• Meta-Analysis •

The relationship of blood cell-associated inflammatory indices and diabetic retinopathy: a Meta-analysis and systematic review

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Abstract

• AIM: To explore the correlation between several blood cell-associated inflammatory indices including mean platelet volume (MPV), platelet distribution width (PDW), neutrophil to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), and the presence and severity of diabetic retinopathy (DR).

• METHODS: We searched for eligible studies from PubMed, EMBASE, Web of Science and CNKI up to December 13, 2017. Standardized mean difference (SMD) calculated with confidence interval (CI) of 95% was used to estimate the values of those indices.

• RESULTS: A total of 31 studies were included in the present Meta-analysis. As compared with type 2 diabetes mellitus (T2DM) patients without DR, the values of MPV, PDW, NLR, and PLR were higher in patients with DR (SMD=0.67; 95%CI: 0.36 to 0.98; SMD=0.51; 95%CI: 0.27 to 0.75; SMD=0.77; 95%CI: 0.49 to 1.05 and SMD=1.18; 95%CI: 0.07 to 2.28). Additionally, it was also observed that MPV was closely correlated with the severity of DR.

• CONCLUSION: MPV, PDW, NLR, and PLR could be recommended as diagnostic biomarkers for DR, and MPV could be applied to assess the severity of DR.

• KEYWORDS: mean platelet volume; platelet distribution width; neutrophil to lymphocyte ratio; platelet-lymphocyte ratio; diabetic retinopathy

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INTRODUCTION

Diabetes mellitus is a heavy burden worldwide, the morbidity and mortality of which keep growing in recent years[1-2]. Diabetes, as a system metabolic disorder disease, is always involved in the injury of many organs and tissues, leading to various micro- and macrovascular complications. Diabetic retinopathy (DR) is one of the most common microangiopathies in patients with type 2 diabetes mellitus (T2DM) and can be divided into the "no-proliferative diabetic retinopathy" (NPDR) and the "proliferative diabetic retinopathy" (PDR) according to its severity[3]. According to the World Health Organization (WHO), DR accounts for 4.8% of the number of cases of blindness (37 million) globally[4]. It is widely accepted that screening, early detection and prompt treatment of vision-threatening DR largely contribute to preventing diabetes-associated visual impairment or loss[5-7]. Nevertheless, until now DR screening services are still at uneven levels between developing and developed countries, and there are no definite guidelines regarding the optimal screen method, which makes it urgent and imperative to develop cost-effective comprehensive screening programs based on DR epidemiology and economical condition of community[5-7]. It has been proposed that diabetes duration, the duration of hyperglycemia, gene polymorphism, aberrant blood lipid levels, obesity, hypertension, and smoking may all contribute to the development and progression of DR[7-8]. Besides, functional and structural changes in retinal arterioles was also been considered as a risk factor for DR as well[9].

Accumulating evidence implicates that several blood cell-associated indices, including mean platelet volume (MPV), platelet distribution width (PDW), neutrophil to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are potential novel biomarkers of systemic inflammatory responses[10-13]. MPV is a parameter reflecting the average size of platelets and high MPV indicates that platelets have large size. Larger platelets usually display more metabolic and enzymatic activities and release more thromboxan-A_2, b-thromboglobulin, and adhesion molecules as compared to the smaller size[14-15]. It has been reported that high MPV might be the risk for some vascular conditions, including peripheral artery disease, coronary artery disease, myocardial infarction and cerebral

ischemia[16]. PDW is an indicator of the distribution of platelet size, and its high value indicates the increased production of larger reticulated platelet. Moreover, PDW may also play a considerable role in some vascular diseases, such as atherosclerosis and thrombosis[17]. Additionally, numerous studies has shown that the NLR and PLR are potential inflammatory biomarkers in tumors[18-23], cardiovascular diseases[24-25]. More importantly, in recent years, many studies have also investigated the association of MPV, PDW, NLR and PLR with DR[26-56]. However, the results of those studies in this regard were inconsistent. Considering that the small sample size in a single study might challenge the statistical power, we herein performed the first Meta-analysis and systematic review to further the relationship of MPV, PDW, NLR and PLR to the presence of DR and its severity.

MATERIALS AND METHODS

Search Strategy This Meta-analysis was performed according to Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines[57]. The database of PubMed, EMBASE, Web of Science and CNKI were systematically search for potential eligible studies up to December 13, 2017. The search terms included: "neutrophil to lymphocyte ratio or NLR", "platelet-lymphocyte ratio or PLR", "platelet distribution width or PDW", "mean platelet volume or MPV", "hematological or hematologic" and "marker or indices" and "diabetic retinopathy". The limitations of language and region were not applied in this Meta-analysis.

Selection Criteria The criteria for eligible studies included the following points: 1) Enrolled patients of the studies were diagnosed with T2DM; 2) Observational or retrospective study design; 3) The data of hematologic inflammatory markers were available including MPV, PDW, NLR and PLR. Exclusion criteria of selection process were as follows: 1) Reviews, letters, editorials, meeting abstracts and case reports; 2) Data were unavailable; 3) If there are overlapping patients in different studies, the earlier published one was excluded.

Data Collection and Quality Assessment Two independent investigators extracted all the data from the eligible literatures, and divergences in data extraction were resolved by discussion between the authors. The collected data included: name of first author, publication year, study design, country, the number of patients, mean age and sex in each group, values of MPV, PDW, NLR, and PLR. The quality of eligible studies was evaluated according to the Newcastle-Ottawa Scale (NOS)[58], which comprises eight points with three aspects: selection, comparability, and exposure. The scores of NOS system range from 0 to 9, and studies with 6 scores or more are considered as high quality[58].

