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The pleiotropic association between IL-10 levels and CVD prognosis: Evidence from a meta-analysis

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ABSTRACT

We examined the precise association between IL-10 levels and cardiovascular disease (CVD) prognosis and explored the pleiotropic role of IL-10 in different cardiac pathologies. We performed a meta-analysis of cross-sectional and longitudinal studies investigating IL-10 levels. Meta-regression analyses were used to determine the cause of the discrepancies. To assess publication bias, funnel plots were constructed, and Egger's tests were performed. Data from the GSE58015 dataset were used to investigate the levels of IL-10 under certain conditions. Because of substantial heterogeneity in the data used to compare the IL-10 levels between patients with CVD and healthy people, we could not determine the differences between the healthy controls and patients with ischemic or nonischemic pathologies ($p > 0.05$). The analysis of the association between IL-10 levels and CVD prognosis indicated that higher IL-10 levels were significantly associated with a poor prognosis in patients with non-ischemic pathologies (HR = 1.10, 95% CI = 1.00–1.20, $p = 0.043$) but differentially associated with the prognosis of patients with ischemic pathologies based on the sampling time point (before percutaneous coronary intervention (PCI): HR = 4.90, 95% CI = 1.24–19.30, $p < 0.001$; after PCI: HR = 0.57, 95% CI = 0.43–0.75, $p = 0.023$). The *meta*-regression analysis showed that the pooled HR of the IL-10 levels was positively correlated with the IL-10/IL-6 ratio ($\beta = 0.644$, $p = 0.024$). The funnel plots and Egger's tests revealed no statistically significant bias in our meta-analysis ($p > 0.1$). Furthermore, our data mining analysis supported our findings. Our analysis showed that IL-10 levels may be pleiotropically associated with the CVD prognosis possibly based on the type of pathology, disease stage and levels of other proinflammatory factors, such as IL-6.

1. Introduction

Cardiovascular disease (CVD) is the greatest cause of human mortality and morbidity worldwide. The most common cardiovascular pathologies leading to morbidity and death are ischemic heart disease and myocardial infarction. Furthermore, different types of cardiomyopathies leading to heart failure are considered to contribute to cardiovascular mortality. Recently, accumulating evidence has shown that the inflammatory response is closely related to the development, progression, and prognosis of various cardiovascular conditions, most notably coronary atherosclerosis and congestive heart failure [1–4]. The inflammatory and postinflammatory phases are characterized by widely changing cytokine profiles; these changes involve both anti-inflammatory and proinflammatory processes [5,6]. Cytokines have been reported to exert a marked and varying influence on the cardiovascular system [7]. Extensive research has provided clear evidence that different cytokines, including TNF-α, TGF-β and various interleukins, are involved in different pathological states in the heart, such as acute myocardial infarction (AMI) and heart failure, and cardiomyopathies of different origins [8–10].

IL-10 is one of the most important anti-inflammatory cytokines and is produced mainly by Th2 cells, macrophages, B cells, and monocytes [11]. Many previous studies have investigated the role of IL-10 in CVD as IL-10 can inhibit the secretion of proinflammatory cytokines, such as TNF-α, IL-1 and IL-6, thus exerting anti-inflammatory effects [12–14]. However, in recent reports, IL-10 seems to play a dual role in heart disease because it exerts deleterious profibrotic effects in a chronic disease setting but potentially benefits inflammation resolution and

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wound healing [15,16]. Moreover, the changes in and the risk associated with IL-10 in various cardiac pathologies remain unclear due to extremely contradictory reports. The existing data differ and are even contradictory among different studies. Thus, the need for a meta-analysis to determine the sources of heterogeneity and clarify the role of IL-10 in CVD is urgent.

In this study, we collected relevant studies and performed a systematic review and meta-analyses to comprehensively investigate the role of IL-10 in individuals with CVD. Subsequently, we aimed to identify conflicting results and analyze the underlying causes. Thus, our study may contribute to the existing literature.

2. Methods

The protocol was registered in PROSPERO (No. 107250).

2.1. Literature search strategy

In our study, we aimed to detect the changes in IL-10 levels in patients with CVD and determine the risk associated with IL-10 levels among patients with CVD. Systematic literature searches were conducted using 3 international electronic databases (PubMed, Embase and Web of Science) and 3 Chinese literature databases (CNKI, Wanfang, and VIP). All relevant articles were published before January 15, 2018. Only publications with sufficient data were included in the assessment. We used two search strategies in our analysis. The following search terms were used to identify articles comparing IL-10 levels between patients with CVD and heathy controls: [IL-10 OR IL 10 OR Interleukin-10 OR Interleukin 10] AND [Heart OR Cardiac OR Cardiovascular OR Coronary OR Infarction] AND [Health OR Healthy]; the following search terms were used to identify articles evaluating the risk associated with IL-10 levels in patients with CVD: [IL-10 OR IL 10 OR Interleukin-10 OR Interleukin 10] AND [Heart OR Cardiac OR Cardiovascular OR Coronary OR Infarction] AND [prognosis OR prognostic].

To identify additional potentially relevant publications, the related references of all retrieved articles and reviews were manually searched. All data were included in the quality assessment and selection phase.

2.2. Study selection

We included original references published in any language. Eligible studies comparing IL-10 levels between cases and healthy controls had to measure IL-10 levels in individuals with CVD and a comparison group of healthy controls. Eligible studies investigating the IL-10 risk had to have adopted a cohort design with a risk value as an endpoint (OR or HR) with 95% confidence intervals (CIs). In addition, if the study populations were reported more than once and the outcome was the same, we used the results with the longest follow-up duration.

The following studies were excluded: (i) case reports or case series ($N < 10$), (ii) studies measuring mediators in specimens/tissues other than blood, (iii) animal studies, and (iv) studies with insufficient data for subsequent analysis. After the exclusion of duplicate studies, two investigators (Shi-Hao Ni and Lu Lu) independently reviewed all remaining articles by the titles and abstracts, followed by reviewing the full texts.

