

Association between blood Interleukin-10 level in coronary artery disease: A systematic review, meta-analysis, and network analyses

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ABSTRACT

Background: Cytokines can be key factors in the pathogenesis of coronary artery disease (CAD). This systematic review and meta-analysis aimed to assess the levels of interleukin-10 (IL-10), an anti-inflammatory cytokine, in the serum/plasma of patients with CAD. **Methods:** An exhaustive search was conducted across the Web of Science, PubMed/Medline, Scopus, and Cochrane Library databases up to March 25, 2022. Review Manager 5.3 software was used to calculate the effect sizes, presenting the standardized mean difference (SMD) along with a 95% confidence interval (CI). STRING software, which maps protein-protein interactions (PPI), was utilized to explore the functional interactions among the genes under study. **Results:** From the 1130 records retrieved from the databases, 26 articles were included in the meta-analysis. The pooled SMD for CAD cases compared to controls was 0.33 ($p = 0.15$). The sample size was adequate for comparing blood IL-10 levels in CAD patients versus controls. **Conclusion:** The findings suggest there was no significant difference in the serum/plasma levels of IL-10 between CAD patients and controls. Hence, the pathogenesis of CAD can be multifactorial and complex.

Key words: heart disease, interleukin-10, serum, plasma, meta-analysis

INTRODUCTION

Heart diseases (HDs) are the leading cause of death worldwide, with the majority of fatalities, approximately 80%, occurring in low- to middle-income countries. If current trends continue, it is projected that by 2030, cardiovascular diseases will claim the lives of about 23.6 million individuals, predominantly through heart attacks and strokes^{1,2}. Ischemic HD is recognized as a significant threat in the 21st century³, also known as coronary artery disease (CAD) or coronary HD. A large number of individuals with CAD live with chronic disabilities and impaired quality of life⁴.

One of the most significant risk factors associated with HD is a family history of HD⁵. The increase in HD risk due to family history can be attributed to shared genetic, environmental, and lifestyle factors. The importance of genetics becomes more apparent with the early onset of HD in the family and the number of family members affected⁶. It is believed that an imbalance between pro- and anti-inflammatory activities plays a crucial role in the development of atherosclerosis⁷. Inflammation contributes to the early stages of HD, and therefore, may drive the progression of this disease^{8,9}.

CAD is the primary cause of deaths related to cardiovascular issues¹⁰, and atherosclerosis is the most

common reason for CAD, which is a longstanding inflammatory condition of the arterial walls that arises from an inappropriate inflammatory response and an imbalance in lipid metabolism¹¹. A multitude of evidence, including both clinical trials and experimental studies, collectively indicates that inflammation is integral to all phases of atherosclerosis development^{9,12,13}.

Several signaling pathways have been reported and linked to CAD pathogenesis¹⁴⁻¹⁷. Cytokines, which are part of the extracellular signaling proteins, are secreted by both immune and non-immune cells, including cells of the vascular endothelium¹⁸. Increased levels of inflammatory cytokines in the plasma have been documented in patients with CAD, especially in those with unstable disease conditions¹⁰. Conversely, the presence of anti-inflammatory mediators is less well documented. Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that plays a vital and often indispensable role in warding off inflammatory and autoimmune conditions¹⁹⁻²². The gene for human IL-10 is located on chromosome 1, specifically at the juncture of regions 1q31 and 1q32²³. IL-10 can reduce the likelihood of atherosclerosis development and improve the progression of atherosclerosis and vascular complications²⁴. Studies have documented the role of plasma/serum IL-10 levels in

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History

- Received: Feb 19, 2024
- Accepted: Jun 18, 2024
- Published Online: Jun 31, 2024

DOI : 10.15419/bmrat.v11i7.907



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Cite this article : Moghadam R H, Rouzbahani M, Salehi N, Sadeghi M. **Association between blood Interleukin-10 level in coronary artery disease: A systematic review, meta-analysis, and network analyses.** *Biomed. Res. Ther.* 2024; 11(7):6603-6621.

CAD patients but with varying and contradictory results²⁵⁻²⁷. The interactions of IL-10 are complex and can vary depending on the specific context and conditions²⁸⁻³⁰.

To our knowledge, this topic has not been the subject of a meta-analysis. Therefore, the goal of this meta-analysis was to assess the levels of IL-10 in the blood of patients with CAD to obtain better and more accurate results and to identify the possible reasons for these discrepancies between the results of individual studies. Another aim was to understand the pathogenesis, protein-protein interactions (PPI), and patient-specific factors as research gaps.

METHODS

Design and Registration

This study adhered to the guidelines set forth by PRISMA³¹. Additionally, the protocol for this meta-analysis was registered in the PROSPERO database under the registration number CRD42022335594. The question posed in terms of PECO was: Is there an association between serum/plasma levels of IL-10 and the risk of CAD in studies with a case-control design?

Article Discovery

An author of the study, M.S., carried out a comprehensive search in databases such as PubMed/MEDLINE, Web of Science, Scopus, and Cochrane Library up until March 25, 2022, without imposing any restrictions, to collect relevant articles. M.S. also reviewed the titles and abstracts of these articles. Subsequently, the full texts of the articles that met the selection criteria were obtained. The search strategy included keywords/title/abstract: ("coronary atherosclerotic heart disease" or "coronary heart disease" or "coronary artery disease" or "ischemic heart disease" or "myocardial infarction" or "acute coronary syndrome" or "angina pectoris") and ("interleukin-10" or "IL-10" or "IL10" or "interleukin 10") and ("plasma" or "serum" or "blood") and ("control" or "normal" or "healthy"). The bibliographies of the retrieved articles were scrutinized to ensure no significant studies were missed. Another author, R.H.M., verified the search and selection procedures. In the event of any discrepancies between the two authors, a third author, N.S., intervened in the resolution.

Criteria for Selection and Rejection

The inclusion criteria were as follows: 1) Any study that reported the levels of IL-10 in the serum or

plasma of CAD patients and control subjects. 2) Studies that included more than 10 cases in both the case and control groups. 3) CAD was defined based on the criteria reported in Alshammary's study³², and **Table 1** shows the criteria for each study. 4) CAD patients without any other systemic diseases and control subjects who were in good health. 5) CAD patients with or without medical treatment, such as statins. Conversely, review articles, meta-analyses, articles with missing data, studies conducted on animals, articles lacking a control group, commentary papers, conference papers, book chapters, duplicate studies, studies that included disease-afflicted controls, and studies involving cases under treatment were excluded.

Data Summary

The authors, M.S. and M.R., independently extracted data from the studies included in the meta-analysis. Extracted data encompassed authors' names, publication year, study country, case ethnicity, the number of coronary artery disease (CAD) patients and control subjects, sample size, average age, IL-10 levels in serum or plasma, and the quality score.