Data Analysis STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used to conducted the statistical analysis. Standardized mean difference (SMD) and its 95% confidence interval (CI) was used to describe the synthesized continuous variables. If the data of hematologic inflammatory markers were both presented in NPDR and PDR patients, the data in NPDR was used in the comparison with DM group. With 95%CI not crossing 0, SMD>0 indicated that the specific hematologic inflammatory marker increased in patients with DR. In addition, Cochrane Q test (χ^2) and I^2 statistic were used to assess the statistical heterogeneity among the included studies. If P<0.01 for Q test and/or I^2>50% for I^2 statistic, the heterogeneity of the synthesized SMD was considered statistically significant, then a random effects model was used to pool the data, otherwise, a fixed effects model was employed for analysis. In order to testify the stabilization of our results, sensitivity analysis was conducted by sequentially dropping single study to investigate the effect of each individual article on the synthesized SMD. Publication bias was detected by Begg's test and Egger's test[59-60]. P<0.01 for Begg's test or Egger's test indicates that significant publication bias might exist. Furthermore, when there was significant publication bias, Duval's nonparametric trim-and-fill method was carried out to assess the potential influence of publication bias on the pooled results in this Meta-analysis[61].

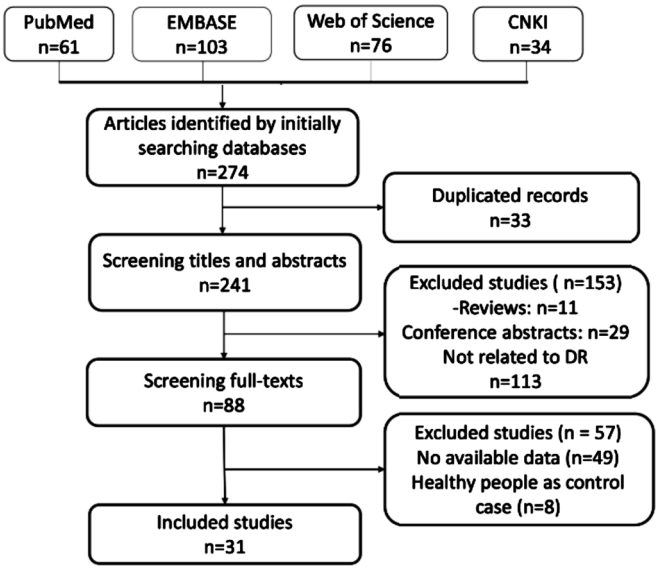

Figure 1 Flow chart of study selection process.

RESULTS

Search Results A total of 668 potential articles were yielded after primary literatures searching for PubMed, EMBASE, Web of Science and CNKI. After removing 156 duplicated studies, 560 were left for title and abstract screening. After omitting reviews, letters, editorials, meeting abstracts, case reports and articles not pertinent T2DM, 234 articles were excluded. Subsequently, full-text review was performed for remaining 60 articles, 56 articles were removed according to our selection criteria. Eventually, 31 articles with 5126 patients were included in this Meta-analysis[26-56]. All the details of literatures screening process were shown in Figure 1.

Table 1 The main characteristics of the included studies on DR

First author	Year	Study design	Country	No. of patients			Age mean/median	Male/female	NOS
				Non-DR	NPDR	PDR			
Akdoğan[26]	2016	Retrospective	Turkey	158		120	Non-DR: 57.3±12.2 DR: 59.8±9.2	Non-DR: 59/99 DR: 47/73	7
Ateş[27]	2009	Retrospective	Turkey	30	30	30	NR	NR	5
Buch[29]	2017	Retrospective	India	220		80	NR	NR	6
Citirik[30]	2015	Prospective	Turkey	43	45	52	Non-DR: 60.4±8.5 NPDR: 61.4±9.3 PDR: 59.4±7.2	Non-DR: 22/21 NPDR: 17/28 PDR: 20/32	6
Demirtas[31]	2015	Prospective	Turkey	240		67	NR	NR	6
Dindar[32]	2013	Retrospective	Turkey	36		24	NR	NR	6
Güngör[33]	2016	Retrospective	Turkey	50		52	NR	Non-DR: 19/31 DR: 18/34	6
Li[34]	2014	Retrospective	China	72	67	70	Non-DR: 54.2±9.2 NPDR: 57.7± 10.0 PDR: 58.3±9.4	Non-DR: 35/37 NPDR: 34/33 PDR: 33/37	7
Li[47]	2013	Retrospective	China	103		132	NR	NR	6
Li[35]	2016	Retrospective	China	52		47	Non-DR: 55.1±15.2 DR: 54.1±10.8	Non-DR: 31/21 DR: 26/21	6
Ma[36]	2017	Retrospective	China	20	20	20	Non-DR: 57.3±6.5 NPDR: 60.8±7.3 PDR: 57.6±7.3	Non-DR: 12/8 NPDR: 8/12 PDR: 12/8	5
Niu[37]	2013	Retrospective	China	20		25	Non-DR: 46.5±8.3 DR: 51.2±8.3	Non-DR: 12/8 DR: 13/12	6
Papanas[38]	2004	Retrospective	Greece	89		167	NR	NR	6
Radha[39]	2016	Retrospective	India	30		14	NR	NR	5
Sheng[40]	2017	Retrospective	China	102		102	NR	NR	7
Tetikoğlu[41]	2016	Retrospective	Turkey	63	56	80	NR	NR	6
Tuzcu[28]	2014	Retrospective	Turkey	70	64	58	Non-DR: 55.8±10.5 NPDR: 60.1±8.6 PDR: 57.5±9.3	Non-DR: 38/32 NPDR: 32/32 PDR: 31/27	6
Wei[42]	2017	Retrospective	China	94	52	40	Non-DR: 58.14±11.93 DR: 58.42±12.09	Non-DR: 50/44 DR: 49/43	7
Xu[43]	2012	Retrospective	China	45		40	NR	Non-DR: 23/22 DR: 26/14	5
Yilmaz[44]	2016	Prospective	Turkey	89	88	86	Non-DR: 60.9±6.3 NPDR: 62.7±7.2 PDR: 61.7±7.9	Non-DR: 49/40 NPDR: 48/40 PDR: 49/37	7
Yu[48]	2000	Retrospective	China	60		40	NR	NR	6
Yue[45]	2015	Retrospective	China	125	62	59	Non-DR: 56.00±3.75 NPDR: 53.50±3.56 PDR: 56.0±3	Non-DR: 73/52 NPDR: 34/28 PDR: 28/3	6
Zhang[49]	2002	Retrospective	China	20		20	Non-DR: 58.0±9.0 DR: 60.0±1.3	Non-DR: 9/11 DR: 8/12	5
Zhou[46]	2016	Retrospective	China	328		51	Non-DR: 57±16 DR: 63±15	Non-DR: 198/130 DR: 34/17	6

DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NR: Not reported; NOS: Newcastle-Ottawa Scale.

Study Characteristics and Quality Assessment All the eligible studies were published from 2000 to 2017. The sample size of the included studies in DM group and in DR group ranged from 20 to 328 and 20 to 192, respectively. Only 3 studies were prospectively designed[30-31,44], and the other studies were retrospectively designed. A total of 16 articles came from China[34-37,40,42-43,45-49,51-52,54-55], 11 articles were conducted in Turkey[26-33,41,44,56], 2 papers were from India, and 2 articles were performed in Greece[38]and Kazakhstan[50], respectively. Of the 31 included articles, 23 reported MPV[26-34,35-44,46-49], 12 reported PDW[26,29-30,35-37,40-44,48], 10 reported NLR[26,45-46,50-56], and 3 reported PLR[26,42,45]. All the basic characteristics and the values of these hematological indices of the included studies were summarized in Tables 1-4. According to the NOS, we evaluated the quality of 31 included studies. Only 4 articles scored 5[27,36,39,49], and the scores of the rest of studies varied from 6 to 7, indicating that most of the eligible studies were high-quality.

Meta-analysis Results

The relationship between mean platelet volume and the presence of diabetic retinopathy A total of 23 studies with 3437 patients reporting the data of MPV were included in

Table 2 The main characteristics of the included studies on the relationship of NLR and PLR to DR

First author	Year	Study design	Country	No. of patients			Age mean/median	Male/female	NOS
				Non-DR	NPDR	PDR			
Akdoğan[26]	2016	Retrospective	Turkey	158	120		Non-DR: 57.3±12.2 DR: 59.8±9.2	Non-DR: 59/99 DR: 47/73	7
Ciray[50]	2015	Retrospective	Kazakhstan	59	55		Non-DR: 57.8±11.5 DR: 61.8±10.8	NR	6
Kuang[51]	2015	Retrospective	China	62	44	22	Non-DR: 60.73±11.24 NPDR: 60.50±8.45 PDR: 55.18±13.05	Non-DR: 29/33 NPDR: 17/27 PDR: 11/11	6
Öztürk[56]	2013	Retrospective	Turkey	97	79	NR	NR	NR	5
Shen[52]	2016	Retrospective	China	118	134	58	Non-DR: 55.19±5.51 NPDR: 58.04±7.53 PDR: 59.84±8.76	Non-DR: 63/55 NPDR: 73/61 PDR: 34/24	6
Ulu[53]	2013	Retrospective	Turkey	34	24		NR	NR	5
Wei[42]	2017	Retrospective	China	94	52	40	Non-DR: 58.14±11.93 DR: 58.42±12.09	Non-DR: 50/44 DR: 49/43	6
Wang[54]	2015	Retrospective	China	138	131		Non-DR: 60.3±6.0 DR: 66.6±5.8	Non-DR: 65/73 DR: 53/78	7
Yin[55]	2015	Retrospective	China	64	28	36	Non-DR: 56.83±9.01 NPDR: 53.09±8.82 PDR: 53.16±10.64	Non-DR: 35/29 NPDR:13/15 PDR:19/17	6
Yue[45]	2015	Retrospective	China	125	62	59	Non-DR: 56.00±3.75 NPDR: 53.50±3.56 PDR: 56.0±3	Non-DR: 73/52 NPDR: 34/28 PDR: 28/31	6
Zhou[46]	2016	Retrospective	China	328	51		Non-DR: 57±16 DR: 63±15	Non-DR: 198/130 DR: 34/17	6

DR: Diabetic retinopathy; NR: Not reported; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet-lymphocyte ratio.