2.3. Data extraction and quality assessment

From the studies comparing the IL-10 levels between patients and healthy controls, we extracted the following data: (i) first author, (ii) publication year, (iii) region, (v) age (mean ± SD), (vi) number of participants, (vii) sample source, (viii) sampling time, and (ix) cardiac pathology. From the studies investigating the risk of CVD associated with IL-10 levels, we extracted the above-mentioned parameters; furthermore, we obtained the IL-10/IL-6 and IL-10/C-reactive protein (CRP) ratios by calculating the mean values and extracted the follow-up time, endpoint events and information regarding whether the results were adjusted. If the studies provided only the median IQR or median/range, we estimated the means and SDs following a standard method [17].

The prospective cohort studies were subjected to a quality assessment, which was performed according to the Newcastle–Ottawa Quality Assessment Scale, which is a validated scale for non-randomized studies in meta-analyses. This scale awards a maximum of 9 points to each study as follows: 4 points for selection of participants and measurement of exposure, 2 points for comparability of cohorts based on the design or analysis, and 3 points for the assessment of outcomes and adequacy of follow-up. We assigned the scores of 0–3, 4–6 and 7–9 to the low, moderate and high quality studies, respectively.

2.4. Statistical analysis

To pool the mean differences in the IL-10 levels, we calculated the standardized mean difference (SMD) by Hedges' method to accurately approximate the bias. To pool the risk associated with the IL-10 levels, we used a generic method for meta-analyses based on inverse variance weighting that requires only the log HRs and standard error according to Greenland and Longnecker's method. The HRs and 95% CIs were considered the effect size in all studies. The heterogeneity of the effect size was evaluated using Cochran's Q and I-squared statistics. A fixed effects model was used if the values were $Q > 0.05$ and I-squared $< 50\%$; otherwise, a random effects model was used. We used Begg's funnel plots and Egger's test to investigate the publication bias of our meta-analysis. To explore the sources of heterogeneity, we performed a meta-regression analysis with weight dependence.

The statistical analysis was performed using IBM SPSS Statistics (version 18) and R statistical software (version 3.4.0; meta and metafor packages).

3. Results

3.1. Study selection

3.1.1. Studies comparing IL-10 levels between patients with CVD and healthy controls

Following the removal of duplicate studies, the titles/abstracts of 127 unique references were screened for eligibility. In total, 113 references were excluded; 14 original studies providing data from 1858 participants (1343 participants with CVD and 515 healthy controls) met the inclusion criteria. Fig. 1A shows the PRISMA flowchart of the study selection. Of the included studies, 9 studies were conducted in China, 2 studies were conducted in Europe (Greece and Italy), 1 study was conducted in the United States, 1 study was conducted in Australia, and 1 study was conducted in Taiwan. The age of the participants ranged from 20 to 89 years. The CVD pathologies of the patients included heart failure, acute coronary syndrome, and hypertrophic cardiomyopathy. The main characteristics of the selected studies are summarized in Table 1.

3.1.2. Studies investigating the relationship between IL-10 levels and CVD prognosis

In total, 85 relevant published articles were identified following the aforementioned retrieval strategy. After review, 70 of these publications were excluded; 15 relevant published articles were identified and selected for our meta-analysis (Fig. 1B). The included studies enrolled a total of 4033 CVD patients. Of the included studies, 12 studies were European trials (Germany, Greece, the Netherlands, Norway, Italy, and Denmark), and 3 studies were East Asian trials (China, Japan, and Taiwan). All studies included patients with CVDs and records of adverse events during follow-up. The mean age of the participants tested to determine their IL-10 level ranged from 31 to 98 years. The follow-up time ranged from 24 h to 6 years. The prognostic value of IL-10 in all

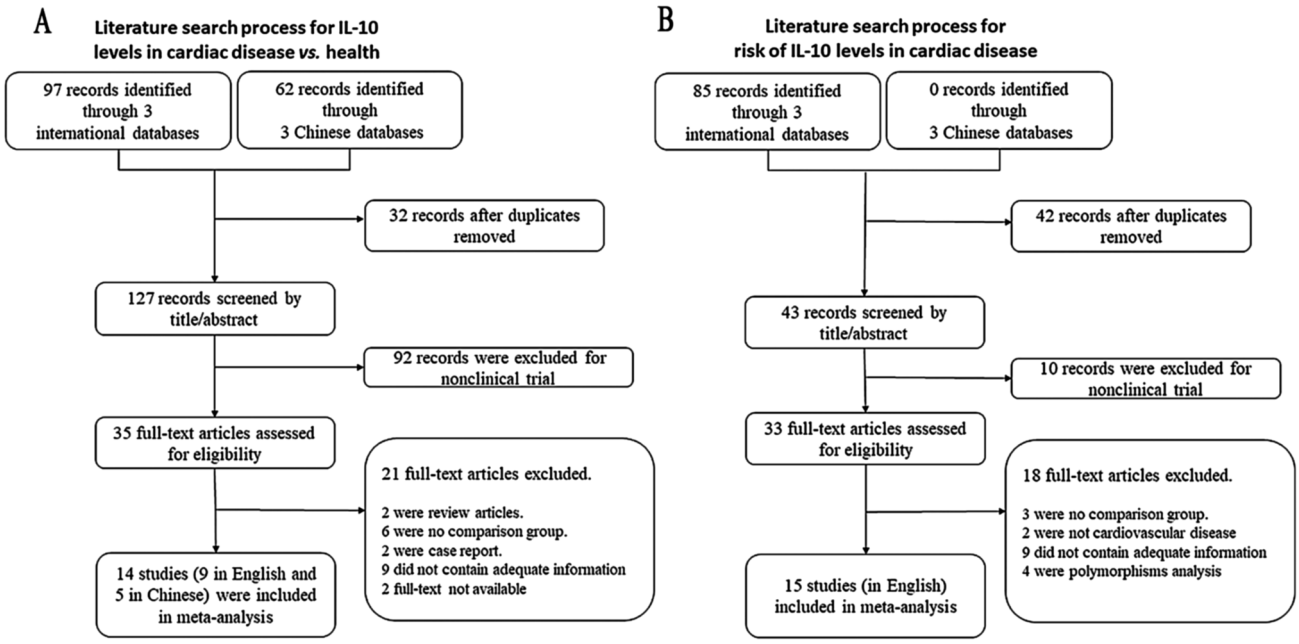

Fig. 1. Flow chart of the included studies: (A) evaluation of the differences in IL-10 levels between patients with CVD and healthy controls and (B) association between IL and 10 levels and prognosis in patients with CVD.

studies was adjusted in at least one regression model. The quality score of thirteen included studies was 8, and that of three studies was 7. The main characteristics of the included studies are summarized in Table 2.

