• Meta-Analysis •

Increased vitreal levels of interleukin-10 in diabetic retinopathy: a Meta-analysis

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Abstract

● **AIM:** To conduct a Meta-analysis for the change of interleukin-10 (IL-10) concentration in vitreous samples of patients with diabetic retinopathy (DR).

● **METHODS:** Systemic search for literature was conducted from the databases of PubMed, Web of Science and Cochrane Library by August 2019. Statistical analyses including standard mean difference (SMD) and its 95% confidence interval (CI) were performed by using RevMan 5.3 software.

● **RESULTS:** Totally 194 studies were screened and finally 11 studies were included in the Meta-analysis. The concentration of IL-10 in the DR group was higher than in the control group (P=0.003, SMD: 0.77, 95%CI: 0.25-1.28). Significant heterogeneity was found among all studies (P<0.00001, I^2=92%). The subgroup analysis showed that the concentration of IL-10 increased in vitreous samples from patients with DR compared to the non-DR controls (P=0.004, SMD: 1.44, 95%CI: 0.46-2.42). Moreover, the concentration of IL-10 in samples of proliferative diabetic retinopathy (PDR) patients was significantly higher than that of non-proliferative diabetic retinopathy (NPDR) patients (P=0.01, SMD: 0.61, 95%CI: 0.13-1.08).

● **CONCLUSION:** The vitreal concentration of IL-10 is significantly increased in patients with DR. Further studies are needed to reveal the mechanisms of IL-10 in DR.

● **KEYWORDS:** diabetic retinopathy; interleukin-10; Meta-analysis; vitreal concentration
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INTRODUCTION

Diabetic retinopathy (DR) is one of the governing causes of visual impairment or even blindness[1-3], and diabetes patients have 2.4 times higher risk of blindness than those without diabetes[4]. DR could be divided into proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) based on the stage of development and severity[5]. Changes in the structure and function of retinal microcirculation are the basic pathological processes of DR[6]. The blood-retinal barrier could be destroyed by high levels of cytokines and inflammatory mediators[7]. Thus, inflammation is considered to be mainly involved in DR pathogenesis. The normal expression of vascular endothelial growth factor (VEGF) could maintain the functional and structural homeostasis of cells in the retina. However, under the influence of pathological factors, overexpression of VEGF may cause retinal angiogenesis[7-9]. It has been proved that intravitreal injection of anti-VEGF agents could lead to the inhibition of retinal neovascularization[10]. Therefore, it is critical to understand the relationship between pathological neovascularization and microvascular degeneration in the pathophysiology of DR, especially for developing new drugs to improve therapeutic efficacy[11].

It is known that the expression of inflammatory mediators are involved in the progression of DR[12]. For instance, it has been indicated that the level of interleukin-6 (IL-6) generally increased in patients with DR, and also identified the association of the increased levels and the severity of DR[13]. Interleukin-10 (IL-10), also known as cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine that suppresses T helper (Th) 1 responses and enhances Th2 responses[14]. IL-10 has been proved to enhance pathological retinal angiogenesis *via* regulation of macrophage response to hypoxia[15]. IL-10 and its downstream STAT3 signaling activity play a conducive role in regulating the phenotype of aging macrophage in the eye, mainly promoting M2 polarization and new blood vessel formation[16]. An early study revealed that

IL-10 promotes laser-induced choroidal neovascularization (CNV) by suppressing macrophage recruitment and infiltration to neovascular complexes[17]. Interestingly, Wu *et al*[18] revealed that IL-10 only inhibits VEGF that generated by M1 macrophages, not M2 phenotype, suggested that macrophage polarization and hypoxia might be involved in the angiogenic regulation by IL-10. There is also a study showing that IL-10 inhibits inflammation, and suppresses retinal pigment epithelial cells proliferation and migration by regulating VEGF in rhegmatogenous retinal detachment[19].

Therefore, the role of IL-10 in DR belongs to complicated immunological mechanisms and remains unclear. In this study, we assess the relationship between DR and IL-10 concentration in different kinds of samples from patients with DR and controls through Meta-analysis, and aim to provide a therapeutic target for treating DR patients.