Quality Evaluation

The quality assessment was conducted by one author, M.S., using the Newcastle-Ottawa Scale (NOS) tool to evaluate the quality and potential bias in case-control studies⁵⁵. The highest possible score on the NOS is nine, with scores of seven or higher indicative of high quality.

Statistical Analyses

The Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, UK) software was utilized to calculate effect sizes, providing the standardized mean difference (SMD) and a 95% confidence interval (CI) for IL-10 levels in the blood of CAD cases and controls. The Z-test determined the significance of the pooled SMD, considering a two-sided p-value of less than 0.05 significant. If heterogeneity was significant, indicated by a Pheterogeneity value of less than 0.1 and an I2 value greater than 50%, a random-effects model⁵⁶ was used. Conversely, a fixed-effect model⁵⁷ was used in cases of insignificant heterogeneity.

Subgroup analysis, random meta-regression analysis, and sensitivity analysis ("one-study-removed" and "cumulative" analyses) were performed using the Comprehensive Meta-Analysis version 2.0 (CMA 2.0; Biostat Inc., Englewood, NJ, USA). Publication bias

Table 1: Definition of CAD used in each study included in the analysis

First author, publication year	CAD definition
Mazzone, 1999 ³³	Standard progressive changes in electrocardiography linked with a rise in CK values exceeding twice the upper normal limit and alterations in the ST-segment
Mizia-Stec, 2002 ³⁴	Coronangiography
Mizia-Stec, 2003 ³⁵	Coronangiography was performed if there was a constriction of the diameter by 75% or more in at least one of the three primary epicardial coronary arteries
Lee, 2006 ³⁶	Cardiac catheterization
Nilsson, 2006 ³⁷	Angiography
Szodoray, 2006 ³⁸	Angiography
Paulsson, 2008 ³⁹	Angiography
Cheng, 2009 ⁴⁰	Scanning with radioactive thallium or coronary angiogram
Jha, 2009 ⁴¹	Angiography
Jha, 2010 ⁴²	Angiography
Khan, 2011 ⁴³	Angiography revealing a stenosis of more than 70% in at least one coronary vessel
Tapp, 2012 ⁴⁴	European Society of Cardiology definition
Karu, 2013 ⁴⁵	NR
Li, 2015 ⁴⁶	Clinical symptoms, ECG alterations, coronary angiography, and cardiac troponin tests
Mirhafez, 2015 ⁴⁷	Angiography
Cheng, 2016 ⁴⁸	Coronary stenosis with at least one main coronary vessel with 50% luminal narrowing
Liang, 2016 ⁴⁹	A narrowing of the lumen by 50% or more was observed in at least one primary coronary artery or its main branches
Bergström, 2017 ²⁵	Non-segment elevation myocardial infarction identified through characteristic ECG alterations and increased levels of troponins
Tajfard, 2017 ⁵⁰	An occlusion of 50% or more in at least one coronary artery
Xu, 2017 ⁵¹	Stenosis exceeding 50% in at least one primary vessel
Boles, 2018 ²⁶	Angiography
Kharaeva, 2018 ²⁷	Angiography
Kumari, 2018 ¹⁸	NR
Ansari, 2019 ⁵²	Angiography revealing stenosis exceeding 70% in a single coronary artery
Shipulin, 2020 ⁵³	Left ventricular ejection fraction \leq 40%, stenosis left main or proximal part of the left descending artery or two or more epicardial vessels \geq 75%
Nowrouzi-Sohrabi, 2022 ⁵⁴	Angiography confirmed stenosis of more than 50% in at least one coronary artery

Abbreviations: CAD: coronary artery disease, NR: not reported, ECG: electrocardiographic

was assessed using Egger's⁵⁸ and Begg's tests⁵⁹, with a 2-sided $p < 0.10$ indicating the presence of publication bias.

The NCSS 2021 version 21.0.2 (NCSS, Kaysville, UT, USA) software generated two plots (Radial and L'Abbé plots). The Radial, or Galbraith, plot displays the z-statistic⁶⁰, and the L'Abbé plot illustrates event rates in cases compared to control groups^{61,62}, with a p-value less than 0.05 indicating statistically significant heterogeneity.

Trial Sequential Analysis (TSA) was conducted using TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark)⁶³. The required information size (RIS) was calculated with an alpha risk of 5%, a beta risk of 20%, and a two-sided boundary type. The studies were considered to have included sufficient cases if the Z-curve intersected the RIS line, adhered to the boundary line, or entered the futility area. Otherwise, additional information and further studies were deemed necessary.

Functional interactions between examined genes were studied using the STRING software, a protein-protein interaction network tool accessed at <https://string-db.org/> (accessed on 5 August 2023)⁶⁴. Interaction settings were limited to "*Homo sapiens*" and required an interaction score threshold of more than 0.900. In the resulting networks, proteins are represented by nodes, and interactions are indicated by edges. STRING was used to identify potential interactions between differentially expressed genes (DEGs) in various tissues, with KEGG analysis obtained from the STRING software.

RESULTS

Choice of Studies

After removing duplicates and records that were not relevant, 63 out of the 1130 records that were initially retrieved from the databases met the criteria for inclusion as full-text articles (**Figure 1**). Subsequently, 37 full texts were removed for reasons. At last, 26 articles including 27 studies were entered into the meta-analysis.

Attributes of the Study

The main features of 26 articles^{18,25-27,33-54} incorporated in the meta-analysis are shown in **Table 2**. The articles were disseminated from 1999 to 2022. Seventeen articles^{25-27,33-35,37-39,43-45,47,50-54} were reported in Caucasians and nine^{18,36,40-42,46,48,49,51} in Asians. Eleven articles^{25,26,33,37,41,42,44,46,51,53,54} were reported IL-10 level in plasma and fifteen^{18,27,34-36,38-40,43,45,47-50,52} in serum. Other

variables and the quality score of each article are shown in **Table 2** and **Table 3**, respectively. A few studies in some cases reported the CAD patients under statin therapy.