Table 3 Values of NLR in T2DM subjects with and without DR

First author	Year	Neutrophil to lymphocyte ratio (%)						Platelet to lymphocyte ratio (%)					
		T2DM patients without DR		Patients with NPDR		Patients with PDR		T2DM patients without DR		Patients with NPDR		Patients with PDR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Akdoğan[26]	2016	2.4	1.9	3.0±4.4				116	66	140±87			
Ciray[50]	2015	1.99	1.03	2.10±1.02				NR	NR	NR		NR	
Kuang[51]	2015	1.68	0.48	2.20	0.40	2.58	0.41	NR	NR	NR		NR	
Öztürk[56]	2013	2.04	0.72	2.58±1.34				NR	NR	NR		NR	
Shen[52]	2016	1.52	0.26	1.68	0.21	1.95	0.17	NR	NR	NR		NR	
Ulu[53]	2013	1.96	0.86	3.59±2.07				NR	NR	NR		NR	
Wei[42]	2017	NR	NR	NR	NR	NR		98.46	10.63	127.25±12.98			
Wang[54]	2015	2.1	1.3	3.7±1.4				NR	NR	NR		NR	
Yin[55]	2015	1.54	0.55	1.83	0.59	2.15	0.77	NR	NR	NR		NR	
Yue[45]	2015	1.74	0.245	2.05	0.3	1.91	0.28	94.04	12.365	105.07	17.47	115.73	14.54
Zhou[46]	2016	2.4	1.5	4.4±2.7				NR	R	NR		NR	

DR: Diabetic retinopathy; NR: Not reported; T2DM: Type 2 diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NLR: Neutrophil to lymphocyte ratio.

this Meta-analysis[26-44,46-49]. When synthesizing the data, the significant heterogeneity among the included studies was found (I^2=94.1%, P<0.01). Therefore, a random effects model was used to pool the data and the results showed that MPV was significantly increased in patient with DR compared to DM group (SMD=0.67; 95%CI: 0.36 to 0.98; Figure 2).

The relationship between mean platelet volume and the presence of diabetic retinopathy The data of PDW from 12 articles with 1681 patients were synthesized in this Meta-analysis[26,29-30,35-37,40-44,48]. Considering the significant heterogeneity among the selected studies (I^2=79.3%, P<0.01), we used random effects model to pool the data. The results showed that PDW was higher in patients with DR compared to DM group (SMD=0.51; 95%CI: 0.27 to 0.75; Figure 3).

The relationship between neutrophil to lymphocyte ratio and the presence of diabetic retinopathy A total of 10 articles involving 1911 patients reported the data of NLR[26,45-46,50-56]. Randomized effects model was applied to synthesize the data since the significant heterogeneity was found among the included studies (I^2=86.5%, P<0.01). The pooled results showed that NLR was substantially increased in DR patients compared to DM patients (SMD=0.77; 95%CI: 0.49 to 1.05; Figure 4).

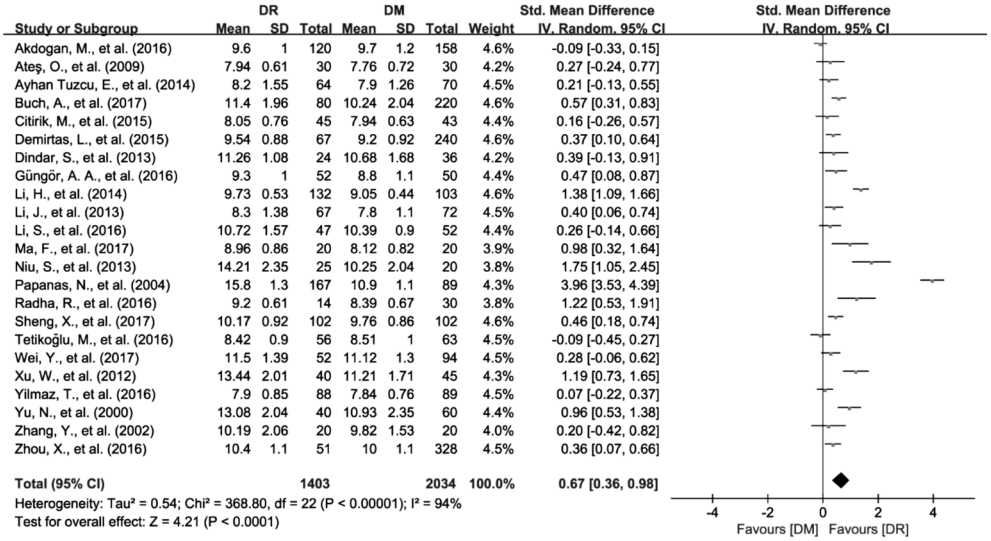

Figure 2 Increased MPV values in DR patients compared with DM patients.