MATERIALS AND METHODS

Search Strategy Comprehensive literature searched from PubMed, Web of Science and Cochrane Library (August 2, 2019), by using the keywords: "IL-10" OR "IL10" OR "IL 10" OR "interleukin-10" OR "interleukin10" OR "interleukin 10" connected with "diabetic retinopathy". We only selected articles written in English. We also evaluated other relevant references cited in the qualified literature.

Criteria of Inclusion and Exclusion We contained qualified literature in this Meta-analysis from the following aspects: 1) the investigation must include the DR group and the control group; 2) IL-10 concentration is available; 3) experiment based on human samples; 4) the literature is presented in English. We excluded the literature according to the following aspects: 1) the studies does not provide mean and standard deviation (SD) even more send an email asking for no results; 2) not find full-text; 3) literature that does not indicate cytokine concentration; 4) the articles provide incomplete data; 5) died sample; 6) previous surgical treatment in vitreous.

Besides, patients and controls with ocular diseases such as uveitis which might largely influence the experimental results were excluded in the Meta-analysis.

Quality Assessment and Data Extraction Two authors (Tan W and Zou JL) respectively extracted the data from the following aspects: first author, publish year, country, types of diabetic mellitus (DM), sample source, study methods, IL-10 concentration, ages, gender ratio. Two reviewers (Tan W and Zou JL) respectively assess all the studies by using the Newcastle Ottawa Scale (NOS)[20]. The NOS system is composed of 3 aspects, including selection (4 points), comparability (2 points), and exposure (3 points). The higher scores stand for better qualities. We only choose articles that are higher than 5 points for further analysis.

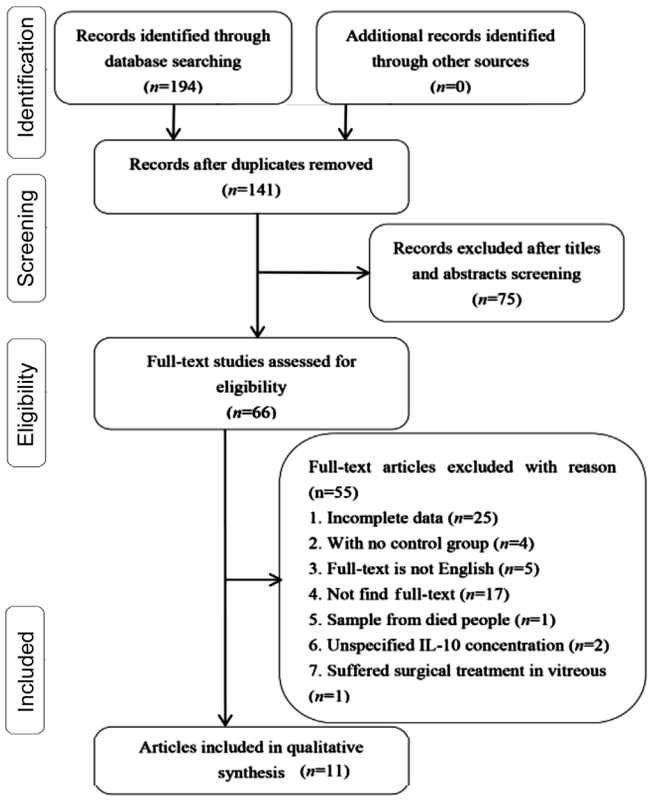

Figure 1 Flowchart of the study selection.

Statistical Analysis The Meta-analysis was conducted by applying RevMan 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark). *P*-values of less than 0.05 ($P<0.05$) were considered as statistically significant. A random-effect model was used for analysis if we observed high heterogeneity ($P<0.10$, $I^2>50\%$). If there was no significant heterogeneity ($P>0.10$, $I^2<50\%$), we used a fixed-effect model. Microsoft Excel software was used to combine the data from different subgroups when necessary. When a study gave a standard error of the mean (SEM), we used the formula to convert it to SD. Potential publication bias was analyzed by the funnel plot, and followed by Begg's test and Egger's test by Stata 12.0 software (Stata Corp, College Station, Texas, USA).

RESULTS

Literature Selection The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[21]. A total of 194 articles were included, from PubMed, Web of Science and Cochrane Library (August 2, 2019). After excluding 53 duplicates, we screened the titles and abstracts, and excluded 75 articles. Then, according to full-text, 55 articles were excluded. Finally, we obtained 11 studies for Meta-analysis. The process of selection was summarized in the flowchart (Figure 1).