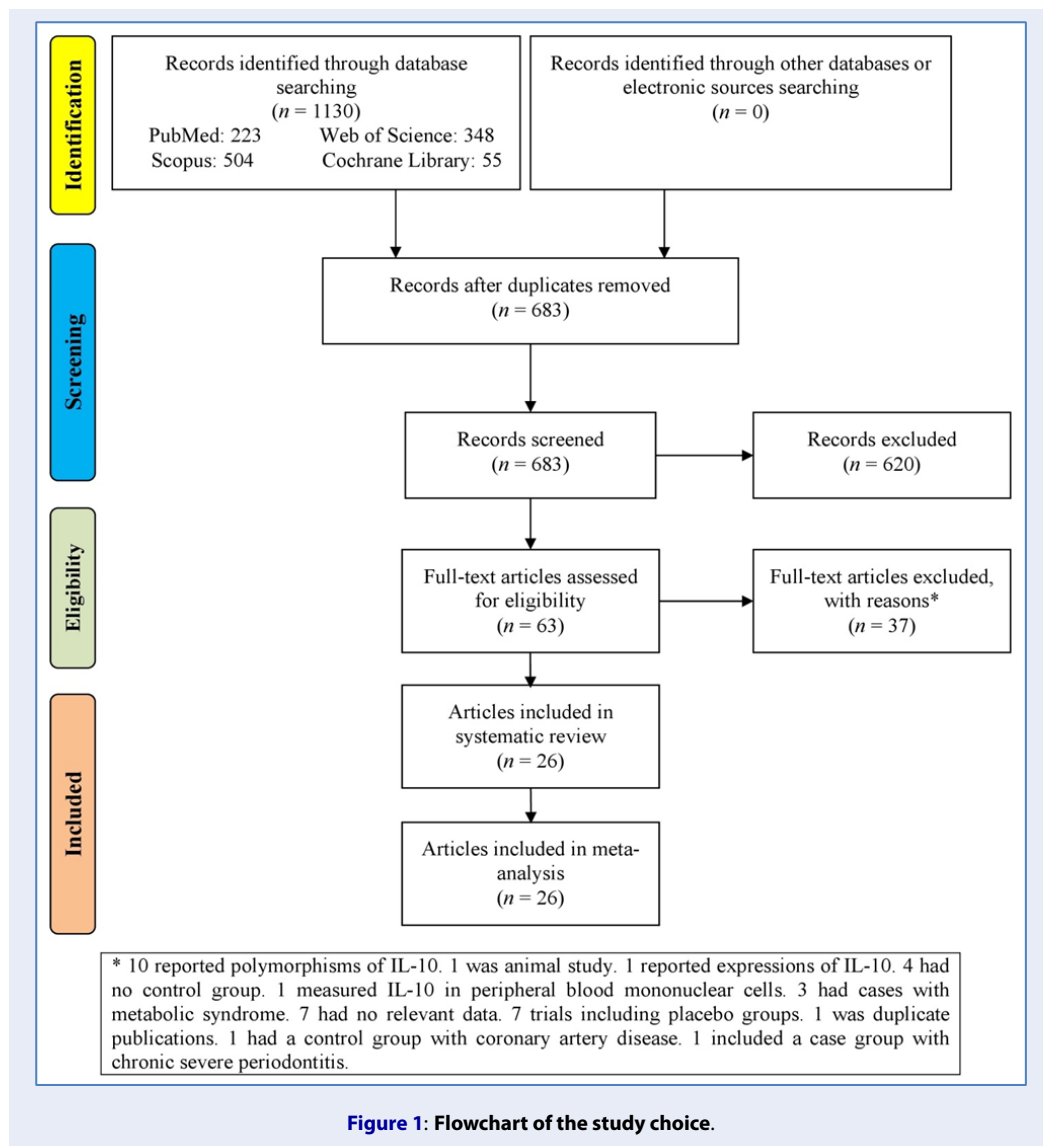


Figure 1: Flowchart of the study choice.

Table 2: Traits of the studies incorporated in the meta-analysis

First author, publication year	Country	Ethnicity	Sample	Groups	Number	Mean age, years	IL-10 level (Mean ± SD)	Detection assay
Mazzone, 1999 ³³	Italy	Caucasian	Plasma	CAD	42	61	10.8 ± 1.8	ELISA
				CO	39	55	1.9 ± 1.1	
Mizia-Stec, 2002 ³⁴	Poland	Caucasian	Serum	CAD	100	58.0	52.37 ± 106.15	ELISA
				CO	20	55.3	14.3 ± 28.5	
Mizia-Stec, 2003 ³⁵	Poland	Caucasian	Serum	CAD	33	60.9	68.0 ± 152.5	ELISA
				CO	20	55.4	14.3 ± 28.5	
Lee, 2006 ³⁶	Taiwan	Asian	Serum	CAD	30	65.5	1.56 ± 1.37	ELISA
				CO	73	63	1.22 ± 0.85	
Nilsson, 2006 ³⁷	Sweden	Caucasian	Plasma	CAD	65	56.9	2.58 ± 2.04	ELISA
				CO	28	52.5	2.4 ± 2.5	
Szodoray, 2006 ³⁸	Hungary	Caucasian	Serum	CAD	62	64.2	32.3 ± 95.3	ELISA
				CO	58	72.3	6.95 ± 15.38	
Paulsson, 2008 ³⁹	Sweden	Caucasian	Serum	CAD	19	61	0.73 ± 0.67	Immunoassay
				CO	19	60	0.55 ± 0.49	
Cheng, 2009 ⁴⁰	Taiwan	Asian	Serum	CAD	138	65.5	2.1 ± 0.2	ELISA
				CO	74	63	1.2 ± 0.1	
Jha, 2009 ⁴¹	India	Asian	Plasma	CAD	192	-	1.83 ± 0.16	ELISA
				CO	192	-	1.95 ± 0.19	
Jha, 2010 ⁴²	India	Asian	Plasma	CAD (male)	148	-	1.83 ± 0.15	ELISA
				CAD (female)	42	-	1.82 ± 0.16	
				CO (male)	142	-	1.94 ± 0.17	
				CO (female)	50	-	1.94 ± 0.18	
Khan, 2011 ⁴³	Pakistan	Caucasian	Serum	CAD	98	40	2.07 ± 1.70	ELISA
				CO	74	35	1.7 ± 1.85	
Tapp, 2012 ⁴⁴	UK	Caucasian	Plasma	CAD	40	60.4	0.55 ± 0.93	Flow cytometry
				CO	40	59.5	0.88 ± 1.16	
Karu, 2013 ⁴⁵	Estonia	Caucasian	Serum	CAD	39	64	0.53 ± 0.19	High-sensitivity array
				CO	40	59.5	0.88 ± 1.16	

