

REVIEW ARTICLE

Premature Coronary Artery Disease and Plasma Levels of Interleukins; a Systematic Scoping Review and Meta-Analysis

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Abstract: **Introduction:** Interleukins (ILs) can act as a predictive indicator of Premature Coronary Artery Disease (pCAD) and may be useful in screening of high-risk patients. However, there is no consensus on the relationship of serum levels of ILs and pCAD, yet. As a result, this study has been conducted in order to review the literature on the relationship between serum levels of different ILs and pCAD. **Methods:** Medline, Scopus, Embase, and Web of Science databases were searched until December 7th 2020. Two reviewers independently screened and summarized eligible articles. A meta-analysis was performed to assess the relationship of ILs and pCAD. **Results:** 12 case-control articles were included. IL-6 plasma changes do happen in pCAD patients with a standardized mean difference (SMD) of 0.51 (95% CI: 0.12-0.90; $p=0.010$) compared with the control group. This difference was also observed when evaluating the plasma levels of IL-1 and IL-17, with an SMD of 1.42 (95% CI: 1.11-1.73; $p<0.001$) and 0.59 (95% CI: 0.14-1.04; $p=0.011$), respectively. Meanwhile, no significant difference existed in plasma levels of IL-10 (SMD=0.26; 95% CI: -0.17-0.70; $p=0.236$), and IL-18 (SMD=1.44; 95% CI: -0.19-3.07; $p=0.083$) between pCAD patients and those in the control group. **Conclusion:** Low level of evidence showed that there may be a significant relationship between increased plasma levels of ILs and the occurrence of pCAD. As a result, prospective cohort studies with serial assessments of serum ILs during follow up period, focusing on controlling classical risk factors of pCAD and increase in level of ILs, should be conducted.

Keywords: Coronary artery disease; cardiovascular disease; interleukins; Prognosis; Biomarkers

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1. Introduction

Coronary artery disease (CAD) is a condition in which buildup of atherosclerotic plaques leads to narrowing of the coronary arteries. This disease manifests in various clinical

forms, including angina and myocardial infarction (MI). CAD is the leading cause of death worldwide (1, 2), having a prevalence of 6.7% (18.2 million individuals) amongst people aged 20 years or older, with one individual having an MI every 40 seconds in US (3). Given its importance and profound burden on the society, identifying its risk factors and managing them could play a key role in helping affected patients.

Furthermore, coronary artery disease can occur in younger ages, which is named Premature Coronary Artery Disease (pCAD). In particular, it has a cut off age, mostly suggested to be less than 55 and 65 years for men and women, respectively (4). Although most studies suggest a low incidence rate for pCAD, it is possible that with the rise in cardiovascular risk

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factors, such as smoking and obesity, among younger population, the number of young individuals with underlying conditions that may lead to pCAD is much higher than currently estimated (5). In addition, because of the devastating effects of this disease on the more active lifestyle of young patients, and also the importance of early detection and treatment of young individuals, prompt and accurate identification of young individuals who are at the greatest risk is necessary (6). pCAD is defined as an inflammatory disease (7), and cardiovascular events are more common in patients with high circulating levels of several inflammatory markers. In this regard, treating patients based on inflammatory parameters, such as hs-C reactive protein (hs-CRP), has been proved to improve outcomes (8). On the other hand, interleukins (ILs) are a group of cytokines with important roles in the regulation of immune and inflammatory responses. Several ILs (such as IL-1 and IL-6) are major players at the downstream of vascular inflammatory cascades (9). As it has been shown in several studies, there might be a relationship between serum level of different types of ILs (IL-1, IL-6, etc.) and coronary artery diseases (10-12). Since other inflammatory cytokines such as hs-C reactive protein have been classically linked to coronary events, it is also reasonable to study the possible relationship between ILs and coronary events. Therefore, ILs can serve as a predictive indicator of pCAD and may be useful in screening of high-risk patients. However, there is no consensus on the relationship of serum levels of ILs and pCAD, yet. As a result, this study has been conducted in order to review the literature on the relationship between serum levels of different ILs and pCAD.

2. Methods

2.1. Study design and search strategy

The current systematic review and meta-analysis is designed for the aim of investigating the changes in the plasma level of different types of ILs following a coronary artery disease in the younger population, or pCAD as previously defined. Accordingly, PICO was defined as follows: patients (P): male patients younger than 55 and female patients younger than 65 years of age, with angiographically confirmed coronary artery stenosis more than 50% in coronary vessels. Index test (I): measuring plasma level of ILs in patients. Comparison (C): comparing results of the case group (with the defined coronary artery stenosis) with those of the control group (patients without the defined coronary artery stenosis). Outcome (O): occurrence of pCAD.

For this purpose, Medline (via PubMed), Scopus, Embase, and Web of Science databases were thoroughly searched using carefully selected keywords. These keywords were selected using MeSH and Emtree vocabularies, reviewing similar articles' relevant keywords, and with the help of experts

in the field. Then, a systematic search strategy was designed based on the defined P and I and using the selected keywords. This search was initially performed for articles published until November 6th, 2020, and then updated until December 7th 2020. The search strategy in Medline database is presented in Appendix 1. In addition, a manual search was also performed in Google and Google scholar to obtain any preprints and possibly missing papers.

2.2. Selection criteria

The inclusion criteria in the present systematic review were reporting plasma levels of ILs, independently in case and control groups, and conducting the research on a population of pCAD patients, regardless of their underlying condition. The exclusion criteria consisted of not having a control group, case report studies, and review articles.