Characteristics and Quality Assessment of the Studies Eleven studies were summarized and analyzed in Table 1, including gender, age, country, DM type and sample origin. The samples research method basically includes multiplex

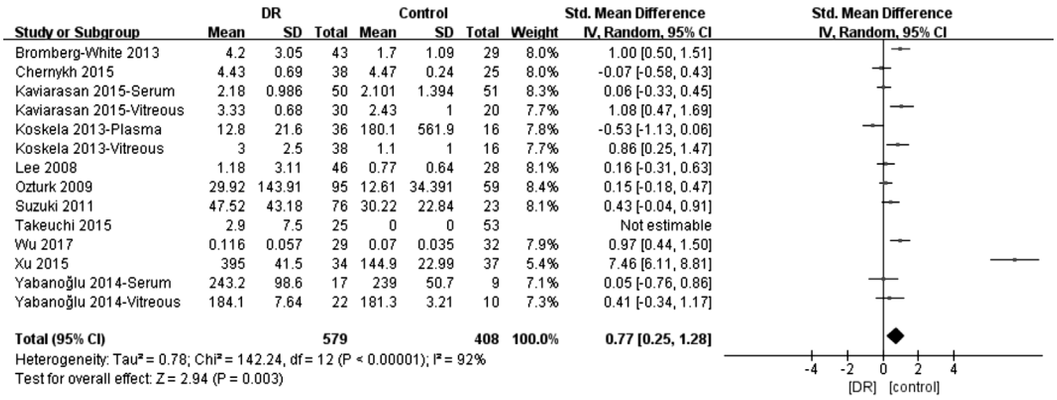

Figure 2 IL-10 level in samples of DR patients compared to controls in the included studies.

Table 1 Characteristics of the included studies in the Meta-analysis

First author	Year	Country	DM type	Sample	Age (y)		Gender (M, F)		No. of samples	
					DR	Control	DR	Control	DR	Control
Bromberg-White	2013	USA	NA	Vitreous	58±11	71±7	22, 21	10, 19	43	29
Chernykh	2015	Russia	NA	Vitreous	50.5±3.2	53.5±2.6	16, 22	13, 12	38	25
Kaviarasan	2015	Indian	2	Serum	55±9.08	47.5±10.93	35, 26	43, 14	61	57
				Vitreous			NA	NA	30	20
Koskela	2013	Finland	Both	Vitreous	59.4±14.3	66.6±9.3	17, 21	5, 11	38	16
				Plasma			NA	5, 11	36	16
Lee	2008	Korea	2	Plasma	59.87±9.00	58.00±8.59	13, 15	24, 22	28	46
Ozturk	2009	Turkey	2	Serum	62.09±7.26	64.04±8.84	39, 56	26, 33	95	59
Suzuki	2011	Japan	NA	Vitreous	57.6±13.6	69.29±10.14	25, 31	7, 33	56	40
Takeuchi	2015	Japan	2	Vitreous	57.0±13.7	64.53±9.8	18, 7	22, 31	25	53
Wu	2017	China	2	Aqueous humor	66.48	69.25	13, 16	8, 24	29	32
Xu	2015	China	NA	Vitreous	52.12±1.474	52.14±2.063	15, 19	22, 15	34	37
Yabanoğlu	2014	Turkey	2	Serum	58±10.5	62.7±7.8	6, 11	NA	17	9
				Vitreous			9, 13	2, 9	22	11

DM: Diabetic mellitus; DR: Diabetic retinopathy; NA: Not available.

bead immunoassay, enzyme-linked immunoassay, the Bio-Plex kit, *etc*. Using NOS evaluate the quality assessment of all studies in Table 2. Six studies[22-27] scored 6, 3 studies[28-30] scored 7, 2 studies[31-32] scored 8. Three studies used samples from serum[27,31-32], 2 studies from plasma[23,29], 8 studies from vitreous[22-28,31] and 1 from aqueous humor[30].

Meta-analysis of IL-10 Concentration in Patients with DR Based on all the included studies, the concentration of IL-10 in samples between the DR group and the control group showed significant heterogeneity (P<0.00001, I^2=92%), and we selected the random-effect model. The Meta-analysis (Figure 2) observed that the concentration of IL-10 in the DR group was significantly higher compared to the control group (SMD: 0.77, 95%CI: 0.25 to 1.28, P=0.003).