Continued on next page

Table 2 continued

First author, publication year	Country	Ethnicity	Sample	Groups	Number	Mean age, years	IL-10 level (Mean ± SD)	Detection assay
				CO	39	62	0.65 ± 0.21	
Li, 2015 ⁴⁶	China	Asian	Plasma	CAD	29	66.9	18.74 ± 20.84	ELISA
				CO	11	62.3	20.92 ± 14.69	
Mirhafez, 2015 ⁴⁷	Iran	Caucasian	Serum	CAD	289	59.1	0.75 ± 0.29	Sandwich Chemiluminescence
				CO	89	58.7	0.84 ± 0.39	
Cheng, 2016 ⁴⁸	China	Asian	Serum	CAD	52	60	7.42 ± 3.81	ELISA
				CO	50	59	17.46 ± 5.01	
Liang, 2016 ⁴⁹	China	Asian	Serum	CAD	128	65.3	134.43 ± 38.24	ELISA
				CO	106	64.7	164.38 ± 36.45	
Bergström, 2017 ²⁵	Sweden	Caucasian	Plasma	CAD	57	66	0.32 ± 0.12	ELISA
				CO	41	67	1.03 ± 0.13	
Tajfard, 2017 ⁵⁰	Iran	Caucasian	Serum	CAD	231	59.5	0.76 ± 0.29	Biochip array
				CO	120	53.3	0.83 ± 0.34	
Xu, 2017 ⁵¹	China	Asian	Plasma	CAD	264	59	98.65 ± 34.79	ELISA
				CO	186	58	32.18 ± 12.15	
Boles, 2018 ²⁶	Sweden	Caucasian	Plasma	CAD	69	64.5	0.29 ± 0.21	ELISA
				CO	140	58.6	0.25 ± 0.15	
Kharaeva, 2018 ²⁷	Russia	Caucasian	Serum	CAD	27	57	53.6 ± 3.2	ELISA
				CO	20	55	10.0 ± 3.0	
Kumari, 2018 ¹⁸	India	Asian	Serum	CAD	290	51.6	5.33 ± 3.34	ELISA
				CO	290	51.7	5.83 ± 2.63	
Ansari, 2019 ⁵²	Pakistan	Caucasian	Serum	CAD	340	42	0.83 ± 0.53	ELISA
				CO	310	39	0.87 ± 0.36	
Shipulin, 2020 ⁵³	Russia	Caucasian	Plasma	CAD	26	59.2	25.16 ± 4.07	ELISA
				CO	14	58.6	20.5 ± 4.44	
Nowrouzi-Sohrabi, 2022 ⁵⁴	Iran	Caucasian	Plasma	CAD	15	58.9	1.98 ± 0.73	ELISA
				CO	15	56.2	1.87 ± 0.92	

Abbreviations: CAD: coronary artery disease; SD: standard deviation; CO: control; IL-10: interleukin-10, ELISA: Enzyme-linked immunosorbent assay

Quality Score

The quality scores for case-control studies incorporated in the meta-analysis are shown in **Table 3**. Most studies involved a high quality (total score ≥ 7).

Pooled Analysis for All Studies

As **Figure 2** shows, the pooled SMD for 85 studies reporting CAD patients was 0.33 (95%CI: $-0.12, 0.78$; $p = 0.15$; $I^2 = 98\%$). Based on the result, the two groups (patients with CAD and controls) did not exhibit a significant difference in blood IL-10 levels.

Subgroup analysis

The subgroup analysis derived from ethnicity, blood sample, and sample size is shown in **Table 4**. The findings reported that sample size could be an effective factor in the pooled result.

Sensitivity Analysis

The results of "one-study-removed" and "cumulative" analyses indicated that the combined analysis was stable.

Publication Bias

Figure 3 indicates funnel plots of blood IL-10 levels in controls compared to CAD patients. With regards to blood IL-10 levels, the p -values of tests were Egger's: 0.274 and Begg's: 0.128 for the CAD patients compared to controls. Publication bias was not observed.

Trial Sequential Analysis

Figure 4 presents the outcome of the TSA for blood IL-10 levels in CAD patients versus controls. The data indicates that there are ample cases for comparing blood IL-10 levels in CAD patients and controls.

Radial and L'Abbé plots

The results of both radial and L'Abbé plots for blood IL-10 levels in the CAD patients versus the controls are identified in **Figure 5** and **Figure 6**, respectively. The radial plot indicated that one possible cause of heterogeneity in the initial analysis could be outliers. Also, the L'Abbé plot shows evidence of high heterogeneity ($p < 0.001$).

Meta-regression

Table 5 represents the random-effects meta-regression of IL-10 levels for CAD patients compared to controls. The results indicated that the publication year and blood sample were moderator factors in the pooled initial analyses ($p < 0.01$).

IL-10/STAT3/SOCS3 axis and PPI interaction

Figure 7 shows the IL-10/STAT3 pathway and its role in suppressing inflammation. IL-10 activates STAT3, and the IL-10/STAT3 axis can have a powerful anti-inflammatory property⁶⁵ and its role can be crucial in limiting undesirable immune reactions. It is possible that this axis could play a role in regulating inflammation in the context of CAD¹⁷. SOCS3 plays a role in the mechanism by which IL-10 modulates inflammation and acts as a feedback inhibitor of the JAK/STAT pathway. Further research would be needed to determine the exact role of the IL-10/STAT3/SOCS3 axis in CAD. The STRING PPI interaction contains 5 nodes with 10 edges with the highest confidence (0.900). The average node degree was 4 and the PPI enrichment p -value was $6.73e^{-5}$. In addition, the KEGG suggested a network analysis for the JAK-STAT signaling pathway based on 5 nodes entered into STRING (**Figure 8**).

DISCUSSION

Coronary artery disease (CAD), a prevalent cardiovascular condition, is characterized by the buildup of plaque within the coronary artery walls, leading to reduced blood flow to the heart muscle⁶⁶. Our main findings showed no difference in the blood levels of IL-10 between the CAD patients and the controls. The analyses reported that factors such as ethnicity, blood sample type (serum or plasma), sample size, and publication year could affect the pooled results.

Limited knowledge exists regarding the function of anti-inflammatory cytokines in CAD. IL-10, an anti-inflammatory cytokine that effectively inhibits immune responses, is produced by T and B cells, monocytes, and macrophages⁶⁷. It suppresses pro-inflammatory cytokines and has a broad range of anti-inflammatory capabilities, including the inhibition of early pro-inflammatory transcription factors, which consequently reduces cytokine production⁶⁸.

In vitro, IL-10 plays a crucial role in diminishing lesion growth and preventing the advancement of atherosclerosis^{69,70}, as well as in modulating the immune response to atherosclerosis, a major contributor to CAD⁷¹. However, in clinical settings, the role of IL-10 in patients with CAD has yielded inconsistent results^{25,26,33}, despite numerous studies investigating the relationship between IL-10 and CAD^{25,27,40}.