2.3. Data collection

Two reviewers independently screened titles and abstracts of the retrieved articles, for inclusion based on the inclusion criteria. Then, eligible articles were obtained and exclusion criteria were applied to select the included articles. Finally, a summary of the included articles' data was recorded using a checklist, consisting of the following variables: first author's name, publication year, country in which the study was conducted, study design, definition of the pCAD patients, number of patients in case group, number of patients in the control group, mean age of the patients in the case group, mean age of the patients in the control group, type of the measured ILs, plasma level of the ILs in the case group, plasma level of the ILs in the control group, and the time interval between angiography and measurement of ILs levels in patients' plasma sample. Any disagreement between the reviewers was resolved via discussion with a third reviewer.

2.4. Quality assessment

Two independent reviewers performed the quality assessments using National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for case-control studies (13). Any disagreement was resolved through discussion with a third reviewer.

2.5. Statistical analysis

All analyses were performed using STATA 14.0 statistical program. Data were recorded as mean and standard deviation (SD) in case and control groups, separately. Then using "metan" command in STATA program a standardized mean difference (SMD) was calculated for each individual study. Finally, a pooled SMD and 95% confidence interval (95% CI) was reported. Heterogeneity among studies was assessed, using I² test. Egger's test and funnel plot were used to assess publication bias.



3. Results

3.1. Study characteristics

The systematic search in the electronic databases yielded 622 records. 269 duplicates were eliminated and 353 articles remained. Afterwards, reviewers performed the initial screening according to the inclusion criteria, gathering 44 articles were found to be potentially eligible to enter the current study. Then, applying the exclusion criteria, the next screening process was performed, resulting in the inclusion of 12 articles (all of them had case-control design) in the present systematic review and meta-analysis (Figure 1) (14-25), three of which measured more than one type of ILs in the studied patients (14, 15, 19). IL-6 was measured in seven studies (14-17, 20, 21, 24), IL-10 was measured in four studies (14, 19, 22, 25), IL-18 was measured in three studies (14, 19, 23) and IL-1 (15) and IL-17 (18) were each measured in one study. Overall, 3098 patients with pCAD and 3711 control subjects were studied in the included articles. Among them, 2696 of the pCAD patients and 2271 of control patients were male. These studies had taken place in various countries: Pakistan (14, 19), Greece (15), India (16), South Korea (17), Turkey (18), South Africa (21), Sweden (20), Mexico (22), Australia (23), Poland (24), and China (25). Regarding the design of the included studies, seven studies were conducted prospectively (14, 15, 18, 19, 21, 24, 25) and the other five were conducted retrospectively (16, 17, 20, 22, 23). All of the included studies confirmed pCAD performing a coronary angiography. Detailed characteristics of the articles is summarized in Table 1.

3.2. Risk of bias assessment

Sample size justification, blinding of the assessors, adjustment of the results based on key confounding variables, and the use of concurrent controls were not recorded in any of the studies. Also, none of the study samples were randomly taken from their target population. Table 2 presents details of risk of bias assessment among the included studies.

3.3. Publication bias

Publication bias was assessed regarding the report of the case and control groups' plasma levels of IL-6, IL-10 and IL-18, while IL-17 and IL-1 were separately measured in only one article each. As depicted on Figure 2, no publication bias exists regarding the assessment of IL-6 ($p=0.440$), IL-10 ($p=0.960$), and IL-18 ($p=0.181$) in the pCAD patients.

3.4. Meta-analysis

The differences in the plasma levels of ILs between pCAD patients and control patients were evaluated, and the results are depicted in Figure 3. It was shown that IL-6 plasma changes do happen in pCAD patients with a standardized mean dif-

ference (SMD) of 0.51 (95% CI: 0.12 to 0.90; $p = 0.010$) compared with the control group. This difference was also observed when evaluating the plasma levels of IL-1 and IL-17, with an SMD of 1.42 (95% CI: 1.11 to 1.73; $p < 0.001$) and 0.59 (95% CI: 0.14 to 1.04; $p = 0.011$), respectively. Meanwhile, no significant difference existed in plasma levels of IL-10 (SMD=0.26; 95% CI: -0.17 to 0.70; $p = 0.236$), and IL-18 (SMD=1.44; 95% CI: -0.19 to 3.07; $p = 0.083$) between pCAD patients and the control group. However, the I² test revealed a considerable amount of heterogeneity among the studies.

4. Discussion

The present systematic review and meta-analysis evaluated the changes of the plasma levels of different types of ILs following pCAD. For this purpose, IL plasma levels were compared between the pCAD patients and the participants in the control groups in the included studies. As mentioned above, an explicit correlation exists between the occurrence of pCAD and the plasma levels of IL-6, IL-1 and IL-17. As a result, it can be concluded that in pCAD patients, a rise in the plasma levels of the three ILs will possibly be observed. However, the heterogeneity among the studies was considerably high, making it tough to firmly conclude on the exact correlation between IL plasma levels and the occurrence of pCAD. Moreover, the existing literature regarding this subject is also controversial. For instance, Satti et al. reports that increased plasma levels of IL-6 is associated with higher risk of CAD (26), while Ghazouani et. al reports no correlation between CAD and IL-6 (27), while in both studies, pCAD patients were present among the study population. Overall, these heterogeneities in the studies can be attributed to many factors. Firstly, none of the studies included in our group of eligible articles reported their results with respect to coronary risk factors, for example diabetes, lipid profile, smoking status, existence of hypertension and etc., which were present in their study populations. These risk factors could result in different amounts of change in IL plasma levels. Thus, we do recommend that in future studies, these risk factors be carefully evaluated and matched between the case and the control groups.

Secondly, the time interval between IL measurement and the occurrence of pCAD was somewhat vague in the studies. As a result, IL plasma levels could change in time following a coronary event in patients. With respect to the definitions of pCAD patient not being exactly the same between the included studies, this limitation could be overturned by adopting exactly similar definitions regarding the occurrence of pCAD and, accordingly calculating the time interval between the coronary event and the measurement of IL's plasma level. In addition, all included studies had case-control design and there were no prospective cohort studies. Therefore, the



overall level of evidence in the present meta-analysis is low.