3.2. Difference in IL-10 levels between patients with CVD and healthy controls

Using a crude analysis of all cardiac pathologies, we could not find a difference in the IL-10 levels between the patients and healthy controls since the pooled SMD was not statistically significant (SMD = −0.21, 95% CI = −1.01 to 0.95, p = 0.607, Fig. 2A). The data were highly heterogeneous (I-squared = 98%, p < 0.01). In the subgroup analysis, the IL-10 levels did not differ between the patients with ischemia and the healthy controls (SMD = −0.17, 95% CI = −2.17 to 1.82, p = 0.628) or between the nonischemia patients and the healthy controls (SMD = −0.22, 95% CI = −1.12 to 0.67, p = 0.865). Furthermore, the heterogeneity did not decrease in the subgroup analysis (ischemia vs. healthy: I-squared = 98%, p < 0.01; nonischemia vs. healthy: I-squared = 98%, p < 0.01). The meta-regression analysis showed no correlation between the SMD and the age of the participants (p > 0.05, Fig. 2B). Therefore, the changes in the IL-10 levels in the cardiac pathologies remain quite controversial, and a larger, more rigorous experiment is needed to address this problem.

3.3. Association between IL-10 levels and CVD prognosis

The crude analysis of the prognostic value of IL-10 indicated that the IL-10 level is not associated with the risk of adverse events in patients with ischemic CVD (HR = 0.95, 95% CI = 0.75–1.19, p = 0.639, Fig. 3A). In addition, the data were highly heterogeneous (I-squared = 85%, p < 0.01). However, in the subgroup analysis, higher IL-10 levels before PCI were associated with a better prognosis in patients with an ischemic pathology (HR = 0.57, 95% CI = 0.43–0.75, p = 0.023), while higher IL-10 levels after PCI were positively correlated with a poor prognosis in patients with an ischemic pathology (HR = 4.9, 95% CI = 1.24–19.30, p < 0.001). The heterogeneity in the subgroup analysis decreased after adjusting for the sampling time point of the IL-10 detection (Crude pool: I-squared = 85%, p < 0.01; before PCI: I-squared = 0%, p = 0.45; after PCI: I-squared = 82%, p < 0.01). In the analysis of the risk associated with IL-10 in patients with nonischemic heart disease, higher IL-10 levels were significantly associated with the risk of adverse events (HR = 1.10, 95%

Table 1
Characteristics of the studies comparing IL-10 levels between patients with CVD and healthy controls.

Study	Year	Ref.	Region	Age (1)	Sample size	Source	Sampling time	Cardiac pathology
Tian, X. et al.	2011	[47]	China	54.8 ± 9.9	99	IL-10+ T cells	Before treatment	Chronic heart failure
Gong, K. et al.	2006	[48]	China	62.4 ± 9.1	80	Plasma	Before treatment	Chronic heart failure
Zhu, H. J. et al.	2014	[49]	China	70.8 ± 8.6	117	Serum	Before treatment	Ischemic cardiomyopathy
Chen, H. Q. et al.	2010	[50]	China	66.6 ± 4.7	130/118	Plasma	Before treatment	Acute coronary syndrome/stable angina pectoris
Yip, H. K. et al.	2007	[40]	Taiwan	60.5 ± 12	270	Plasma	Before treatment	ST segment elevation AMI
Fink, A. M. et al.	2012	[51]	U.S.	59.8 ± 2.6	84	Plasma	Before treatment	Chronic heart failure
Valgimigli, M. et al.	2005	[52]	Italy	64.2 ± 11.1	229	Serum	Baseline	Chronic heart failure
Fang, L. et al.	2017	[38]	Australia	48.1 ± 13.3	70	Plasma	Baseline	Hypertrophic cardiomyopathy
Efthimiadis, I. et al.	2011	[53]	Greece	47.2 ± 11.2	32	Plasma	Baseline	Dilated cardiomyopathy
Xu, J. et al.	2002	[54]	China	66.2 ± 7.6	70	Serum	Before treatment	Chronic heart failure
Chen, H. et al.	2005	[55]	China	69.4 ± 5.7	106	Serum	Before treatment	Chronic heart failure
Li, B. et al.	2004	[56]	China	54.3 ± 11.4	132	Plasma	Before treatment	Chronic heart failure
Gao, Y. et al.	2003	[57]	China	59.4 ± 9.8	55	Serum	Before treatment	Chronic heart failure
Luo, J. et al.	2018	[58]	China	74.6 ± 9.2	266	Serum	Before treatment	Chronic heart failure

Note: (1) Age in years is presented as the mean ± SD.

Table 2
Characteristics of the studies evaluating the association between IL and 10 levels and CVD prognosis.