One study suggested that CAD patients of both sexes who smoked and consumed alcohol had lower levels of IL-10⁴², while another demonstrated that CAD patients with low serum iron had significantly higher levels of IL-10 compared to normal controls or CAD

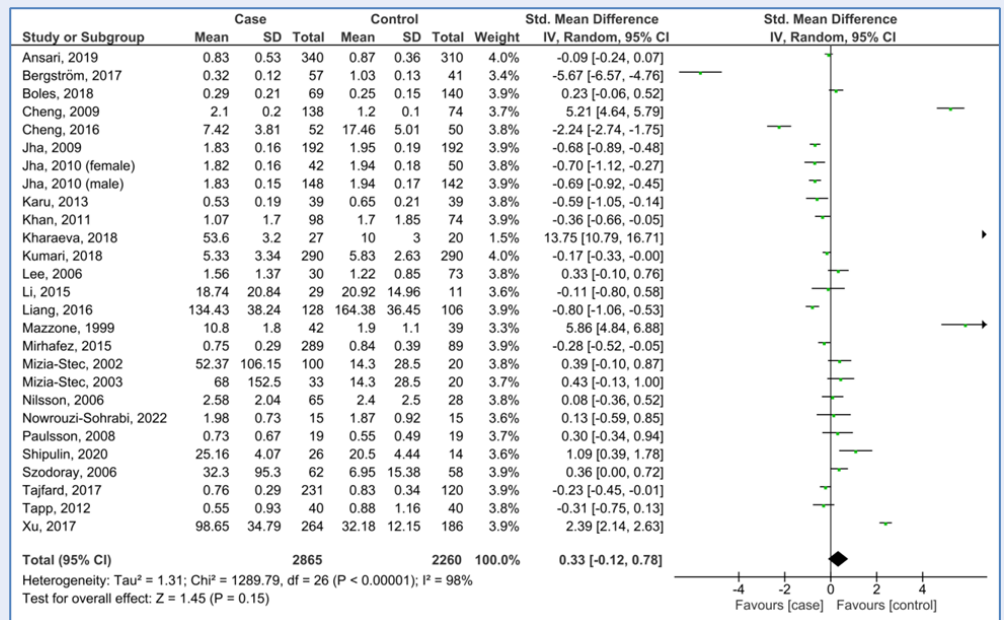


Figure 2: Forest plot analysis of blood interleukin-10 level in patients with coronary artery disease compared to controls.

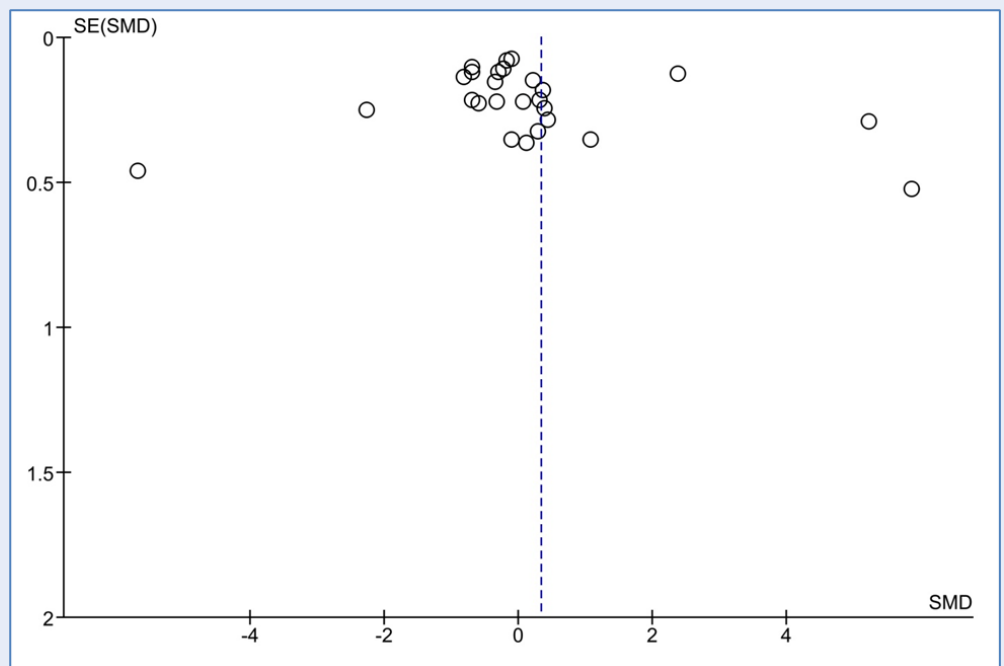


Figure 3: Funnel plot analysis of blood interleukin-10 level coronary artery disease patients compared to controls.

Table 3: Newcastle - Ottawa Scale for studies

First author, publication year	Selection [#]	Comparability ^{&}	Exposure [§]	Total score
Mazzone, 1999 ³³	***	*	**	6
Mizia-Stec, 2002 ³⁴	****	**	**	8
Mizia-Stec, 2003 ³⁵	****	**	**	8
Lee, 2006 ³⁶	****	**	**	8
Nilsson, 2006 ³⁷	****	**	**	8
Szodoray, 2006 ³⁸	****	**	**	8
Paulsson, 2008 ³⁹	****	**	**	8
Cheng, 2009 ⁴⁰	****	**	**	8
Jha, 2009 ⁴¹	****	**	**	8
Jha, 2010 ⁴²	****	**	**	8
Khan, 2011 ⁴³	***	**	**	7
Tapp, 2012 ⁴⁴	****	**	**	8
Karu, 2013 ⁴⁵	****	**	**	8
Li, 2015 ⁴⁶	****	**	**	8
Mirhafez, 2015 ⁴⁷	****	**	**	8
Cheng, 2016 ⁴⁸	****	**	**	8
Liang, 2016 ⁴⁹	****	**	**	8
Bergström, 2017 ²⁵	****	**	**	8
Tajfard, 2017 ⁵⁰	****	**	**	8
Xu, 2017 ⁵¹	****	**	**	8
Boles, 2018 ²⁶	***	**	**	7
Kharaeva, 2018 ²⁷	****	**	**	8
Kumari, 2018 ¹⁸	****	**	**	8
Ansari, 2019 ⁵²	***	**	**	7
Shipulin, 2020 ⁵³	****	**	**	8
Nowrouzi-Sohrabi, 2022 ⁵⁴	***	**	**	7

[#]Maximum 4 stars, [&]Maximum 2 stars, [§]Maximum 3 stars

Each asterisk shows one score. The selection process is divided into four parts: defining the cases, ensuring that the cases are representative, selecting the controls, and defining the controls. The comparability process has two parts: one based on age and the other based on other risk factors. The exposure process has three parts: evaluating exposure, using the same methods to ascertain cases and controls, and determining the non-response rate.

patients with normal/high serum iron³⁶. The current meta-analysis suggested that factors such as ethnicity, blood sample, sample size, and publication year could significantly influence the pooled results. Therefore, CAD progression and development may be influenced by several factors, and future studies should examine the effect of each factor individually to identify the most significant influences. According to one study, there was no significant correlation be-

tween serum IL-10 levels in CAD patients and factors such as smoking, hypertension, diabetes, obesity, and dyslipidemia⁷². The findings suggest that certain risk factors for CAD, such as dietary habits (e.g., low intake of fruits and vegetables, high intake of saturated fats), smoking, physical inactivity, and obesity, may reduce IL-10 levels and increase inflammation in the body⁷³⁻⁷⁶, thus contributing to the disease's development. Understanding the underlying mechanisms of

Table 4: Subgroup analysis

Variable	Number of studies	SMD	95%CI	p-value	Heterogeneity, %
Ethnicity					
Caucasian	18	0.30	- 0.16, 0.76	0.20	96
Asian	9	- 0.29	- 1.07, 0.49	0.46	99
Sample					
Serum	15	0.42	- 0.08, 0.93	0.10	97
Plasma	12	0.12	- 0.77, 1.01	0.78	99
Sample size					
≥ 200	11	0.93	0.24, 1.63	0.008	99
< 200	16	- 0.08	- 0.72, 0.56	0.81	96

SMD: Std. Mean difference. CI: Confidence interval. Bold data donates statistical significance (p < 0.05).