5. Conclusion

Low level of evidence showed that there may be a significant relationship between plasma levels of ILs and the occurrence of pCAD. Since, there were no prospective cohort studies, included in the present meta-analysis, the screening value of ILs in prediction of pCAD is not clear. As a result, prospective cohort studies with serial assessments of serum ILs during follow up period, focusing on controlling classical risk factors of pCAD and increase in level of ILs, should be conducted, with respect to the mentioned limitations, to resolve this uncertainty.

6. Declarations

6.1. Acknowledgments

None.

6.2. Availability of data and materials

All data generated or analyzed during this study are included in this published article.

6.3. Authors' contributions

Study design: MY, MHA

Performing search and designing search strategy: All authors.

Data gathering and quality assessment of included studies: KA, AMN, AT, MHA

Analysis: MY

Drafting: AMN, AT, KA, MY

Critically revised: MY and MHA

6.4. Funding and supports

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6.5. Conflict of interest

There is no conflict of interest.

6.6. Role of the Sponsor

The Prevention of Cardiovascular Disease Research Center, Shahid Beheshti University of Medical Sciences had no role in the design and conduct of the study; collection, management, and analysis of the data.

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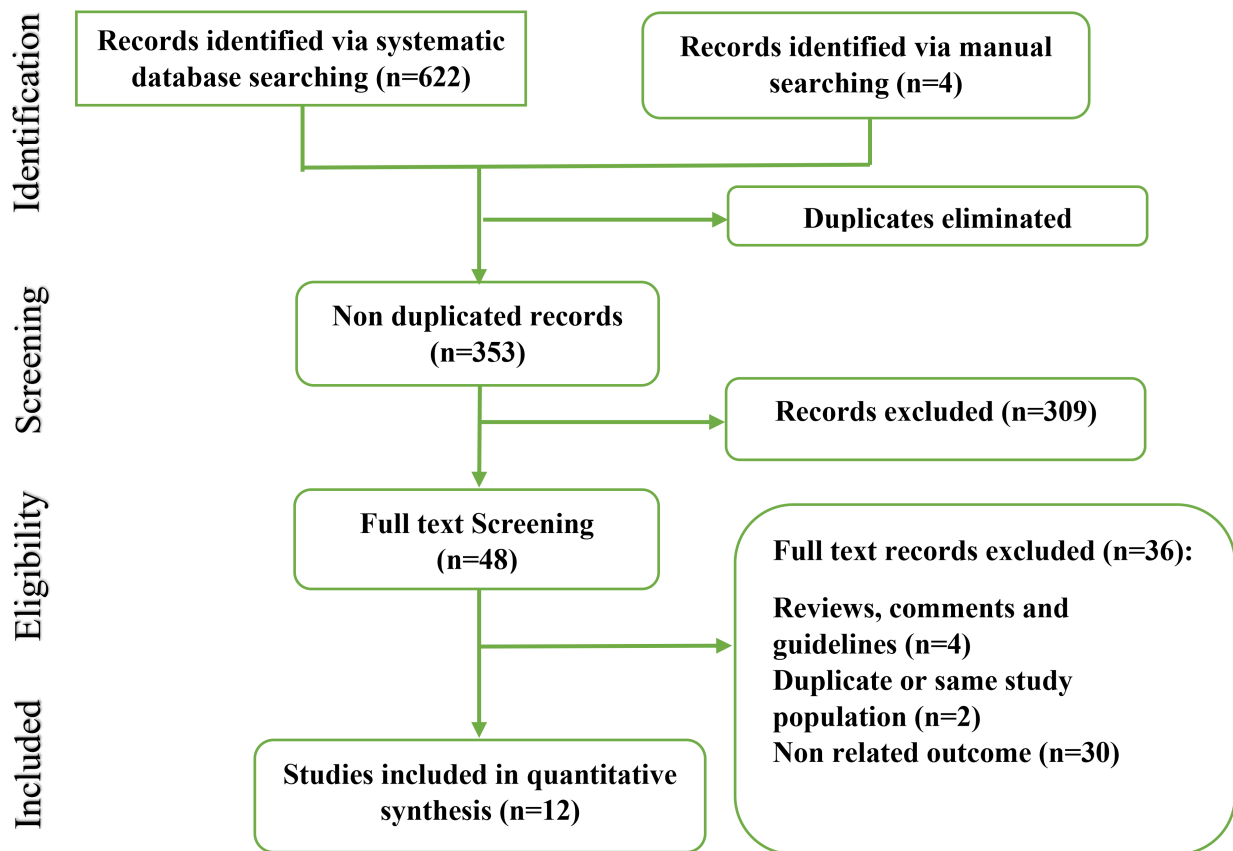
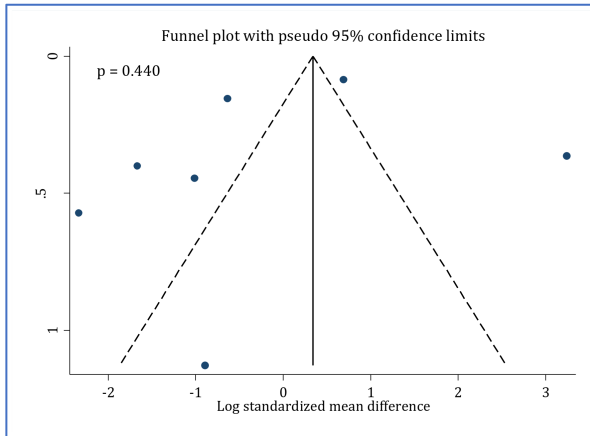
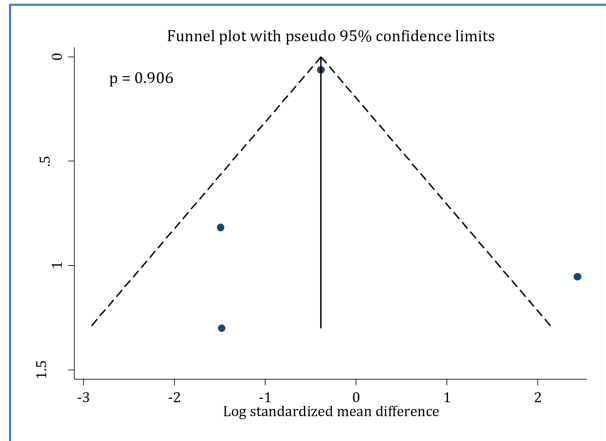