Table 4 Values of MPV and PDW in T2DM subjects with and without DR

First author	Year	MPV (fL)						PDW (%)					
		T2DM patients Without DR		Patients with NPDR		Patients with PDR		T2DM patients Without DR		Patients with NPDR		Patients with PDR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Akdoğan[26]	2016	9.7	1.2	9.6±1.0				16.2	0.8	16.2±0.5			
Ateş[27]	2009	7.76	0.72	7.94	0.61	8.18	0.89	NR	NR	NR	NR	NR	NR
Buch[29]	2017	10.24	2.04	11.40±1.96				13.94	3.33	14.92±4.14			
Citirik[30]	2015	7.94	0.63	8.05	0.76	8.10	0.68	14.85	1.27	15.15	1.19	14.92	1.15
Demirtas[31]	2015	9.20	0.92	9.54±0.88				NR	NR	NR	NR	NR	NR
Dindar[32]	2013	10.68	1.68	11.26±1.08				NR	NR	NR	NR	NR	NR
Güngör[33]	2016	8.8	1.1	9.3±1.0				NR	NR	NR	NR	NR	NR
Li[34]	2014	7.8	1.1	8.3	1.38	8.9	1.65	NR	NR	NR	NR	NR	NR
Li[47]	2013	9.05	0.44	9.73±0.53				NR	NR	NR	NR	NR	NR
Li[35]	2016	10.39	0.90	10.72±1.57				13.80	3.32	16.17±1.66			
Ma[36]	2017	8.12	0.82	8.96	0.86	10.76	1.12	15.66	2.37	17.85	2.26	17.90	2.41
Niu[37]	2013	10.25	2.04	14.21±2.35				16.05	1.56	18.12±1.25			
Papanas[38]	2004	10.9	1.1	15.8±1.3				NR	NR	NR	NR	NR	NR
Radha[39]	2016	8.39	0.67	9.2±0.61				NR	NR	NR	NR	NR	NR
Sheng[40]	2017	9.76	0.86	10.17±0.92				11.31	1.67	12.04±1.88			
Tetikoğlu[41]	2016	8.51	1.0	8.42	0.9	8.91	0.7	16.9	0.7	16.8	0.7	17.3	3.1
Tuzcu[28]	2014	7.90	1.26	8.20	1.55	8.78	1.73	NR	NR	NR	NR	NR	NR
Wei[42]	2017	11.12	1.3	11.50	1.39	11.56	1.06	13.70	2.90	14.40	2.88	14.20	1.99
Xu[43]	2012	11.21	1.71	13.44±2.01				15.98	1.23	17.41±1.42			
Yilmaz[44]	2016	7.84	0.76	7.90	0.85	8.31	0.76	13.02	1.29	13.49	1.18	13.77	1.26
Yu[48]	2000	10.93	2.35	13.08±2.04				17.77	1.97	21.48±5.94			
Yue[45]	2015	NR	NR	NR				NR	NR	NR			
Zhang[49]	2002	9.82	1.53	10.19±2.06				NR	NR	NR	NR	NR	NR
Zhou[46]	2016	10.0	1.1	10.4±1.1				NR	NR	NR	NR	NR	NR

DR: Diabetic retinopathy; NR: Not reported; T2DM: Type 2 diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; MPV: Mean platelet volume; PDW: Platelet distribution width.

The relationship between platelet-lymphocyte ratio and the presence of diabetic retinopathy Three articles with 611 patients referring to PLR were included in this Meta-analysis[26,42,45]. Heterogeneity test showed I^2=97.2% with P<0.01, so random effects model was applied to synthesize the data. As the results showed, PLR was elevated in patients with DR than in DM patients (SMD=1.18; 95%CI: 0.07 to 2.28; Figure 5).

The relationship of mean platelet volume, platelet distribution width and neutrophil to lymphocyte ratio the severity of diabetic retinopathy To investigate the relationship of MPV, PDW and NLR the severity of DR, we further analyzed the differences of MPV, PDW and NLR in patients between NPDR and PDR. There were 8 studies with 858 patients reporting the association of MPV with the severity

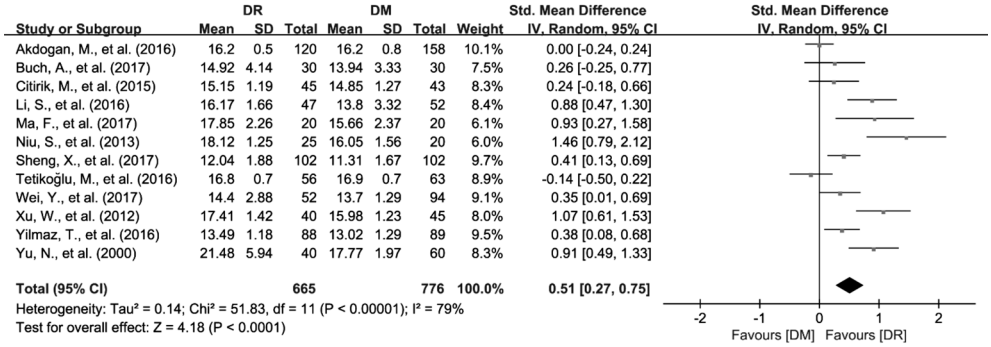

Figure 3 Increased PDW values in DR patients compared with DM patients.

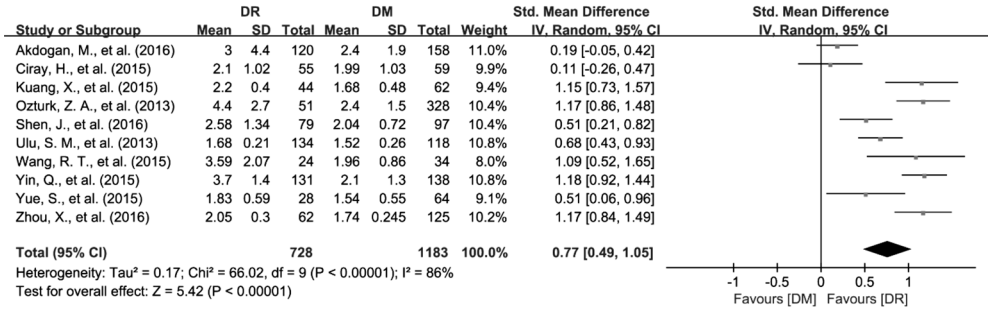

Figure 4 Increased NLR values in DR patients compared with DM patients.