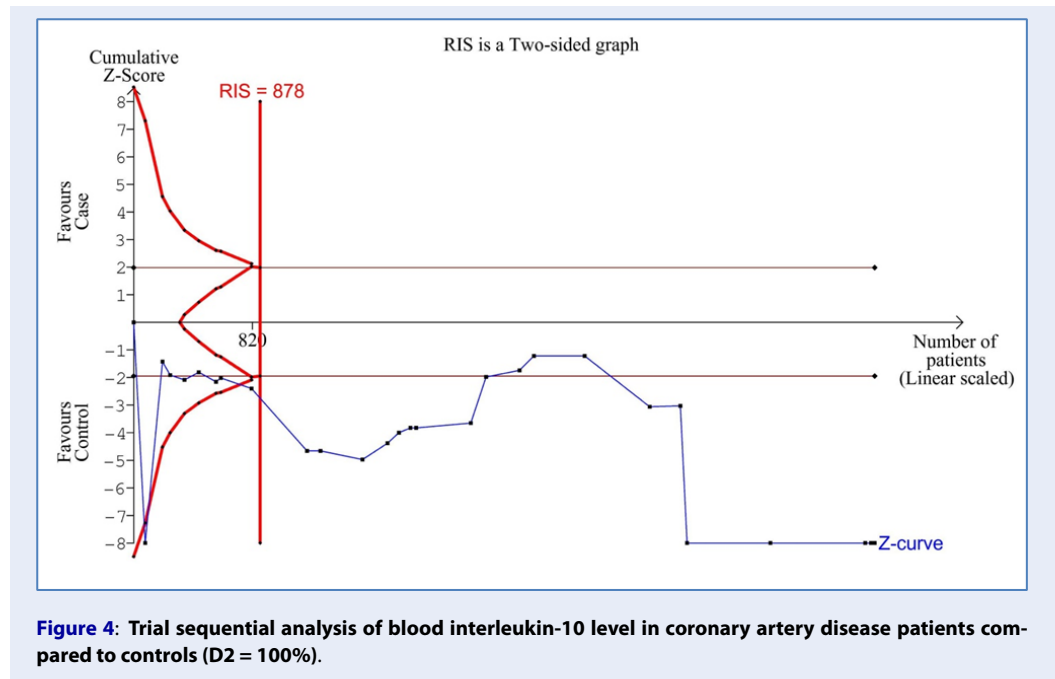


Figure 4: Trial sequential analysis of blood interleukin-10 level in coronary artery disease patients compared to controls (D2 = 100%).

these associations may assist in identifying new preventive and therapeutic strategies for CAD.

IL-10 has been shown to suppress the generation of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and IL-1 β , which are key contributors to the formation of atherosclerotic plaques^{68,77}. Additionally, IL-10 has been found to promote the survival of endothelial cells that line the inner surfaces of blood vessels and prevent their apoptosis, thereby reducing the risk of plaque formation^{78,79}.

Various studies have indicated that increased IL-10 levels in the bloodstream could signal ongoing systemic inflammation in CAD patients^{27,33,40}, while other studies noted that in human coronary disease, IL-10 is present and associated with diminished signs of inflammation^{71,80}. The available evidence suggests that IL-10 plays a protective role against CAD by modulating the inflammatory response and promoting endothelial cell survival. Nonetheless, additional studies are needed to fully comprehend the mechanisms underlying the relationship between IL-10 and CAD.

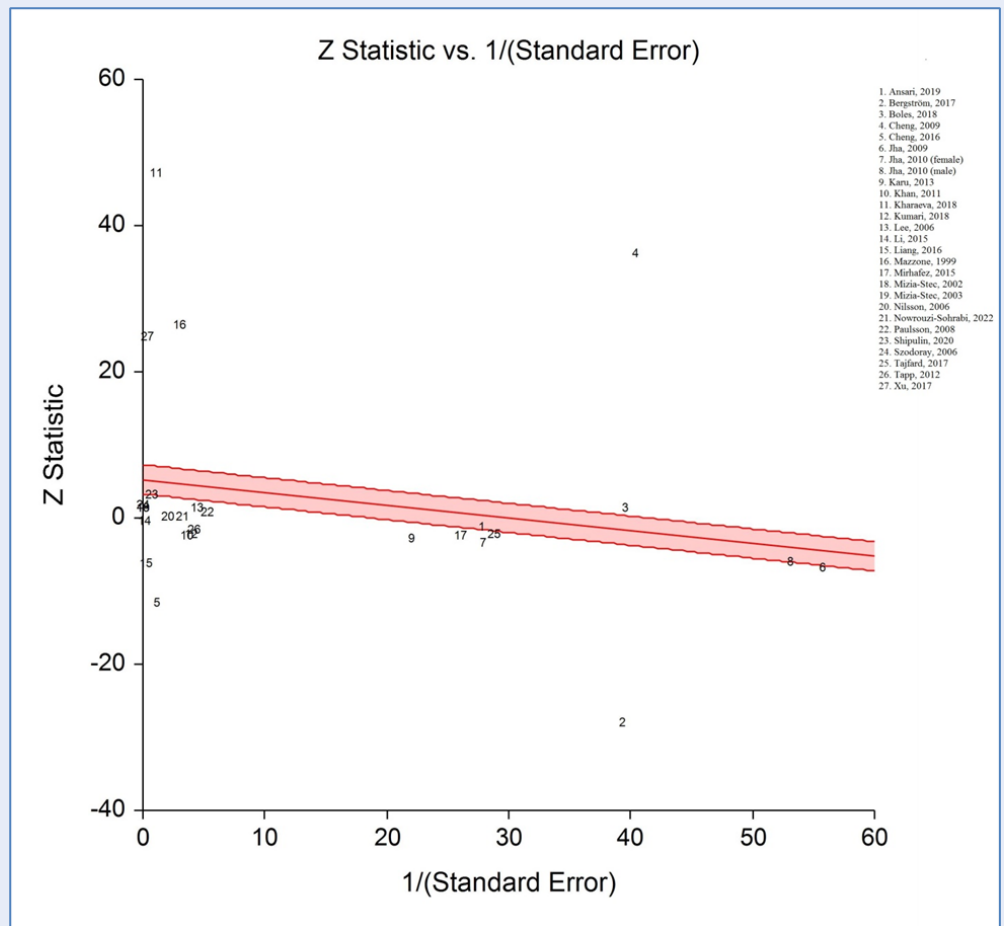


Figure 5: Radial plot of studies on blood IL-10 levels for patients with coronary artery disease versus controls.