Study	Year	Ref.	Region	Age (1)	Sample size	Sample source (Sampling time)	Cardiac pathology	Cut-off value	Adverse events	Follow-up time	Adjusted results (2)	Quality Score
Heeschen, C. et al.	2003	[13]	Germany	61.5 ± 10.7	547	Serum (Baseline, before PCI)	Acute coronary syndrome	ROC cut-off (3.5 pg/mL)	All-cause death	72 h/6 months	Yes	8
Chalikias, G. K. et al.	2005	[59]	Greece	66 (62, 69)	107	Serum (Baseline, before PCI)	Acute coronary syndrome	Median (4.7 pg/mL)	Cardiac death and major adverse cardiac events	During hospitalization	Yes	8
Kwaijtaal, M. et al.	2005	[60]	The Netherlands	53.6 ± 7.5	234	Serum (Baseline/6 months, after PCI)	Myocardial infarction	Median (2.3 pg/mL)	Late cardiac events	25.5 months	Yes	8
Ueland, T. et al.	2005	[18]	Norway	68 ± 10	213	Plasma (Baseline/1 month)	Acute myocardial infarction	Median (0.35 pg/mL)	All-cause death	2 years	Yes	8
Valgimigli, M. et al.	2005	[52]	Italy	65 ± 11	368	Serum (Baseline)	Acute myocardial infarction	Median	Death and new-onset heart failure (HF)	At least 12 months	Yes	8
Chalikias, G. K. et al.	2007	[61]	Greece	65.4 (62, 69)	186	Serum (Baseline, after PCI)	Acute coronary syndrome	Quartiles	Recurrent coronary event	Median 15 months	Yes	7
Yip, H. K. et al.	2007	[40]	Taiwan	60.5 ± 12.1	250	Serum (Baseline, after PCI)	Acute myocardial Infarction	30 pg/ml	All-cause death	30 days	Yes	7
Miettinen, K. H. et al.	2008	[62]	Finland	77 (40, 98)	423	Plasma (within 48 h)	Acute decompensated heart failure	Tertiles (1.74 pg/mL)	All-cause death	12 months	Yes	8
Parissis, J. T. et al.	2009	[63]	Greece	65 ± 12	144	Plasma/serum (Baseline)	Chronic heart failure	Median (4.4 pg/mL)	Death and other major adverse cardiac events	12 months	Yes	8
Izumi, T. et al.	2012	[39]	Japan	52.6 ± 21.3	29	Serum(Baseline)	Acute myocarditis	ROC cut-off (8.4 pg/mL)	Heart assist device use	1 month	Yes	8
Kardys, I. et al.	2012	[64]	The Netherlands	59.4 ± 11.3	161	Plasma (Baseline, after PCI)	Ischemic cardiomyopathy with PCI	Tertiles	Death and other major adverse cardiac events	6 years	Yes	8
Bro-Jeppesen,J. et al.	2015	[65]	Denmark	61 ± 11.3	169	Plasma (Baseline, after cardiac arrest)	Cardiac arrest	Median (99.2 pg/mL)	All-cause death	30 days	Yes	8
Novo, G. et al.	2015	[66]	Italy	67.5 ± 13.3	33	Plasma (within 24 h)	Acute myocardial infarction	Median	Death and other major adverse cardiac events	6 years	Yes	8
Zhang, D. F. et al.	2016	[67]	China	59.1 (51.9, 66.8)	566	Serum (Baseline)	Mild to moderate coronary artery lesions	Median (60.02 pg/mL)	Death and other major adverse cardiac events	6 years	Yes	7
Aleksova, A. et al.	2017	[68]	Italy	58 (50, 67)	156	Plasma (Baseline)	Idiopathic dilated cardiomyopathy	Median (2.7 pg/mL)	Death or heart transplantation	Median 89.6 months	Yes	8

Notes: (1) Age in years is presented as the mean ± SD or mean (range). (2) "Yes" indicates that the effect estimate was adjusted in at least one regression model.