Figure 1: Flow diagram of the present meta-analysis.

IL-6



IL-10



IL-18

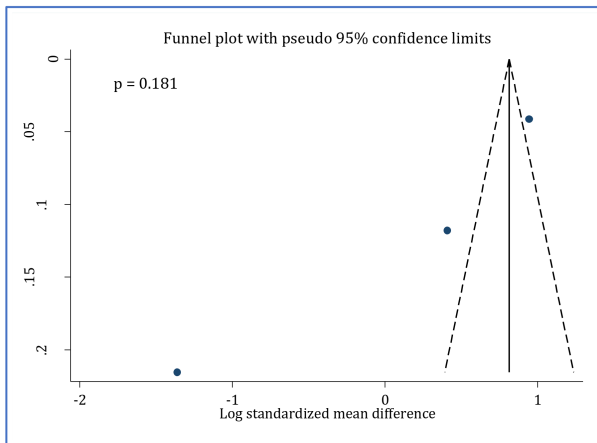


Figure 2: Funnel plot for the analysis of publication bias regarding the correlation between the occurrence of premature coronary artery disease and the changes in the plasma level of interleukins (ILs). No publication bias was observed for IL-6 (p=0.440), IL-10 (p=0.960) and IL-18 (p=0.181).



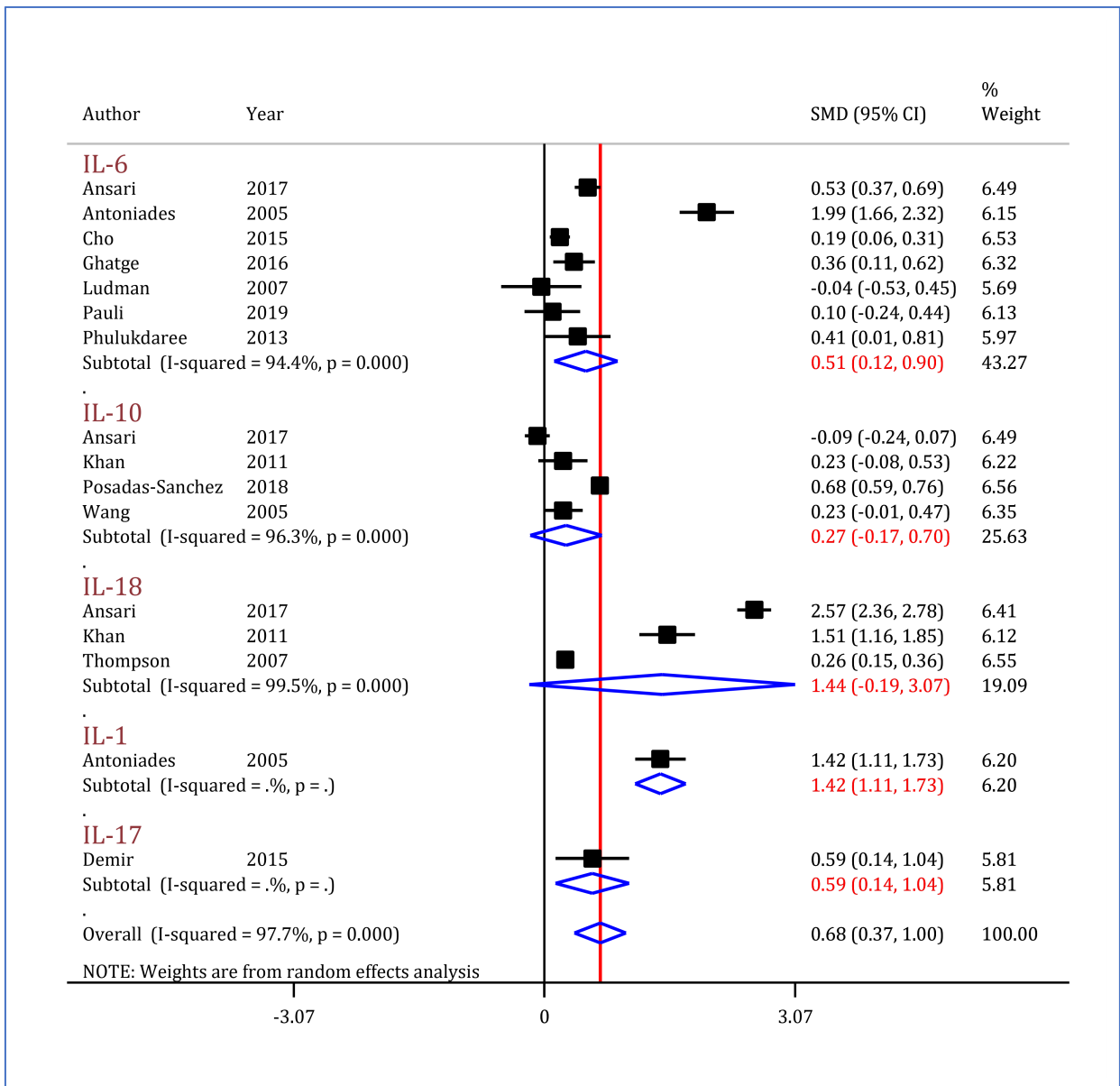


Figure 3: Forest plot for the assessment of the changes in the plasma levels of interleukins (ILs) in premature coronary artery disease (pCAD) patients compared with that of the control group. SMD: Standardized mean difference; CI: Confidence interval.