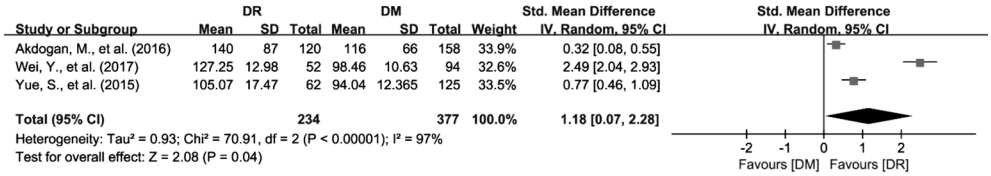

Figure 5 Increased PLR values in DR patients compared with DM patients.

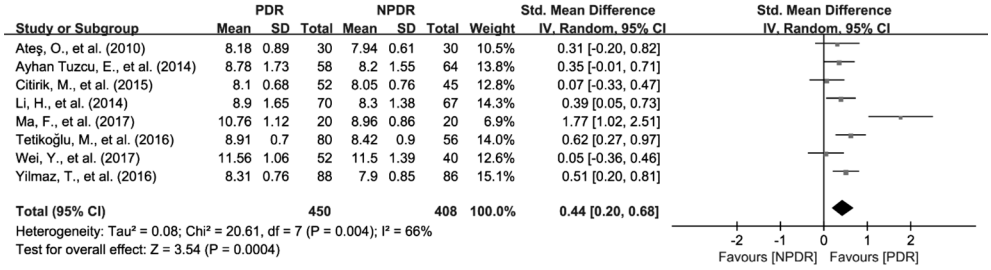

Figure 6 Increased MPV values in PDR patients compared with NPDR patients.

of DR[27-28,30,34,36,41-42,44]. Because of the significant heterogeneity among the included studies (I^2=66%, P<0.01), random effects model was applied to pool the data, and the results revealed that MPV was significantly increased in patients with PDR compared to NPDR group (SMD=0.44; 95%CI: 0.20 to 0.68; Figure 6). In addition, 5 articles with 539 patients provide available data for the pooled analysis of the association of PDW with the severity of DR[30,36,41-42,44]. Fixed effects Meta-analysis was performed since the significant heterogeneity was not found and (I^2=0, and P=0.42). However, the results showed that the difference of PDW was not observed between NPDR and PDR patients (SMD=0.08; 95%CI: -0.09 to 0.25; Figure 7). As for NLR, 4 studies involving 443 patients were included for the Meta-analysis of its association with NLR[45,51-52,55]. Similar to PDW, the difference of NLR was not found between NPDR and PDR patients (SMD=0.56; 95%CI: -0.34 to 1.46) either (Figure 8).

Sensitivity Analysis Sensitivity analyses were conducted by omitting single study in each step to assess the effect of each individual study on the pooled SMDs for MPV, PDW and NLR in DR patients as compared with DM patients. The results showed that the pooled SMDs for MPV (Figure 9A), PDW (Figure 9B) and NLR (Figure 9C) did not alter significantly when any individual study was excluded, indicating that the results of this Meta-analysis were vigorous. Additionally, we also applied the sensitivity analysis to test the stability of the pooled SMD for MPV in patients with PDR as compared with NPDR. Similarly, the result also indicated that the pooled

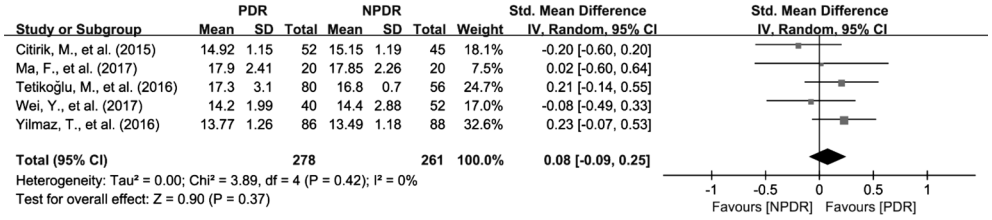

Figure 7 Increased PDW values in PDR patients compared with NPDR patients.

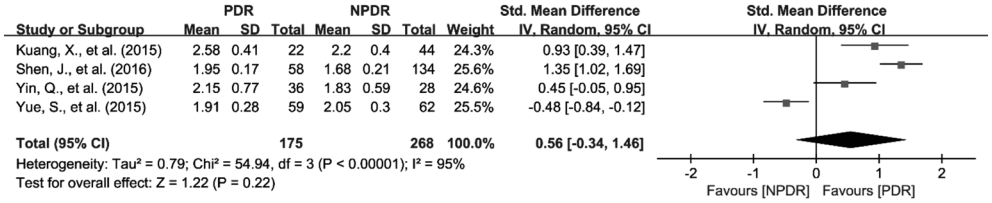

Figure 8 Increased NLR values in PDR patients compared with NPDR patients.