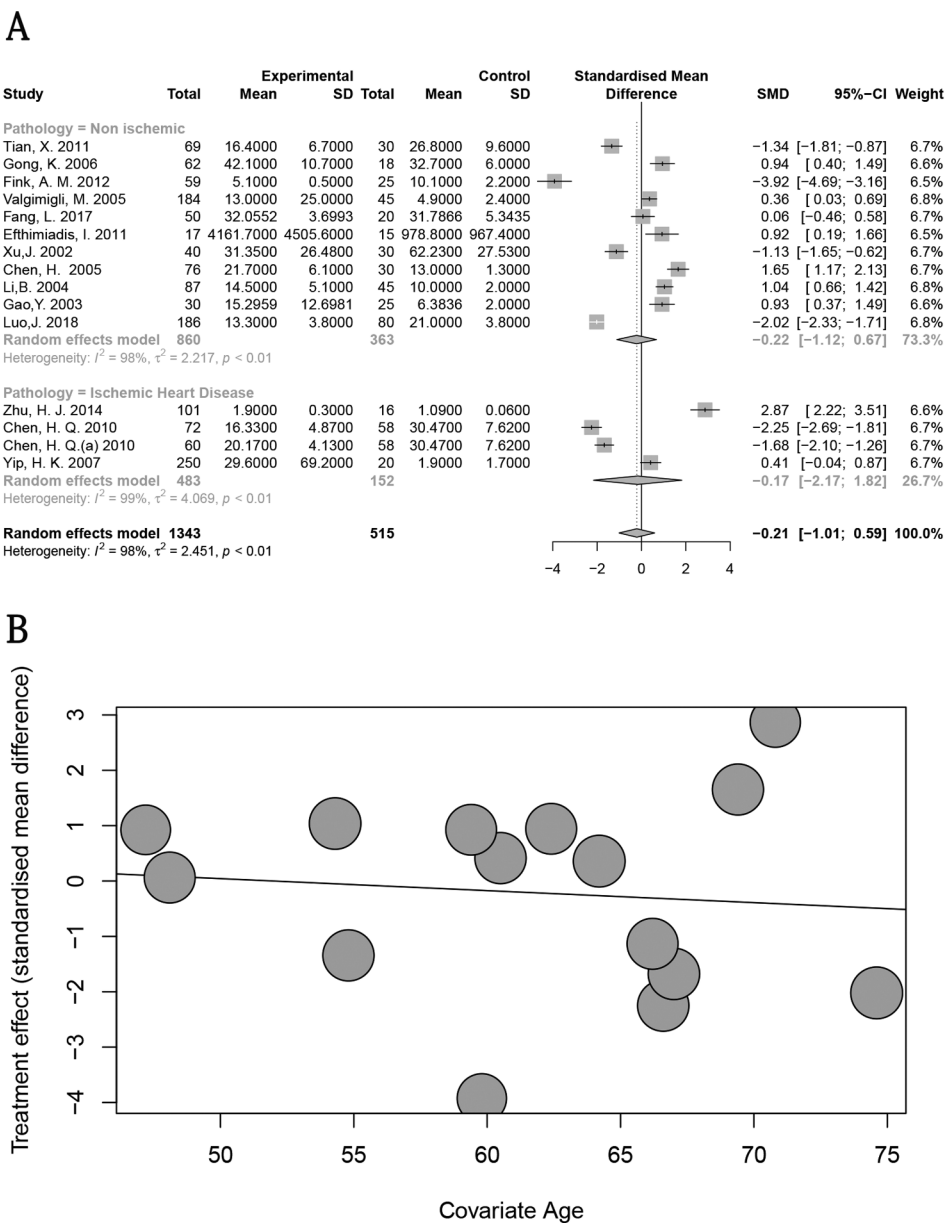

Fig. 2. Meta-analysis of IL-10 levels in patients with CVD and healthy controls. (A) Forest plot of pooled data of patients with ischemic or nonischemic cardiac pathologies. (B) Meta-regression data of the SMD in IL-10 levels based on the ages of the participants.

CI = 1.00–1.20, p = 0.043, Fig. 3B). The meta-regression analysis indicated that a possible positive correlation exists between the IL-10/CRP ratio and adverse events, but this correlation was not statistically significant (β = 0.013, p = 0.483, Fig. 3D). Additionally, our data showed that no correlation exists between the risk of adverse events and the age of the participants or cut-off value (p > 0.05, Fig. 3E and F). However, the risk of adverse events and the IL-10/IL-6 ratio were positively correlated with (β = 0.644, p = 0.024, Fig. 3C) or without correcting for the average age (β = 0.601, p = 0.0036).

Subsequently, we performed a subgroup analysis to determine the association between the HR of IL-10 and CVD under different conditions (Table 3 and Figs. S1–S3). The results showed no significance differences in the IL-10 levels and coronary artery disease in both the crude analysis and age/gender subgroup analysis (p > 0.05, Table 3). Higher IL-10 levels seem to be associated with a poor prognosis of heart failure (HR = 1.49, 95% CI = 1.08–2.05, p = 0.016, Table 3). We also found that the HR of IL-10 increased from 1.08 in studies with less than 50% statin treatment to 2.5 in studies with more than 50% statin treatment (Table 3). This finding may be partially explained by statins reducing the levels of metabolic inflammation, and with a lower IL-10/IL-6 ratio status, IL-10 may be related a poor prognosis. The data from the sensitivity test show that the heterogeneity of each experiment is within the acceptable range (does not exceed the 95% confidence interval) in all subgroup analyses (Figs. S4–S6).

3.4. Analysis of publication bias

To examine the quality of the included data, we analyzed the publication bias of all pooled studies (Fig. 4). The funnel plots showed no publication bias in the meta-analysis of the pooled SMD (p = 0.481), pooled HR in nonischemic cardiomyopathy (p = 0.621) and HR in ischemic cardiomyopathy (p = 0.210).