Research has established that CAD is associated with a continuous inflammatory response⁸¹. STAT3 has been identified as a crucial molecule in IL-10's operation, with its activation necessary for the cytokine's anti-inflammatory effects^{82,83}. Furthermore, evidence suggests that SOCS3 plays a role in how IL-10 modulates inflammation^{17,84}. Acting as a feedback inhibitor of the JAK/STAT pathway, SOCS3 is crucial in preventing STAT3 activation, cytokine signaling, and the expression of inflammatory genes in immune cells such as macrophages and microglia⁸⁵. One study found that IL-10 increased SOCS3 expression in cultured cardiomyocytes¹⁷. With regards to protein-protein interactions between IL-10, STAT3, and SOCS3, evidence supports that both STAT3 and SOCS3 are involved in IL-10's regulation of inflammation. Additionally, the KEGG analysis reported several biomarkers.

The effects of statins on IL-10 levels in CAD patients versus controls have varied across studies³⁹. One trial reported that statin therapy did not affect IL-10 mRNA expression in patients with CAD⁸⁶, while another study confirmed this for serum IL-10 levels⁸⁷. Our meta-analysis included a few studies that involved cases with statin therapy; thus, we were unable to analyze data related to the effect of statins on IL-10 levels comprehensively. Future research should investigate the impact of statins on IL-10 levels in CAD patients. The meta-regression identified the publication year as a confounding factor in the pooled result, indicating possible significant differences in the therapeutic approach to CAD patients over time. The significant limitations of this meta-analysis include heterogeneity among the studies, limited case count in some analyses, and the lack of patient-level data; diverse criteria for study inclusion, such as varying definitions of CAD, which could introduce bias;

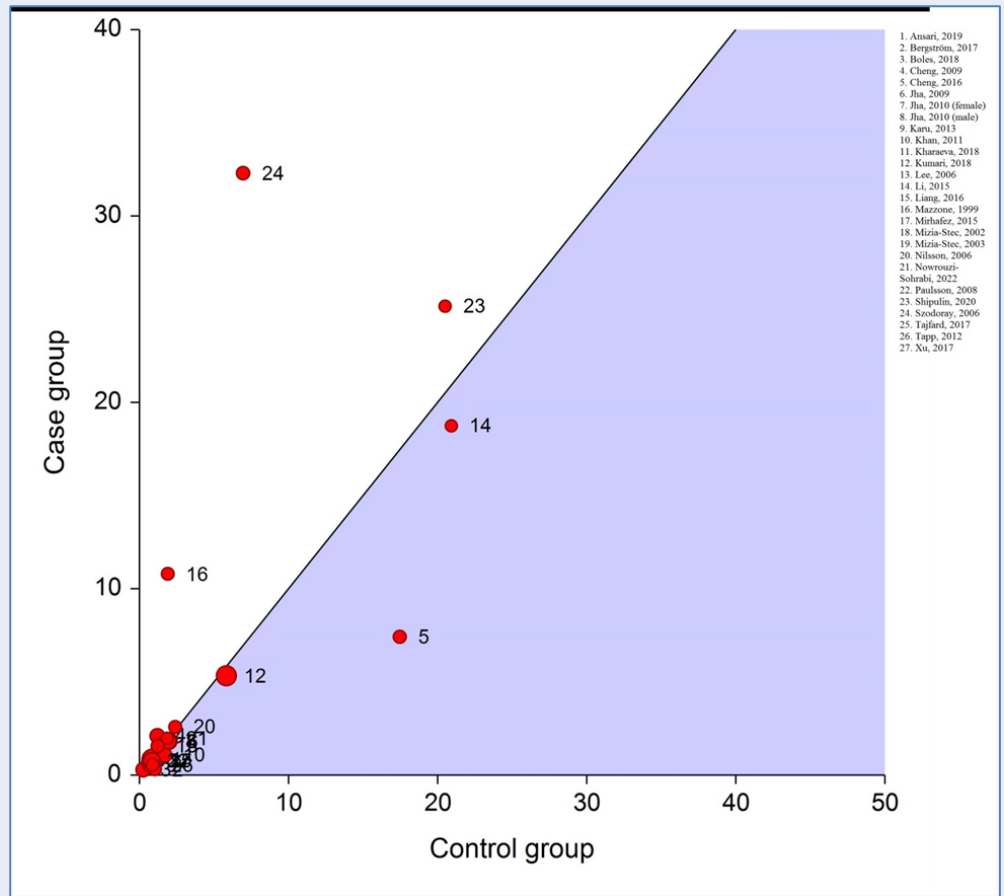


Figure 6: L'Abbé plot of studies on plasma/serum interleukin-10 (IL-10) levels for patients with coronary artery disease versus controls. In the plot, each circle stands for a separate study, with the size of the circles being proportional to the weight of the study, which is determined by the number of participants. The diagonal line signifies that, within the studies, the average IL-10 levels were the same in both groups.

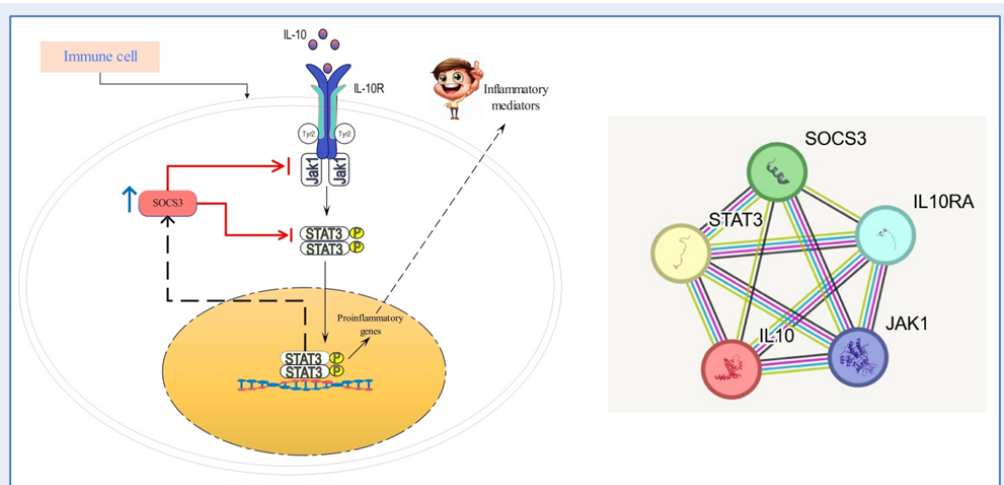


Figure 7: IL-10/STAT3/SOCS3 axis in coronary artery disease (left) and PPI interaction between mentioned proteins in the axis.