Table 1: Summary and characteristics of the included studies

Author; Year; Country	Study design	Definition of pCAD in the study	No. of patients in the case group	No. of patients in the control group	Mean age of patients in the case group	Mean age of patients in the control group	No. of males in the case group	No. of males in the control group	Type of IL	Time interval between angiography and IL measurement (hours)	IL plasma level in the case group	IL plasma level in the control group	Unit
Ansari; 2017; Pakistan	Prospective	>70% stenosis in at least one coronary vessel & age<45	329	310	42	39	329	298	IL-18	0	236.6± 42.5	175.6±21.8	pg/ml
									IL-6		3.8± 1.5	2.9±1.9	ng/dl
									IL-10		0.83± 0.53	0.87±0.36	pg/ml
Antoniades; 2005; Greek	Prospective	ST Segment Elevation MI & age<49	58	205	48.6	49.7	58	180	IL-1b	24	1.37± 1.41	0.31±0.37	pg/ml
									IL-6		7.7±4.3	2.16±2.15	pg/m
Ghatge; 2016; India	Retrospective	>70% stenosis in at least one coronary vessel & age<45 in males or age<50 in females	93	120	41.79	41.78	93	93	IL-6	12	3.66± 0.19	2.98±0.15	pg/ml
Cho; 2015; Korea	Retrospective	>50% stenosis in at least two coronary vessels & age<55 in males or age<60 in females	414	503	49.3	48.6	414	414	IL-6	NR	9.6±44.1	3.6±8.9	pg/ml
Demir; 2015; Turkey	Prospective	angiography confirmed coronary artery disease & age<45	45	35	39.6	40.1	35	19	IL-17A	12	2 ± 1.88	0.9±1.86	pg/ml
Khan; 2011; Pakistan	Prospective	>70% stenosis in at least one coronary vessel & age<45	98	74	40	35	89	65	IL-18	0	302.25±114.81	145±88.89	pg/ml
									IL-10		2.03±1.7	1.63±1.85	pg/ml
Ludman; 2007; Sweden	Retrospective	Myocardial infarction and age between 45-55	41	26	51	51	41	26	IL-6	NR	3.7± 2.28	3.81±3.49	ng/dl
Phulukdare; 2013; South Africa	Prospective	angiography confirmed coronary artery disease & age<45	41	61	NR	NR	41	61	IL-6	NR	0.91±0.01	0.86±0.13	pg/ml



Table 1: Summary and characteristics of the included studies

Author; Year; Country	Study design	Definition of pCAD in the study	No. of patients in the case group	No. of patients in the control group	Mean age of patients in the case group	Mean age of patients in the control group	No. of males in the case group	No. of males in the control group	Type of IL	Time interval between angiography and IL measurement (hours)	IL plasma level in the case group	IL plasma level in the control group	Unit
Posadas-Sanchez; 2018; Mexico	Retrospective	infarction or >50% stenosis in coronary vessel & age<55 in males and age<65 in females	1160	1106	54	51	940	455	IL-10	NR	1.01±0.83	0.53±0.55	pg/ml
Thompson; 2007; Australia	Retrospective	>50% stenosis in at least one coronary vessel & age<60	556	1109	50	53	487	558	IL-18	NR	366.2±156	327.8±146.6	pg/ml
Pauli; 2019; Poland	Prospective	angiography confirmed coronary artery disease & age<55 in males and age<60 in females	100	50	49.9	48	75	37	IL-6	12	1.69±2.77	1.47±0.33	pg/ml
Wang; 2005; China	Prospective	infarction or >50% stenosis in coronary vessel & age<55 in males and age<65 in females	163	112	51	49	94	65	IL-10	NR	33.28±11.26	30.83±10.07	pg/ml

pCAD: Premature Coronary Artery Disease; IL: interleukin.



Table 2: Risk of bias assessment of the included studies

Author; Year	Items											
	1	2	3	4	5	6	7	8	9	10	11	12
Ansari; 2017	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Antoniades; 2005	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Ghatge; 2016	YES	YES	NO	YES	NR	YES	NA	NR	YES	YES	NR	NO
Cho; 2015	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Demir; 2015	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Khan; 2011	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Ludman; 2007	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Phulukdaree; 2013	NR	NO	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Posadas-Sanchez; 2018	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO
Thompson; 2007	YES	YES	NO	NO	YES	YES	NA	NR	YES	YES	NR	NO
Pauli; 2019	YES	YES	NO	YES	YES	YES	YES	NR	YES	YES	NR	NO
Wang; 2005	YES	YES	NO	YES	YES	YES	NA	NR	YES	YES	NR	NO

NA: Not applicable; NR: Not reported. Items:

1. Was the research question or objective in this paper clearly stated and appropriate?
2. Was the study population clearly specified and defined?
3. Did the authors include a sample size justification?
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
6. Were the cases clearly defined and differentiated from controls?
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
8. Was there use of concurrent controls?
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
11. Were the assessors of exposure/risk blinded to the case or control status of participants?
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?