Subgroup Analyses Subgroup analyses were conducted by sample source and DR type, respectively (Table 3). According to the sample source subgroups, IL-10 increased significantly in vitreous from patients with DR compared with the controls (SMD: 1.44, 95%CI: 0.46 to 2.42, P=0.004; Figure 3A).

Table 2 Newcastle-Ottawa scale scores of the included studies

Study	Selection	Comparability	Exposure	Total score
Bromberg-White *et al*, 2013	3	2	2	7
Chernykh *et al*, 2015	3	1	2	6
Kaviarasan *et al*, 2015	4	2	2	8
Koskela *et al*, 2013	3	1	2	6
Lee *et al*, 2008	3	2	2	7
Ozturk *et al*, 2009	4	2	2	8
Suzuki *et al*, 2011	3	1	2	6
Takeuchi *et al*, 2015	3	1	2	6
Wu *et al*, 2017	3	2	2	7
Xu *et al*, 2015	3	1	2	6
Yabanoğlu *et al*, 2014	3	1	2	6

Aqueous humor samples had significant difference (SMD: 0.97, 95%CI: 0.44 to 1.50, P=0.0004), but there was only one study included (Figure 3B). On the other hand, no significant difference was found in serum (SMD: 0.11, 95%CI: -0.13 to

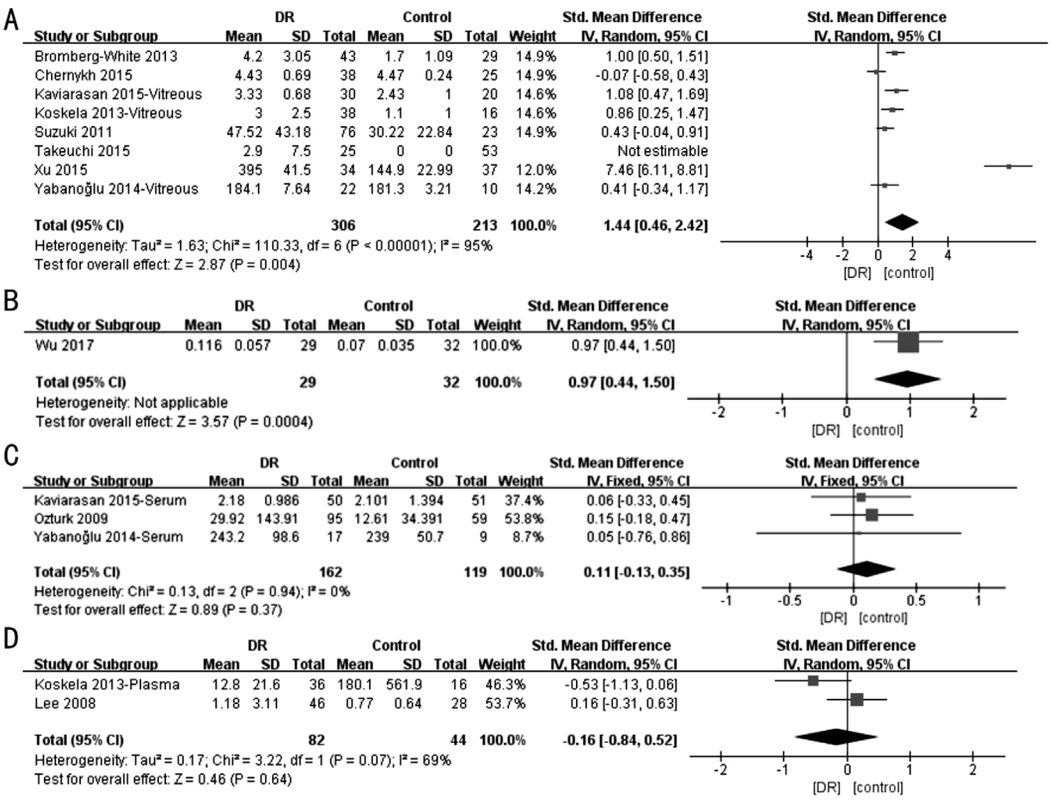

Figure 3 Subgroup analyses of IL-10 level in DR according to sample source A: Vitreous; B: Aqueous humor; C: Serum; D: Plasma.