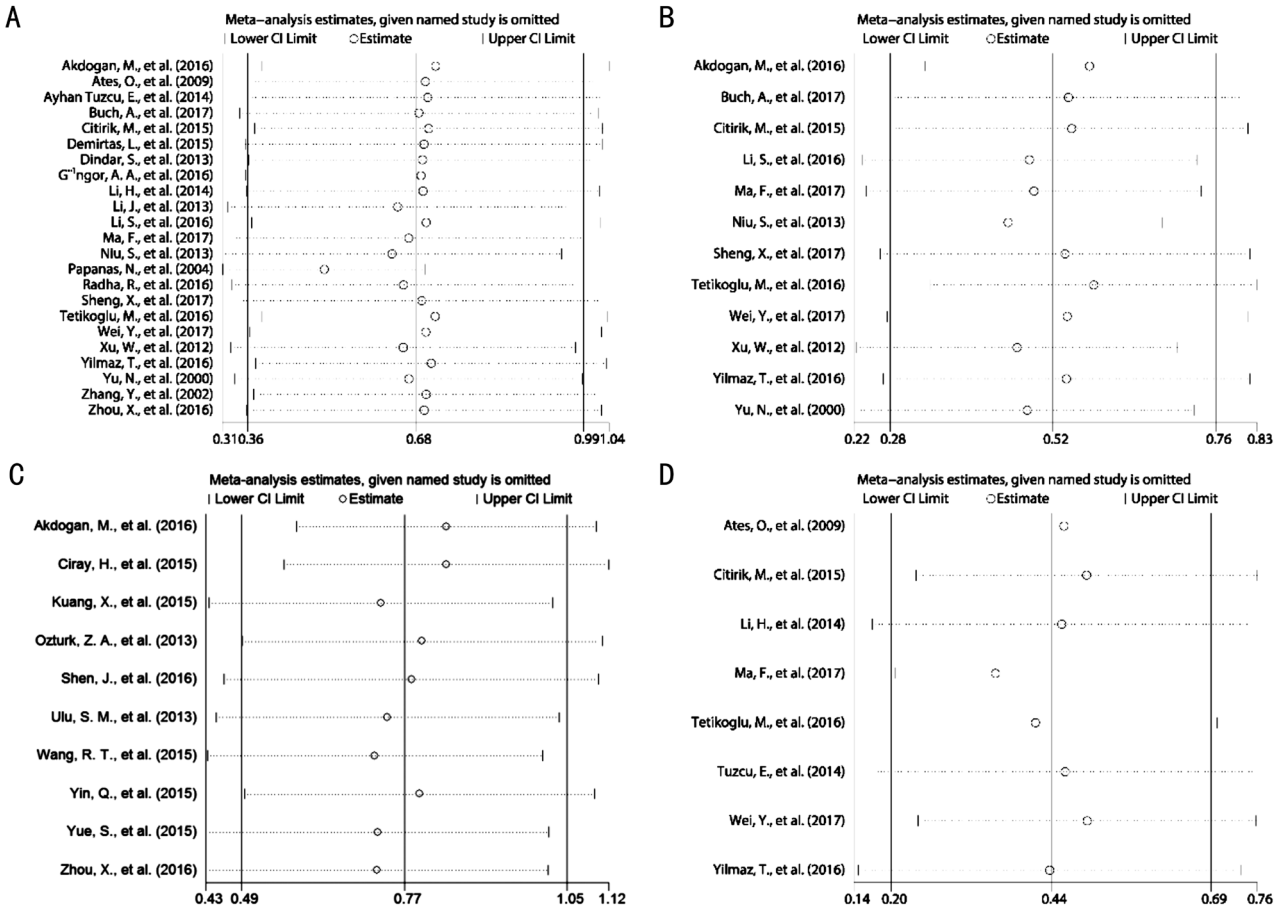

Figure 9 Sensitivity analysis on SMD by removing each study in each model A: SMD on the relationship between MPV value and the risk of DR; B: SMD on the relationship between PDW value and the risk of DR; C: SMD on the relationship between NLR value and the risk of DR; D: SMD on the relationship between MPV value and the severity of DR.

SMD for MPV in patients with PDR as compared with NPDR was robust (Figure 9D). Due to the limited number of studies, sensitivity analyses were not applicable to verify the robustness of the pooled SMD for PLR in DR patients as compared with DM patients, as well as of the pooled SMDs for NLR and PDW in patients with PDR as compared with NPDR.

Publication Bias We used Begg's and Egger's test to evaluate the publication bias among included studies. The result showed that there was no significant bias for the synthesized SMDs for NLR (Begg's tests, *P*=0.929; Egger's tests, *P*=0.588) in DR patients as compared with DM patients. However, the publication bias might exist among the included studies for the synthesized SMDs for MPV (Begg's test, *P*=0.039; Egger's test, *P*=0.148) and PDW (Begg's tests, *P*=0.06; Egger's tests, *P*=0.02) in DR patients as compared with DM patients. Therefore, Meta-trim method was conducted to investigate

the influence of publication bias on the reliability of pooled SMDs for MPV and PDW. From the results of meta-trim method, we observed that the adjusted SMDs of MPV (0.68; 95%CI: 0.36-0.99) and PDW (0.68; 95%CI: 0.36-0.99) did not change substantially, which implicated that the pooled results of the MPV and PDW for DR were still reliable, although the publication bias existed in this Meta-analysis. Besides, the publication bias test was not available for the pooled SMD of PLR due to the limitation of the number of the eligible studies.

DISCUSSION

In our Meta-analysis, a total of 31 eligible studies were included for pooling analysis. As compared with T2DM patients without DR, the values of MPV (SMD=0.67; 95%CI: 0.36 to 0.98), PDW (SMD=0.51; 95%CI: 0.27 to 0.75), NLR (SMD=0.77; 95%CI: 0.49 to 1.05), and PLR (SMD=1.18; 95%CI: 0.07 to 2.28) were much higher in patients with DR. Additionally, patients with PDR had much higher MPV value than NPDR patients (SMD=0.44; 95%CI: 0.20 to 0.68), indicating that MPV might be closely correlated with the severity of DR. Furthermore, our sensitivity analysis showed that the pooled SMDs mentioned above did not change significantly when sequentially omitting any of the included studies, which demonstrated that our pooled results were stable and reliable. Meanwhile, the results of publication bias assessment indicated that publication bias did not substantially affect our pooled results either.

