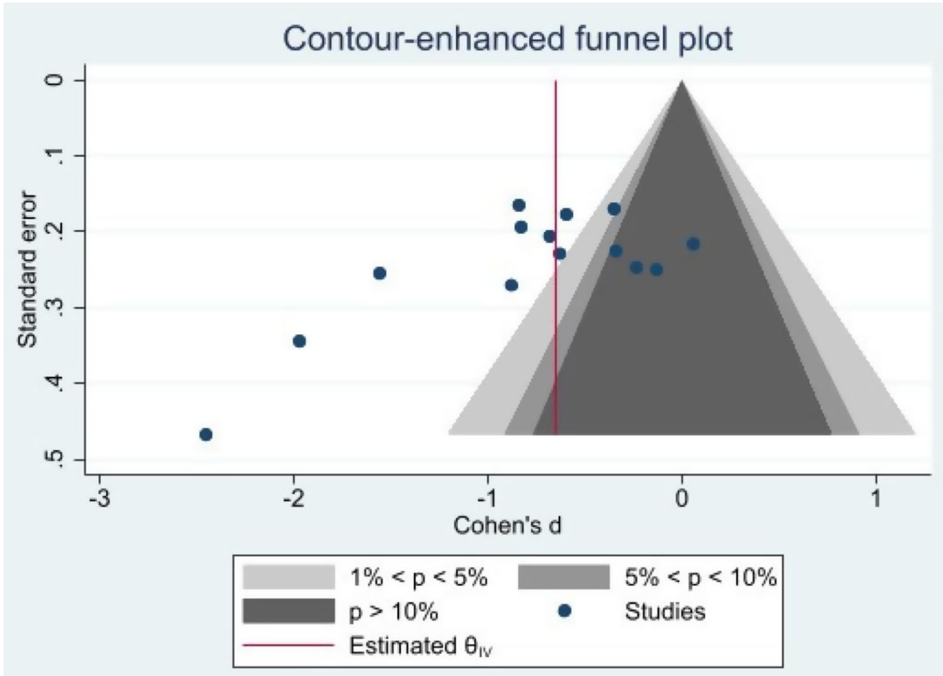

Fig. 5 Publication bias assessment. Association between IDA and average RNFLT

we found few variables that justified the high heterogeneity observed. Therefore, scientists working in these fields are encouraged to report more covariates and confounders when describing associations between IDA and OCT/OCTA findings. By doing this, we can evaluate the effect of heterogeneity on more variables in future meta-analyses. It is therefore necessary to conduct more studies in order to reach a more definitive conclusion.

Conclusion

The results of this meta-analysis demonstrated that, in comparison with healthy controls, individuals with iron deficiency anemia had thinner retinal nerve fiber layers, smaller foveal avascular zones, and lower vessel densities. These studies show that other scientists and clinicians should pay more attention to the alterations in the retina of individuals with iron deficient anemia. However, further studies are needed to reach conclusive results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12886-024-03751-9.

Supplementary Material 1

Acknowledgements
The author acknowledges Clinical Research Development Unit of Torfeh Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, which have been invaluable in the completion of this research.

Author contributions
Conceptualization: HN, MG; Data curation: MG, AG, SZ, SK; Formal analysis: MM, HN; Methodology: HN, MM, AG ; Project administration: HN, MG ; Visualization: MG ; Writing - original draft: HN, MG, AG, SZ, SK, AKS; Writing - review & editing: HN, MG, AG, SZ, SK, AKS. All authors read and approved the final version of manuscript.

Funding
There are no funds allocated for our project.

Data availability
The datasets used and/or analysed during the current study available from the corresponding author or first author on reasonable request.

Declarations

Ethics approval and consent to participate
There are no ethical considerations associated with this review. Ethical approval is not required because this protocol does not involve any individuals directly.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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Received: 14 April 2024 / Accepted: 29 October 2024
Published online: 05 November 2024

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