Table 3 Subgroup analyses according to sample source and DR type

Subgroups	*n*		SMD (95%CI)	*P*	Test of heterogeneity	
					I^2 (%)	*P*
Sample source	DR	Control				
Vitreous	306	213	1.44 (0.46, 2.42)	0.004	95	<0.00001
Aqueous humor	29	32	0.97 (0.44, 1.50)	0.0004	Not applicable	Not applicable
Serum	162	119	0.11 (-0.13, 0.35)	0.37	0	0.94
Plasma	82	44	-0.16 (-0.84, 0.52)	0.64	69	0.07
DR type	PDR	NPDR				
PDR+NPDR	92	128	0.61 (0.13, 1.08)	0.01	58	0.07

SMD: Standard mean difference; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy.

0.35, *P*=0.37) and plasma (SMD: -0.16, 95%CI: -0.84 to 0.52, *P*=0.64) samples (Figure 3C, 3D). Significant heterogeneity was existed in the analyses of vitreous (*P*<0.00001, I^2=95%) and plasma (*P*=0.07, I^2=69%), but not in the analysis of serum (*P*=0.94, I^2=0). Data of patients with DR from 4 studies can be subdivided into PDR and NPDR groups (Figure 4). According to the Meta-analysis, IL-10 concentration was upregulated in PDR patients compared with NPDR patients (SMD: 0.61, 95%CI: 0.13 to 1.08, *P*=0.01), and significant heterogeneity was existed (*P*=0.07, I^2=58%).

Assessment of Publication Bias Publication bias was firstly assessed by a funnel plot (Figure 5), which was not symmetry. Then we estimated by Begg's test and Egger's test. The results showed there might be publication bias (Begg's test: *P*=0.300, Egger's test: *P*=0.026).

Sensitivity Analysis To prove the reliability, we performed a sensitivity analysis in Table 4. Each study was individually excluded to ensure that each item met the objectives of the study. The value of SMD ranged from 0.38 to 0.87 in a sensitivity analysis comparing IL-10 levels in both DR and control groups by excluding one article at a time. The range of lower limits of 95%CI was from 0.11 to 0.34, and the upper limit was from 0.65 to 1.42. The I^2 values remained significant heterogeneity. Therefore, this sensitivity analysis suggested that the results of the study are stable and reliable.

DISCUSSION

DR, the microvascular complication of diabetes, is a blinding eye disease that affects life quality in adults[33-35]. Studies have shown that the prevalence of DR in diabetic patients is about one-third or higher[36]. The number of patients

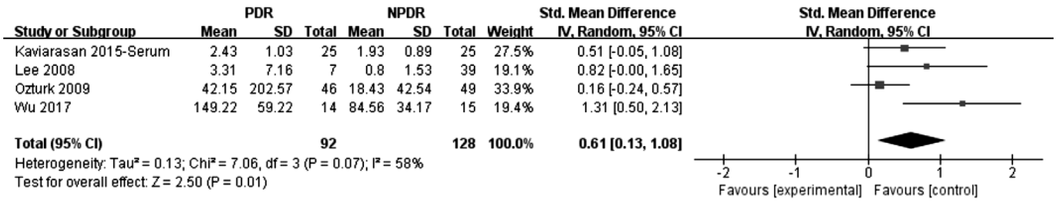

Figure 4 Subgroup analysis of IL-10 level according to DR type.

Table 4 Sensitivity analysis

Study	SMD (95%CI)	Heterogeneity	I^2 (%)
Bromberg-White *et al*, 2013	0.75 (0.20, 1.30)	*P*<0.00001	92
Chernykh *et al*, 2015	0.85 (0.30, 1.40)	*P*<0.00001	92
Kaviarasan *et al*, 2015-serum	0.84 (0.28, 1.41)	*P*<0.00001	92
Kaviarasan *et al*, 2015-vitreous	0.74 (0.20, 1.28)	*P*<0.00001	92
Koskela *et al*, 2013-plasma	0.87 (0.34, 1.40)	*P*<0.00001	92
Koskela *et al*, 2013-vitreous	0.76 (0.22, 1.31)	*P*<0.00001	92
Lee *et al*, 2008	0.83 (0.27, 1.39)	*P*<0.00001	92
Ozturk *et al*, 2009	0.84 (0.26, 1.42)	*P*<0.00001	92
Suzuki *et al*, 2011	0.81 (0.25, 1.37)	*P*<0.00001	92
Takeuchi *et al*, 2015	0.77 (0.25, 1.28)	*P*<0.00001	92
Wu *et al*, 2017	0.75 (0.21, 1.30)	*P*<0.00001	92
Xu *et al*, 2015	0.38 (0.11, 0.65)	*P*=0.0002	69
Yabanoğlu *et al*, 2014-serum	0.82 (0.29, 1.36)	*P*<0.00001	92
Yabanoğlu *et al*, 2014-vitreous	0.80 (0.26, 1.34)	*P*<0.00001	92