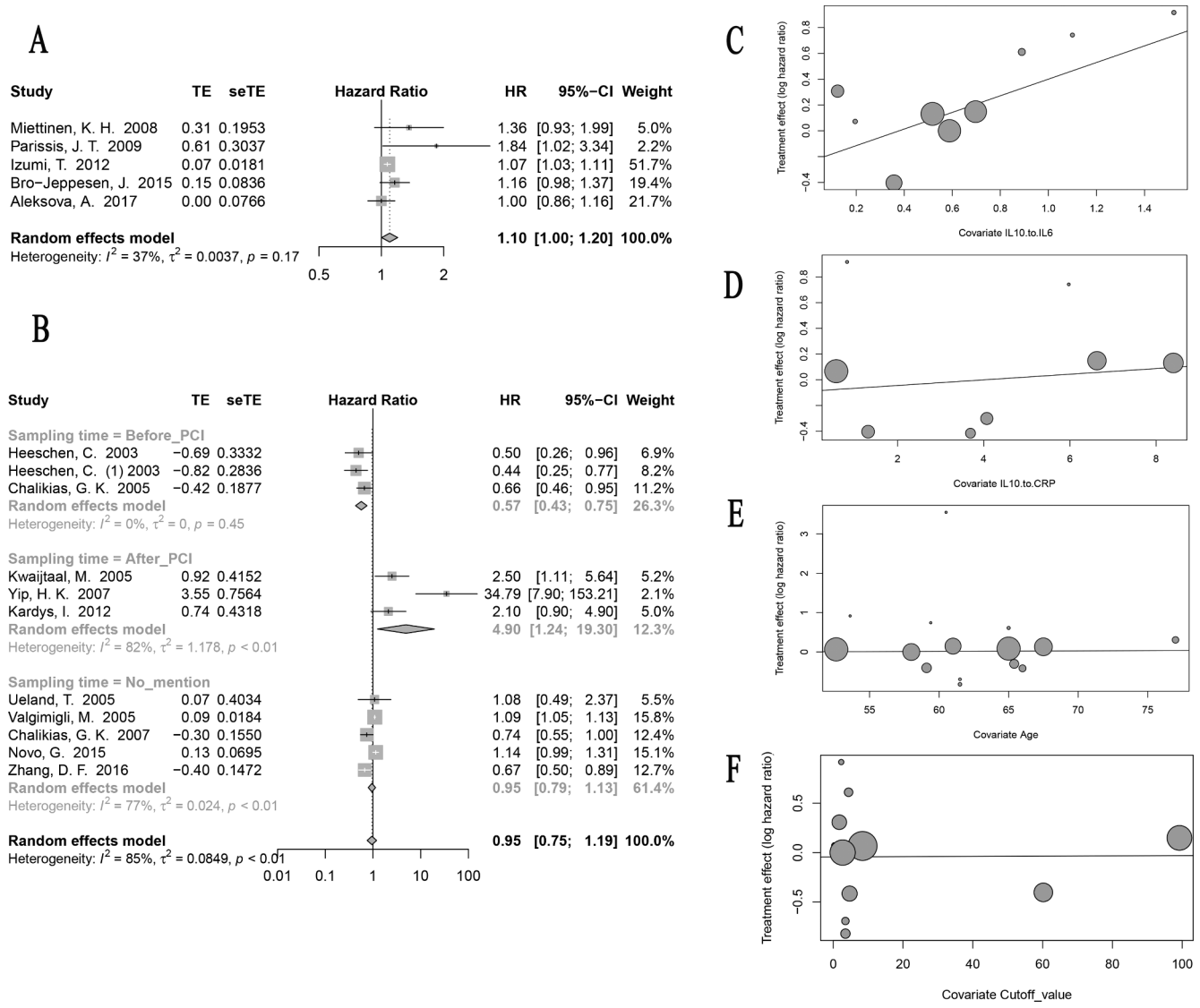

Fig. 3. Meta-analysis of the association between IL-10 levels and CVD prognosis. (A) Forest plot of pooled data of patients with ischemic cardiac pathologies based on the sampling time point. (B) Forest plot of the pooled data of patients with nonischemic cardiac pathologies. Meta-regression data of the SMD in IL-10 levels based on (C) the IL-10/IL-6 ratio, (D) the IL-10/CRP ratio, and (E) the participants' age. (F) Cut-off value of IL-10. Note: (1) Heeschen, C. et al., evaluating the hazard risk of IL-10 at 48 h and at 6 months.

Table 3
Results of the subgroup analysis.

Cardiopathy	Subgroup	No. of studies	Heterogeneity test			Pooled HR		
			Q	I^2	P-Value	HR	[95% CI]	p-Value
Coronary syndrome or myocardial infarction	Crude analysis	10	46.01	80.4	< 0.001	0.878	[0.720, 1.071]	0.199
	% of Males > 70	6	32.45	84.6	< 0.001	0.792	[0.554, 1.133]	0.202
	% of Males ≤ 70	4	13.43	77.7	0.004	1.037	[0.691, 1.556]	0.861
	Average age > 60	7	29.02	79.3	< 0.001	0.84	[0.690, 1.032]	0.097
	Average age ≤ 60	3	13.82	85.5	0.001	1.43	[0.540, 3.788]	0.473
Heart failure		2	0.71	0	0.401	1.49	[1.080, 2.050]	0.016*
Cardiovascular disease	% of Statin > 50	1	–	–	–	2.5	[1.110, 5.640]	0.027*
	% of Statin ≤ 50	2	2.48	59.6	0.115	1.08	[0.830, 1.440]	0.514

Note: - Values could not be calculated due to an insufficient number of studies.
* $p < 0.05$; HR was considered statistically significant.

3.5. Change in the IL-10/IL-6 ratio across different phases of MI prognosis and different ages

To explore the changes in the IL-10/IL-6 ratio across different phases of recovery and different ages, we extracted relevant data from a cohort study and a genomic profiling set (GSE58015) separately [18,19]. We calculated the IL-10/IL-6 ratio at one-year follow-up intervals after myocardial infarction and found that this ratio notably

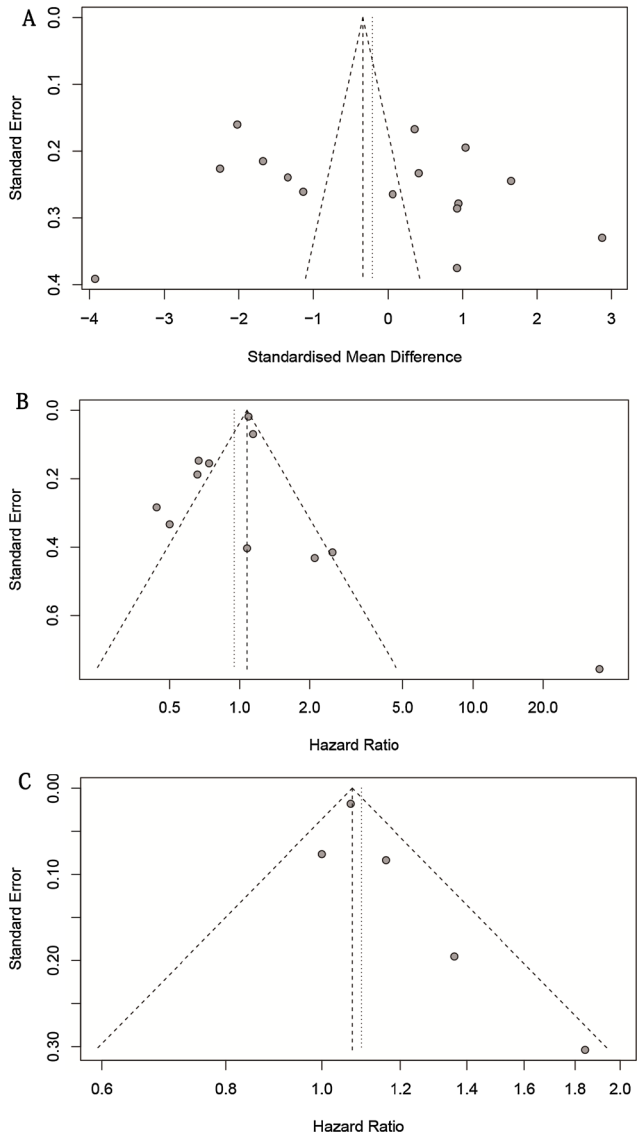

Fig. 4. Funnel plots: pooled analysis of (A) IL-10 levels in patients with CVD and healthy controls, (B) the association between IL-10 levels and prognosis of ischemic cardiac pathologies, and (C) the association between IL-10 levels and the prognosis of nonischemic cardiac pathologies.