Appendix 1: Medline search query

	Search terms
1.	<p>“Coronary Artery Disease” [mh] OR “Myocardial Infarction” [mh] OR “Myocardial Ischemia” [mh] OR “Acute Coronary Syndrome” [mh] OR “Coronary Stenosis” [mh] OR “ST Elevation Myocardial Infarction” [mh] OR “Non-ST Elevated Myocardial Infarction” [mh] OR Premature CAD[tiab] OR Premature coronary artery disease[tiab] OR Coronary Artery Disease[tiab] OR Artery Disease, Coronary[tiab] OR Artery Diseases, Coronary[tiab] OR Coronary Artery Diseases[tiab] OR Disease, Coronary Artery[tiab] OR Diseases, Coronary Artery[tiab] OR Coronary Arteriosclerosis[tiab] OR Arterioscleroses, Coronary[tiab] OR Coronary Arterioscleroses[tiab] OR Atherosclerosis, Coronary[tiab] OR Atheroscleroses, Coronary[tiab] OR Coronary Atheroscleroses[tiab] OR Coronary Atherosclerosis[tiab] OR Arteriosclerosis, Coronary[tiab] OR Myocardial Infarction[tiab] OR Infarction, Myocardial[tiab] OR Infarctions, Myocardial[tiab] OR Myocardial Infarctions[tiab] OR Cardiovascular Stroke[tiab] OR Cardiovascular Strokes[tiab] OR Stroke, Cardiovascular[tiab] OR Strokes, Cardiovascular[tiab] OR Myocardial Infarct[tiab] OR Infarct, Myocardial[tiab] OR Infarcts, Myocardial[tiab] OR Myocardial Infarcts[tiab] OR Heart Attack[tiab] OR Heart Attacks[tiab] OR Myocardial Ischemia[tiab] OR Ischemia, Myocardial[tiab] OR Ischemias, Myocardial[tiab] OR Myocardial Ischemias[tiab] OR Ischemic Heart Disease[tiab] OR Heart Disease, Ischemic[tiab] OR Disease, Ischemic Heart[tiab] OR Diseases, Ischemic Heart[tiab] OR Heart Diseases, Ischemic[tiab] OR Ischemic Heart Diseases[tiab] OR Acute Coronary Syndrome[tiab] OR Acute Coronary Syndromes[tiab] OR Coronary Syndrome, Acute[tiab] OR Coronary Syndromes, Acute[tiab] OR Syndrome, Acute Coronary[tiab] OR Syndromes, Acute Coronary[tiab] OR Premature heart attack[tiab] OR Coronary Stenosis[tiab] OR Stenoses, Coronary[tiab] OR Stenosis, Coronary[tiab] OR Coronary Artery Stenosis[tiab] OR Artery Stenoses, Coronary[tiab] OR Artery Stenosis, Coronary[tiab] OR Coronary Artery Stenoses[tiab] OR Stenoses, Coronary Artery[tiab] OR Stenosis, Coronary Artery[tiab] OR Coronary Stenoses[tiab] OR ST Elevation Myocardial Infarction[tiab] OR ST Segment Elevation Myocardial Infarction[tiab] OR ST Elevated Myocardial Infarction[tiab] OR STEMI[tiab] OR Non-ST Elevated Myocardial Infarction[tiab] OR Non ST Elevated Myocardial Infarction[tiab] OR NSTEMI[tiab] OR Non-ST-Elevation Myocardial Infarction[tiab] OR Infarction, Non-ST-Elevation Myocardial[tiab] OR Infarctions, Non-ST-Elevation Myocardial[tiab] OR Myocardial Infarction, Non-ST-Elevation[tiab] OR Myocardial Infarctions, Non-ST-Elevation[tiab] OR Non ST Elevation Myocardial Infarction[tiab] OR Non-ST-Elevation Myocardial Infarctions[tiab]</p>
2.	Premature[tiab] OR early onset[tiab]
3.	<p>“Interleukin-1” [mh] OR “Interleukin-1alpha” [mh] OR “Interleukin-1beta” [mh] OR “Interleukin-10” [mh] OR “Interleukin-11” [mh] OR “Interleukin-12” [mh] OR “Interleukin-12 Subunit p35” [mh] OR “Interleukin-12 Subunit p40” [mh] OR “Interleukin-13” [mh] OR “Interleukin-15” [mh] OR “Interleukin-16” [mh] OR “Interleukin-17” [mh] OR “Interleukin-18” [mh] OR “Interleukin-2” [mh] OR “Interleukin-23” [mh] OR “Interleukin-12 Subunit p40” [mh] OR “Interleukin-23 Subunit p19” [mh] OR “Interleukin-27” [mh] OR “Interleukin-3” [mh] OR “Interleukin-33” [mh] OR “Interleukin-4” [mh] OR “Interleukin-5” [mh] OR “Interleukin-6” [mh] OR “Interleukin-7” [mh] OR “Interleukin-8” [mh] OR “Interleukin-9” [mh] OR Interleukins[tiab] OR Interleukin[tiab] OR Interleukin-1[tiab] OR Interleukin 1[tiab] OR IL-1[tiab] OR T Helper