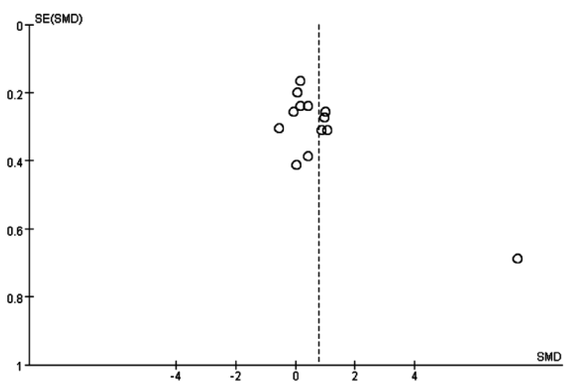

Figure 5 Assessment of publication bias. A funnel plot analysis of all included samples.

with type 2 diabetes is increasing in both developed and developing countries, which may lead to an increase in DR[37]. Inflammatory factors play an essential role in the progression of diabetes[38]. In addition to elevated levels of pro-inflammatory cytokines like IL-1 and IL-6, chemokines such as macrophage inflammatory protein-1β, interferon gamma-induced protein 10, and IL-8 were also elevated in PDR[39]. Meanwhile, it also produces anti-inflammatory cytokines such as IL-10 that regulate the inflammatory process. IL-10 is mainly produced by monocytes and has an inactivated property against macrophages[32,40]. IL-10 can inhibit antigen presentation by suppressing MHC-II expression in antigen-presenting cells[38]. At present, some literatures have been found to study the relationship between IL-10 and DR. Myśliwiec *et al*[41] suggested that in type 1 diabetes patients with different stages of DR, IL-10 levels allow for higher secretion activity and appear to be associated with protective functions for the progression of advanced diabetic complications. Suzuki *et al*[24] and Takeuchi *et al*[25] found that significantly elevated levels of IL-10 were detected in the vitreous of DR patients, but those studies did not analyze plasma samples. On the other hand, however, Wang *et al*[38] discovered that IL-10 was suppressed in peripheral B cells of patients with DR. Chernykh *et al*[22] did not found any significant change in the concentration of IL-10 in patients with DR. Therefore, further studies about the functions and mechanisms of IL-10 in DR are needed.

This Meta-analysis included 11 literature with 987 participants indicating that the IL-10 levels were higher in the DR group than in the control group. To better explain these results, we conducted subgroup analyses. First of all, we performed subgroup analyses according to sample sources. We recognized that the vitreous-derived samples and the aqueous humor-derived sample showed a significant increase in IL-10 concentration, while its concentrations in serum and plasma did not change significantly. As Figure 2 shows, in Takeuchi *et al*'s study[25], IL-10 was not detected from all of the vitreous samples in the control group, the data was not included in the

calculated results of Meta-analysis. However, the trend of that study also supported the increase of IL-10 in vitreous from patients with DR.

Wu *et al*[30] found that the concentration of IL-10 gradually increases as the degree of DR increases. Thus, we performed a subgroup analysis based on the types of DR, and the outcomes showed a significant difference between the PDR group and the NPDR group.

Nevertheless, some limitations still remain in this Meta-analysis. For example, the majority of the control samples were collected from the hospital, thus selection bias could not be avoided. Besides, the number of included studies is not large enough. Moreover, significant heterogeneity and publication bias may be existed, while sensitivity analysis showed that sequentially omitting one study did not change the conclusion of the Meta-analysis. Despite these shortcomings, we still believe that the Meta-analysis could provide valuable evidence for the clinical significance of IL-10 in patients with DR.

According to the Meta-analysis, the concentration of IL-10 was significantly higher in the samples of DR group compared to the control group, particularly in vitreous samples. Further investigations are needed to reveal the roles and mechanisms of IL-10 in DR pathogenesis.

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