increased over time (2.1-fold at 2 months, 2.7-fold at 1 year and 2.3-fold at 2 years compared with the baseline value, Fig. 5A). Based on gene expression data of human monocyte-derived dendritic cells (MDDCs) from young and aged healthy donors, we found that the levels of IL-10 mRNA in the aged individuals were significantly higher than those in the young individuals ($p = 0.049$, Fig. 5B). Although the difference was not statistically significant, the levels of IL-6 mRNA in the aged individuals were lower than those in the young individuals ($p = 0.164$, Fig. 5C). In addition, the IL-10/IL-6 ratio was significantly higher in the aged individuals ($p = 0.036$, Fig. 5D). Interesting, in contrast to the data of the heathy people, the average age is negatively correlated with the IL-10/IL-6 ratio in patients with CVD (R square = 0.247, Fig. 5E). This finding may be due to the long-term microinflammation status of aging patients with CVD and other primary diseases, such as hypertension and diabetes. Nonetheless, our data suggest that the IL-10/IL-6 ratio varies across different phases of MI prognosis and different ages, which may partially explain the bias.

4. Discussion

The inflammatory response plays an important role in the pathological process of CVD and primary diseases, such as hypertension and diabetes [20,21]. Numerous studies have shown that high levels of proinflammatory factors are associated with cardiovascular risk [22–25]. During the inflammatory phase, atherosclerotic plaque formation, hemodynamic abnormalities and ventricular remodeling occur along with endothelial damage and a reduction in vasodilatory factors, especially nitric oxide. Many inflammatory factors can be used as risk indicators of cardiovascular events; however, combining multiple indicators may better reflect the inflammation levels or trends and may lead to better risk prediction results [26,27].

IL-10 is a main anti-inflammatory cytokine that is widely involved in the pathological processes of disease [28]. The conclusions of previous studies regarding the role of IL-10 in individuals with CVDs are inconsistent. Initially, a series of reports noted that IL-10 exerts cardioprotective effects primarily in ischemia-reperfusion injury [29–31]. Furthermore, some cohort studies claimed that elevated IL-10 serum levels are associated with a more favorable prognosis in patients with acute coronary syndrome and other cardiac pathologies [13,14,32]. Additionally, treatment with cardioprotective compounds has been shown to be associated with an increase in IL-10 content [31,33–35]. Cardioprotection has been observed to be conferred both in vitro and in vivo by the modulation of IL-10, which involves stress and immune signaling pathways, such as the P38-MAPK, NF-Kappab and JAK/STAT pathways [36,37]. In contrast to observations showing beneficial effects, other observations have shown that IL-10 is positively correlated with diastolic dysfunction in patients with MI, hypertrophic cardiomyopathy and other cardiac pathologies [38–41]. Thus, IL-10, which was originally identified as an anti-inflammatory cytokine exerting pleiotropic effects in the body, seems to play a dual role in heart disease. No consensus or reasonable explanation for the above contradictions currently exists. Our pooled data for the comparison of the difference in IL-10 levels between CVD patients and healthy controls were highly heterogeneous. In the analysis of the prognostic value of IL-10, we found that higher IL-10 levels were associated with an increased risk of adverse events in nonischemic cardiac pathologies, but these results were not consistent with the results of a series of animal studies. Interestingly, in patients with ischemic pathologies, we found that IL-10 played opposite roles before and after PCI, suggesting that IL-10 may play diverse roles during different stages of cardiac pathology. Evidence explaining these results are lacking, and we must consider the different pathological status of the heart before PCI (predominant ischemic pathology) and after PCI (ischemia-reperfusion). First, the cytokine profile differs before and after PCI [42,43], which may cause some risk cytokines correlated with IL-10 to not be corrected after PCI. In addition, although IL-10 has anti-inflammatory effects, the role of IL-10 in ischemia reperfusion is controversial [44,45], and further research is needed to explore the heterogeneity. In addition, higher baseline IL-10 levels may signal future excess IL-10 during the repair period, which may induce an expansion in the fibrosis area during the late stage of myocardial remodeling; however, these hypotheses require more evidence. Our meta-regression analysis showed that the CVD risk associated with IL-10 levels may be related to IL-6 levels, thus indicating that the role of IL-10 may depend on the levels of other inflammatory factors. The IL-10/IL-6 ratio changes during different stages of disease. Thus, we suspect that IL-10 plays a protective role in the hyperinflammatory state but may be a risk factor for disease; this hypothesis is supported by recent evidence suggesting that IL-10 is also a profibrogenic factor that can stiffen heart tissue [16,15].

Although most basic research has reported only the protective effect of IL-10, most studies are based on its anti-inflammatory effects. Recently, Hulsmans M et al. noted an excess production of IL-10 in the setting of diastolic dysfunction caused by the combination of salty