Various factors including systematic inflammation, elevated phosphorylation and glycosylation of cellular proteins, oxidative stress, abnormal calcium metabolism, reduced bioavailability of nitric oxide may promote the release of prothrombotic and proinflammatory substances and contribute to the platelet activation in diabetic patients[62]. Furthermore, it was proposed that elevated activation of platelets play an important role in the development of coagulation abnormalities and thromboembolic events in diabetic patients[63]. MPV is a parameter evaluating the average size of platelets and high MPV indicates that platelets have large size. Larger platelets usually display more metabolic and enzymatic activities and release more thromboxan-A_2, b-thromboglobulin, and adhesion molecules as compared to the smaller size[14-15]. Considering that microthrombosis plays a key role in the vascular complications, many studies were conducted to explore the association of MPV with vascular complications including DR[26-44,46-49]. However, the results of those studies were inconsistent. Hence, we conducted the present Meta-analysis to further determine the association of MPV with DR. From the results of this Meta-analysis, we found that MPV was significantly higher in diabetic patients with DR than in those without DR, as well as higher in diabetic patients with PDR as compared to those with NPDR. As with MPV, PDW has also been thought as a marker of platelet activation[64]. Conflicting results have been reported for the association of PDW with the presence of DR and the degree of DR[26,29-30,35-37,40-44,48]. Herein, our Meta-analysis indicated that higher PDW was closely associated with the presence of DR, but not with the severity of DR. Based on our results, we may speculate that PDW was only linked with the formation of DR, but not with the progression of DR. However, considering that only 5 studies provide available data for our Meta-analysis of the correlation of PDW to the severity of DR, the small sample size may partly be responsible for the negative association of PDW with the severity of DR. Therefore, further studies are in need to investigate the association between PDW and the severity of DR.

The counts of WBCs and its subtypes are important inflammation response biomarkers. In addition, the NLR and PLR have also been considered as potential markers that reflect the status of inflammation and immune responses[13]. More importantly, the stability of NLR and PLR is superior to independent blood neutrophils, monocyte and lymphocytes due to their less susceptibility to various physiological and pathological condition, which indicates that the alteration of NLR and PLR can reflect the status of inflammation and immune responses better. Furthermore, a body of literature suggested that NLR and PLR had diagnostic and prognostic values in various diseases, including DM, acute coronary syndromes, and various malignancies[11-12,18,24-25,56,65-67]. In particular, it has been reported that neutrophils could promote the development and progression of microangiopathy and inflammation, when adhering to the endothelial cell wall[68-69]. For instance, a study by Woo *et al*[70], showed that neutrophil count in circulation increased in patients with DR, and was significantly correlated with the severity of DR, suggesting the key role of neutrophil-mediated inflammation in the development and progression of DR. Moreover, several recent studies reported that NLR, as a novel inflammation marker, NLR was found to be elevated in patients with DR and associated with the severity of DR[13,56,70-72]. Nevertheless, in a study by Ciray *et al*[73], NLR was not found to be correlated with DR. Additionally, there were also several studies focusing on investigating the relationship of PLR to DR and its severity[26,42,45]. However, the reliability of conclusions on the association of NLR, and PLR with DR were challenged by the limitation of small sample size in an individual study. Thus, we herein conducted a Meta-analysis to further determine the link of NLR and PLR with DR. In the present study, we found that the levels of NLR, and PLR were higher in patients with DR than in patients with DM and without DR, but there were no differences in NLR levels between patients with NPDR and PDR. These results implicated that NLR may only play a key role in the initiation of DR, but not in

the progression of DR. Similar to PDW, only 4 studies with a small sample size had available data for the Meta-analysis of the correlation of NLR to the severity of DR, suggesting that a weak statistical power might also be responsible for the no associations of NLR with the severity of DR. Hence, further studies are needed to investigate the association between NLR and the severity of DR.

When we interpreted the results of our study, some limitations should be taken into account. First, although random effect model was used to conduct this Meta-analysis, substantial heterogeneities among the included studies still existed. The potential sources of the heterogeneity might come from the differences in some characteristics of the included studies, such as age, ethnicity, diseases duration and body mass index, etc. Second, the definition of the DR severity was not uniform, which may introduce bias. Third, the number of included studies was limited for a reliable Meta-analysis of the correlation of NLR and PDW with the DR severity. At last but not least, our study only focused on systematically analyzing the link between blood cell-related inflammatory indices and DR. Actually, in addition to blood cell-related inflammatory indices, there were many other serum biomarkers that are also closely correlated with inflammation, and these serum biomarkers have been considered to play key roles in DR development as well, such as pentosidine[74-81], C-reactive protein[82-83], interleukin-6[84-86] and TNF-alpha[87]. However, because of lacking available data, our Meta-analysis failed to systematically assess the association of blood cell-related inflammatory indices with other serum inflammatory biomarkers. Therefore, in future more studies should be conducted to analyze the associations of MPV, PDW, NLR, and PLR with other serum inflammatory biomarkers, which will further confirm our findings in this present Meta-analysis.

In conclusion, our study suggested that MPV, PDW, NLR and PLR may be associated with the presence of DR and MPV is also correlated with the severity of DR, but NLR and PDW might not be linked with the severity of DR. Overall, MPV, PDW, NLR and PLR could be recommended as inexpensive diagnostic markers for DR. However, considering several limitations in our study, further high-quality studies are needed to investigate the association of these hematologic inflammatory indices with DR, especially the correlation of NLR and PDW with the severity of DR.

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