Table 5: Random meta-regression of IL-10 levels for patients with coronary artery disease versus controls

Variable		Data
Publication year	Point Estimate	- 0.00065
	SE	0.00020
	Lower Limit	- 0.00103
	Upper Limit	- 0.00026
	Z	- 3.30123
	P	0.00096*
Sample Size	Point Estimate	0.00023
	SE	0.00016
	Lower Limit	- 0.00008
	Upper Limit	0.00053
	Z	1.45301
	P	0.14622
Blood sample	Point Estimate	- 0.26738
	SE	0.06390
	Lower Limit	- 0.39263
	Upper Limit	- 0.14214
	Z	- 4.18444
	P	0.00003*

*Bold data donates statistical significance ($p < 0.05$). SE: Standard Error

different patient populations; and varying methodologies. Additionally, the study mentions factors such as statin therapy that could influence IL-10 levels in CAD patients, but these confounding variables were not fully explored in the analysis. The quality assessment of the included studies was conducted by a single author, which may introduce subjective bias. A more systematic and independent quality assessment process could enhance the reliability of the results. While no evidence of publication bias was found, it is possible that studies with significant results may have been more likely to be published, leading to an over representation of certain findings in the meta-analysis. However, the strengths of the meta-analysis include the absence of publication bias, the high quality of most included studies, and the consistency of the combined results.

CONCLUSIONS

According to this systematic review and meta-analysis, no significant difference was observed in blood IL-10 levels between CAD patients and controls, suggesting that IL-10 may not serve as a reliable

biomarker for CAD. The analysis included a sufficient number of cases for robust comparison, highlighting the complex and multifactorial nature of CAD. Further research is needed to better understand the role of inflammation and specific inflammatory markers in the development of CAD. Future studies should include larger sample sizes and explore the interaction of IL-10 with other proteins to enhance our understanding of CAD's pathogenesis and identify potential therapeutic targets. This study underscores the importance of continued research efforts to improve our comprehension of the mechanisms and risk factors involved in CAD.

This meta-analysis is clinically significant as it informs clinicians and researchers that IL-10 levels may not be useful for diagnosing or predicting CAD. It highlights the complex and multifactorial nature of CAD, indicating that many factors, not just IL-10, contribute to the disease's development. This insight is vital for clinicians when diagnosing and treating CAD.

ABBREVIATIONS

CAD - Coronary Artery Disease, CI - Confidence Interval, CK - Creatine Kinase, CO - Control, DEGs -

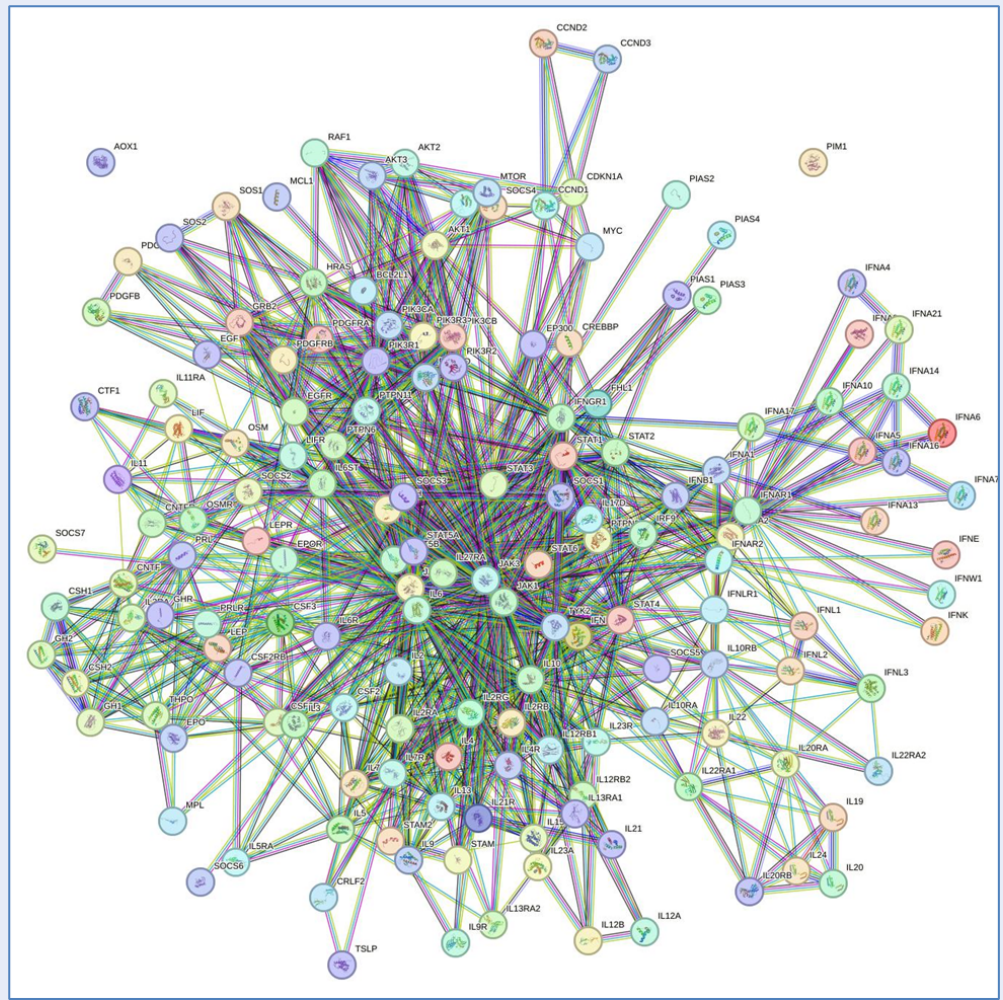


Figure 8: KEGG analysis of JAK-STAT signaling pathway.

Differentially Expressed Genes, ECG - Electrocardiographic/Electrocardiography, HDs - Heart Diseases, IL-10 - Interleukin-10, JAK - Janus Kinase, KEGG - Kyoto Encyclopedia of Genes and Genomes, NR - Not Reported, NOS - Newcastle-Ottawa Scale, PECO - Population, Exposure, Comparator, Outcome, PPI - Protein-Protein Interactions, PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO - International Prospective Register of Systematic Reviews, RIS - Required Information Size, SD - Standard Deviation, SE - Standard Error, SMD - Standardized Mean Difference, SOCS3 - Suppressor of Cytokine Signaling 3, STAT3 - Signal Transducer and Activator of Transcription 3, TNF- α - Tumor Necrosis Factor-Alpha, TSA - Trial Sequential Analysis

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

Conceptualization, R.H.M.; methodology, M.S.; software, M.S.; validation, R.H.M., and N.S.; formal analysis, M.S.; investigation, M.R. and M.S.; resources, M.S.; data curation, M.S.; writing—original draft preparation, N.S.; writing—review and editing, M.R. and M.S.; visualization, R.H.M.; supervision, N.S.; project administration, R.H.M.; funding acquisition, N.S. All authors have read and agreed to the published version of the manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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