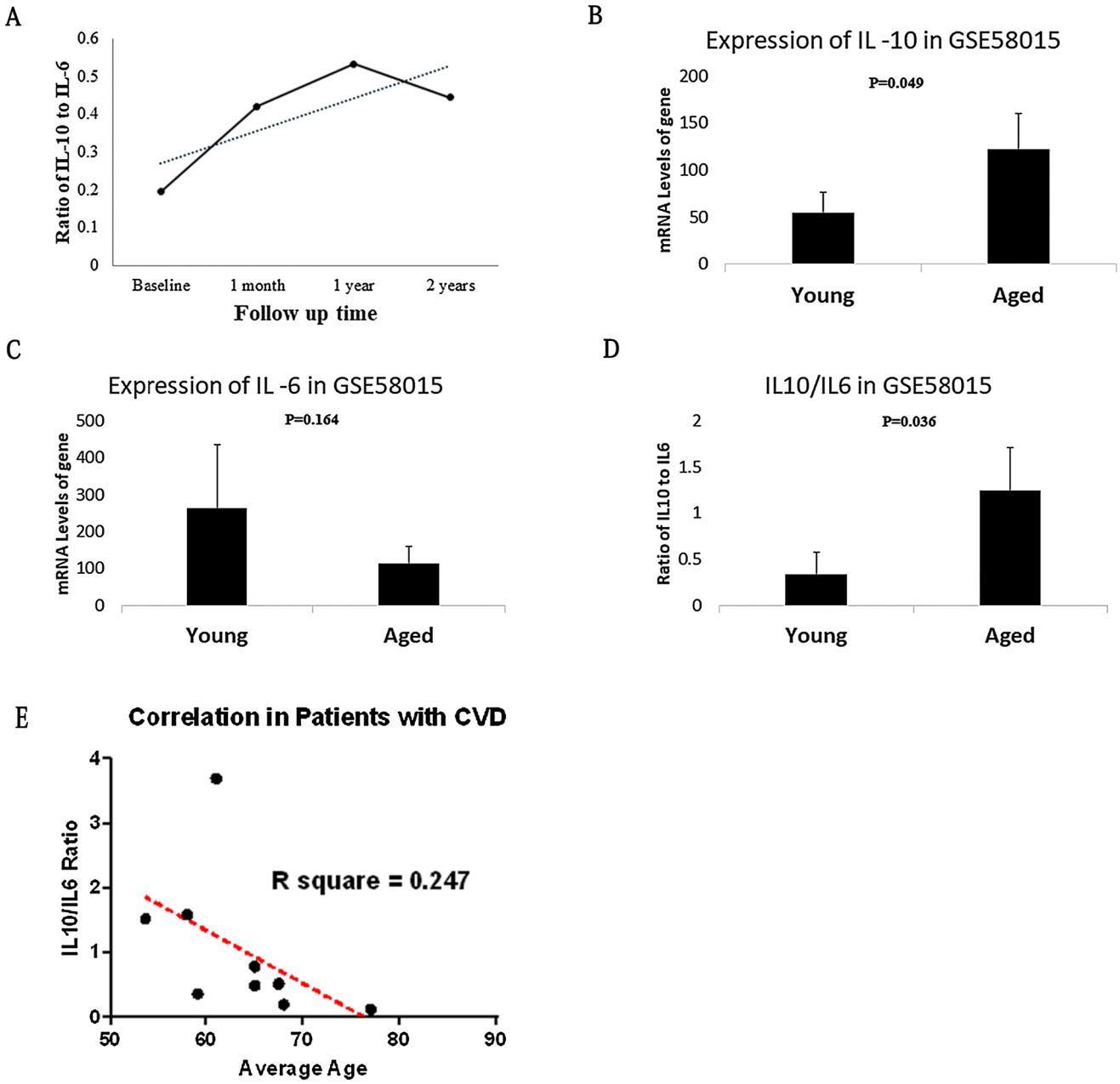

Fig. 5. Trend in IL-10/IL-6 ratio in different disease states. (A) IL-10/IL-6 ratio (mean value) was increased 2 years after PCI was performed. mRNA levels of (B) IL-10 and (C) IL-6 and (D) the IL-10/IL-6 ratio in human MDDCs from healthy young and aged people. (E) Correlation in patients with CVD.

drinking water, unilateral nephrectomy, and chronic aldosterone exposure (SAUNA) and old age [16]. These authors found that macrophage-specific IL-10 deletion reduced fibrosis and improved diastolic function, suggesting that IL-10 may exert deleterious profibrotic effects in aging-related heart failure, although it may be beneficial for inflammation resolution and wound healing. In our study, the IL-10/IL-6 ratio in aged individuals was significantly higher than that in young individuals, which may explain the contradiction as follows: in the elderly, IL-10 may play a leading role in promoting fibrosis rather than conferring protective anti-inflammatory effects. In addition, lipids and lipoprotein profiles are important prognostic indicators of cardiovascular events and are closely related to metabolic inflammation [46]. We also found that the HR of IL-10 increased in studies with more than 50% statin treatment, which may be partially ascribed to statins reducing the levels of metabolic inflammation, and with a lower IL-10/IL-6 ratio status, IL-10 may related to a poor prognosis.

Nevertheless, although some clinical observations and most basic trials suggest that IL-10 has a protective effect on ischemic cardiac pathology, we found that the association between IL-10 levels and myocardial infarction prognosis may be pleiotropic, suggesting that IL-10 cannot be used as an independent risk indicator of MI. Second, our meta-regression analysis showed that the risk associated with IL-10 levels in CVDs may be related to IL-6 levels, suggesting that compared with a single indicator, it may be more reasonable to predict prognosis by combining multiple cytokines. In addition, we found that higher IL-10 levels were significantly associated with a poor prognosis in patients with nonischemic pathologies, suggesting that IL-10 may be considered a prognosis indicator in some nonischemic pathologies, such as chronic heart failure.

Our meta-analysis contains possible limitations. First, due to the high data heterogeneity, we did not confirm the trend in the IL-10 levels in different cardiac pathologies. Second, due to the limited collection of

data, we could not precisely determine the risk associated with IL-10 levels in various cardiac disorders. Finally, although reduced in the subgroup and meta-regression analyses, heterogeneity remained, suggesting that the risk associated with the IL-10 levels may depend on other unreported factors.

5. Conclusion

The major finding of our study is that the risk associated with IL-10 levels in CVD, which is determined by the levels of some inflammatory factors, may be pleiotropic. The existing evidence indicates that higher levels of IL-10 are associated with a higher risk of adverse events in nonischemic cardiac pathologies. However, the correlation between IL-10 and ischemic cardiac pathologies may depend on the stage of the disease. Nevertheless, an investigation of the mixed effect of IL-10 and some inflammatory factors, such as IL-6, IL-18 and TNF-α, in CVD is needed. Thus, further studies are warranted to comprehensively investigate the precise role of IL-10 in all phases and pathologies of CVD.

Conflict of interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.02.017.

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