Factor[tiab] OR Lymphocyte-Activating Factor[tiab] OR Lymphocyte Activating Factor[tiab] OR Macrophage Cell Factor[tiab] OR Epidermal Cell Derived Thymocyte-Activating Factor[tiab] OR Epidermal Cell Derived Thymocyte Activating Factor[tiab] OR Interleukin I[tiab] OR Interleukin-1alpha[tiab] OR Interleukin 1alpha[tiab] OR IL-1 alpha[tiab] OR Interleukin-1 alpha[tiab] OR Interleukin 1 alpha[tiab] OR Hematopoietin-1[tiab] OR Hematopoietin 1[tiab] OR Interleukin-1beta[tiab] OR Interleukin 1beta[tiab] OR IL-1 beta[tiab] OR Interleukin-1 beta[tiab] OR Interleukin 1 beta[tiab] OR Catabolin[tiab] OR Interleukin-10[tiab] OR Interleukin 10[tiab] OR IL10[tiab] OR IL-10[tiab] OR CSIF-10[tiab] OR Cytokine Synthesis Inhibitory Factor[tiab] OR Interleukin-11[tiab] OR Interleukin 11[tiab] OR IL-11[tiab] OR IL11[tiab] OR Adipogenesis Inhibitory Factor[tiab] OR Factor, Adipogenesis Inhibitory[tiab] OR Inhibitory Factor, Adipogenesis[tiab] OR Interleukin-12[tiab] OR Natural Killer Cell Stimulatory Factor[tiab] OR IL-12[tiab] OR Cytotoxic Lymphocyte Maturation Factor[tiab] OR IL 12[tiab] OR IL-12 p70[tiab] OR Interleukin-12 p70[tiab] OR Interleukin 12 p70[tiab] OR Interleukin 12[tiab] OR IL12[tiab] OR Edodekin Alfa[tiab] OR Interleukin-13[tiab] OR IL-13[tiab] OR Interleukin 13[tiab] OR IL 13[tiab] OR IL13[tiab] OR Interleukin-15[tiab] OR IL15[tiab] OR Interleukin 15[tiab] OR IL-15[tiab] OR Interleukin-16[tiab] OR Interleukin 16[tiab] OR IL16[tiab] OR Lymphocyte Chemoattractant Factor[tiab] OR Chemoattractant Factor, Lymphocyte[tiab] OR IL-16[tiab] OR LCF Factor[tiab] OR Interleukin-17[tiab] OR Interleukin 17[tiab] OR CTLA-8[tiab] OR IL-17[tiab] OR Interleukin-17F[tiab] OR Interleukin 17F[tiab] OR IL-17F[tiab] OR Cytokine ML-1[tiab] OR Cytokine ML 1[tiab] OR Interleukin-17C[tiab] OR Interleukin 17C[tiab] OR IL-17C[tiab] OR Cytokine CX2[tiab] OR CX2, Cytokine[tiab] OR Interleukin-17E[tiab] OR Interleukin 17E[tiab] OR Interleukin-25[tiab] OR Interleukin 25[tiab] OR IL-17E[tiab] OR IL 17E[tiab] OR Interleukin-17A[tiab] OR Interleukin 17A[tiab] OR Cytotoxic T lymphocyte-Associated Antigen 8[tiab] OR Cytotoxic T lymphocyte Associated Antigen 8[tiab] OR IL-17A[tiab] OR CTLA8[tiab] OR Interleukin-17B[tiab] OR Interleukin 17B[tiab] OR IL-17B[tiab] OR Interleukin-18[tiab] OR Interleukin 18[tiab] OR IFN-gamma-Inducing Factor[tiab] OR IL-18[tiab] OR Interferon-gamma Inducing Factor[tiab] OR Inducing Factor, Interferon-gamma[tiab] OR Interferon gamma Inducing Factor[tiab] OR Interferon-gamma-Inducing Factor[tiab] OR IFN-gamma Inducing Factor[tiab] OR IFN gamma Inducing Factor[tiab] OR Inducing Factor, IFN-gamma[tiab] OR IL18[tiab] OR Interleukin-2[tiab] OR Interleukin 2[tiab] OR IL-2[tiab] OR IL2[tiab] OR TCGF[tiab] OR Interleukine 2[tiab] OR Lymphocyte Mitogenic Factor[tiab] OR Mitogenic Factor, Lymphocyte[tiab] OR T-Cell Growth Factor[tiab] OR T Cell Growth Factor[tiab] OR T-Cell Stimulating Factor[tiab] OR T Cell Stimulating Factor[tiab] OR Thymocyte Stimulating Factor[tiab] OR Interleukin II[tiab] OR Ro-23-6019[tiab] OR Ro 23 6019[tiab] OR Ro236019[tiab] OR Ro-236019[tiab] OR Ro 236019[tiab] OR RU 49637[tiab] OR RU-49637[tiab] OR RU49637[tiab] OR Interleukin-23[tiab] OR Interleukin 23[tiab] OR IL-23[tiab] OR Interleukin-27[tiab] OR Interleukin 27[tiab] OR IL-17D[tiab] OR IL27[tiab] OR IL-27[tiab] OR Interleukin-17D[tiab] OR Interleukin 17D[tiab] OR Interleukin-3[tiab] OR Interleukin 3[tiab] OR IL-3[tiab] OR Mast-Cell Colony-Stimulating Factor[tiab] OR Multipotential Colony-Stimulating Factor[tiab] OR Multipotential Colony Stimulating Factor[tiab] OR Erythrocyte Burst-Promoting</p>



Appendix 1: Medline search query

Search terms
Factor[tiab] OR Erythrocyte Burst Promoting Factor[tiab] OR Burst-Promoting Factor, Erythrocyte[tiab] OR Burst Promoting Factor, Erythrocyte[tiab] OR Colony-Stimulating Factor 2 Alpha[tiab] OR Colony-Stimulating Factor, Mast-Cell[tiab] OR Colony Stimulating Factor, Mast Cell[tiab] OR Colony-Stimulating Factor, Multipotential[tiab] OR Colony Stimulating Factor, Multipotential[tiab] OR Eosinophil-Mast Cell Growth-Factor[tiab] OR Eosinophil Mast Cell Growth Factor[tiab] OR Hematopoietin-2[tiab] OR Hematopoietin 2[tiab] OR P-Cell Stimulating Factor[tiab] OR P Cell Stimulating Factor[tiab] OR Interleukin-33[tiab] OR Interleukin 33[tiab] OR IL33[tiab] OR IL-33[tiab] OR Interleukin-4[tiab] OR Interleukin 4[tiab] OR B-Cell Growth Factor-1[tiab] OR B Cell Growth Factor 1[tiab] OR B-Cell Growth Factor-I[tiab] OR B Cell Growth Factor I[tiab] OR B-Cell Proliferating Factor[tiab] OR B Cell Proliferating Factor[tiab] OR B-Cell Stimulating Factor-1[tiab] OR B Cell Stimulating Factor 1[tiab] OR B-Cell Stimulatory Factor 1[tiab] OR B-Cell Stimulatory Factor-1[tiab] OR BCGF-1[tiab] OR Binetrakin[tiab] OR BSF-1[tiab] OR IL-4[tiab] OR IL4[tiab] OR Mast Cell Growth Factor-2[tiab] OR Mast Cell Growth Factor 2[tiab] OR MCGF-2[tiab] OR B Cell Stimulatory Factor-1[tiab] OR B Cell Stimulatory Factor 1[tiab] OR Interleukin-5[tiab] OR Interleukin 5[tiab] OR BCGF-II[tiab] OR Differentiation Factor, Eosinophil[tiab] OR T-Cell- Replacing Factor[tiab] OR T Cell Replacing Factor[tiab] OR IL-5[tiab] OR IL5[tiab] OR T-Cell Replacing Factor[tiab] OR Replacing Factor, T-Cell[tiab] OR B-Cell Growth Factor-II[tiab] OR B Cell Growth Factor II[tiab] OR Eosinophil Differentiation Factor[tiab] OR Interleukin-6[tiab] OR Interleukin 6[tiab] OR IL6[tiab] OR B-Cell Stimulatory Factor 2[tiab] OR B-Cell Stimulatory Factor-2[tiab] OR Differentiation Factor-2, B-Cell[tiab] OR Differentiation Factor 2, B Cell[tiab] OR B-Cell Differentiation Factor-2[tiab] OR B Cell Differentiation Factor 2[tiab] OR BSF-2[tiab] OR Hybridoma Growth Factor[tiab] OR Growth Factor, Hybridoma[tiab] OR IFN-beta 2[tiab] OR Plasmacytoma Growth Factor[tiab] OR Growth Factor, Plasmacytoma[tiab] OR Hepatocyte-Stimulating Factor[tiab] OR Hepatocyte Stimulating Factor[tiab] OR MGI-2[tiab] OR Myeloid Differentiation-Inducing Protein[tiab] OR Differentiation-Inducing Protein, Myeloid[tiab] OR Myeloid Differentiation Inducing Protein[tiab] OR B-Cell Differentiation Factor[tiab] OR B Cell Differentiation Factor[tiab] OR Differentiation Factor, B-Cell[tiab] OR Differentiation Factor, B Cell[tiab] OR IL-6[tiab] OR Interferon beta-2[tiab] OR Interferon beta 2[tiab] OR Interferon beta-2, Interferon[tiab] OR B Cell Stimulatory Factor-2[tiab] OR B Cell Stimulatory Factor 2[tiab] OR Interleukin-7[tiab] OR Interleukin 7[tiab] OR IL7[tiab] OR Lymphopoietin-1[tiab] OR Lymphopoietin 1[tiab] OR IL-7[tiab] OR Interleukin-8[tiab] OR Interleukin 8[tiab] OR IL8[tiab] OR Monocyte-Derived Neutrophil Chemotactic Factor[tiab] OR Neutrophil Activation Factor[tiab] OR Neutrophil-Activating Peptide, Lymphocyte-Derived[tiab] OR Lymphocyte-Derived Neutrophil-Activating Peptide[tiab] OR Neutrophil Activating Peptide, Lymphocyte Derived[tiab] OR Neutrophil-Activating Peptide, Monocyte-Derived[tiab] OR Monocyte-Derived Neutrophil-Activating Peptide[tiab] OR Neutrophil Activating Peptide, Monocyte Derived[tiab] OR Alveolar Macrophage Chemotactic Factor-I[tiab] OR Alveolar Macrophage Chemotactic Factor I[tiab] OR AMCF-I[tiab] OR Anionic Neutrophil-Activating Peptide[tiab] OR Anionic Neutrophil Activating Peptide[tiab] OR Neutrophil-Activating Peptide, Anionic[tiab] OR Peptide, Anionic Neutrophil-Activating[tiab] OR Chemokine CXCL8[tiab] OR CXCL8, Chemokine[tiab] OR Chemokines, CXCL8[tiab] OR CXCL8 Chemokines[tiab] OR Chemotactic Factor, Macrophage-Derived[tiab] OR Chemotactic Factor, Macrophage Derived[tiab] OR Macrophage-Derived Chemotactic Factor[tiab] OR Chemotactic Factor, Neutrophil[tiab] OR Neutrophil Chemotactic Factor[tiab] OR Chemotactic Factor, Neutrophil, Monocyte-Derived[tiab] OR CXCL8 Chemokine[tiab] OR Chemokine, CXCL8[tiab] OR Granulocyte Chemotactic Peptide-Interleukin-8[tiab] OR Chemotactic Peptide-Interleukin-8, Granulocyte[tiab] OR Granulocyte Chemotactic Peptide Interleukin 8[tiab] OR IL-8[tiab] OR Interleukin-9[tiab] OR Interleukin 9[tiab] OR T-Cell Growth Factor P40[tiab] OR T Cell Growth Factor P40[tiab] OR P40 T-Cell Growth Factor[tiab] OR P40 T Cell Growth Factor[tiab] OR IL-9[tiab] OR IL9[tiab]
4. #1 AND #2 AND #3

