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Systematic Review

# Unravelling the Role of IL-6, TNF-alpha and CRP in Pathogenesis of Coronary Artery Disease: A Systematic Review

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## Abstract

**Background:** India has high incidence of cardiovascular disease and coronary artery disease (CAD). Coronary artery disease is attaining epidemic proportions in India. Higher levels of C-reactive protein were connected to an augmented risk of coronary heart disease (CHD). TNF-alpha & IL-6 contribute in the pathogenesis of CHD and their levels are closely linked with the extent of coronary heart disease.

**Aim and objectives:** This objective of this review is to analyze the status of inflammatory markers and to establish their relation with the extent of CAD.

**Methodology:** The literature search for this review was done through databases incorporated are PubMed, Web of sciences, Scopus, Medline, Research Gate and Google scholar. The keywords used were “coronary artery disease”, “inflammatory markers,” and “cytokines in inflammation”. The Preferred Reporting Items for Systematic Research and Meta-Analysis (PRISMA) were used to build this review article.

**Results:** There were 1860 articles found which were relevant to the aim of our review, out of which only 57 fulfilled the inclusion criteria. A substantial variability across the studies was found. To figure out its correlation with inflammatory processes, these studies employed a variety of inflammatory markers. Most studies found a high level of inflammatory markers such as IL-6, TNF-alpha, and CRP in patients with coronary artery disease and cardiovascular disease.

**Conclusion:** Data from the literature searched highlighted a significant association between inflammatory markers and CAD.

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## 1. INTRODUCTION

Coronary artery disease is a common cardiac disorder in which atherosclerotic plaque builds up in the lumen of an artery supplying the heart. This results in reduced blood flow and oxygen supply to the myocardium. (1) In 2022, there were 315 million prevalent cases of coronary artery disease seen globally.(2) Global burden of disease estimates state that the prevalence of coronary artery disease worldwide was 154 million in 2016 which is 32.7 % of total cardiovascular disease and 2.2% of the total global burden of disease.(3) Mangala Rao et al. in conducting a systematic review of coronary artery disease in 2015 of 3885 studies and 288 observational studies done in India of coronary artery disease, found that the prevalence was 2.5%-12.6% in urban areas and 1.4%-4.6% in rural areas. Moreover, it was also found that the prevalence of different risk factors was smoking 8.9-40.5%, hypertension 13.1-36.9%, and diabetes mellitus 0.2-24.0%.(4) In the 60th round of surveys conducted by the National Statistical Survey Organization (NSS0) in 2004-2005, it was reported that the prevalence rate of CHD was 10% in the urban population and 4% in the rural population.(5) Prevalence rates evaluated by different studies according to year and place of studies have been shown in the **Table 1** below.

CAD is the inflammatory disease which indicates the formation atherosclerotic plaque within the coronary arteries of the heart. The atherosclerotic plaque leads to blockage of coronary artery resulting in inadequate supply of oxygen to cardiac muscles. (11) There are many risk factors related with CAD and plaque buildup, some can be controlled and some cannot be controlled. The risk factors that can be manageable are high blood pressure, raised cholesterol levels, diabetes mellitus, obesity, lack of exercise, nutritionally deficient diet, and smoking. The risk factors that cannot be managed are age, gender family history, and race. (12)

Inflammation participated in the progression and development of atherosclerotic plaque. (13) In this review, we will discuss the role of different inflammatory markers associated with the pathophysiology of atherosclerosis thereby resulting in coronary artery disease. Some of the inflammatory markers are: IL-6, IL-1, IL-18, TNF-alpha, C-reactive protein (CRP), lipoprotein phospholipase A2, and metalloproteinase (14), White blood cells (WBC)/ Leukocytes, Macrophage colony-stimulation factor (MCSF), Monocyte chemoattractant protein-1 (MCP1/CCL2).(15)

C-reactive protein (CRP) is acute-phase protein that can be elevated by as much as 1,000-fold in the zone of inflammation. (16) C-reactive protein is the final product of inflammation-related events. CRP has a direct proinflammatory effect on the endothelial tissue due to stimulation of proinflammatory activity inducible nitric oxide synthase (NOS) and inhibition of atheroprotective endothelial NOS. This shows that CRP may reflect the overall impact of local vascular inflammation. (17) CRP causes vascular smooth muscle cells to undergo apoptosis which contributes to plaque instability and has a procoagulant effect through suppression of prostacyclin. CRP can be useful in predicting long-term survival in acute coronary syndrome independent of LDL levels and it shows additional prognostic value of myocardial necrosis markers. (18) Paul M Ridker et al. had shown in their study that groups having high levels of CRP in patients with metabolic syndrome are at more risk of cardiovascular disease. (19)

TNF-alpha is the cytokine involved in inflammation that participated in the pathophysiology and progression of cardiovascular disorder. Also, the overexpression of TNF-alpha leads to the pathogenesis of various disorders like arthritis, coronary artery disease, and myocardial infarction. Polymorphism associated with the TNF-alpha gene may affect cardiovascular problems. (20) IL-6 is a pleiotropic cytokine that is involved in humoral and cellular immune responses related to inflammation, host defense, and tissue damage. (21) Interleukin-6 is mostly expressed by leukocytes, especially by active macrophages, and also expressed by smooth muscle and endothelial cells. The primary cause of CAD is the pathophysiology of atherosclerosis which is significantly influenced by IL-6 signalling. (22)

## 2. METHODS

The review was conducted in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

### 2.1. Eligibility criteria

This review included original research articles, meta-analyses and systematic reviews analysing the association of inflammatory markers such as IL-6, TNF-alpha and CRP with coronary artery disease and its severity. Studies relevant to the inflammatory markers in CAD patients and studies associating these inflammatory markers with the severity of the disease were included. Studies only in English language were considered for the inclusion in this review. Studies published between 1990 to 2023 were included. Exclusion criteria comprise of studies which particularly not related to status of inflammatory markers specially IL-6, TNF-alpha and CRP in CAD patients or there was no correlation of

**Table 1.** Prevalence of CAD in India.

| Authors | Year | Place | Sample size | CAD% |
|---|---|---|---|---|
| Anand Krishnan et al.[6] | 2012 | Delhi NCR (2nd survey) | 2052 | 14.1 |
| | 1994 | Delhi NCR (1st survey) | 3048 | 10.3 |
| Murthy PD et al.[7] | 2012 | Andhra Pradesh | 534 | 5.4 |
| Rajeev B et al.[8] | 2009 | Himachal Pradesh | 812 | 4.1 |
| Kamili M et al.[9] | 2007 | Jammu & Kashmir | 3128 | 7.5 |
| Clara Chow et al.[10] | 2004 | Andhra Pradesh | 345 | 2.5 |

these markers with severity. Exclusion criteria covered non-scientific articles, articles published before 1990 and after 2023 and also the articles which were published in language other than English. Moreover, in addition to relevance-based exclusions, duplicates, incomplete data, commentary articles, conference abstracts that do not include full manuscripts, and non-peer-reviewed sources were excluded to preserve the quality and consistency of the data. A number of potentially relevant articles were excluded owing to language barriers or the absence of full-text access. Studies not in English were excluded mainly because of translation limitations and the lack of trustworthy linguistic resources, which could have compromised the accuracy of data extraction and interpretation. We acknowledge that this introduces a potential language bias, which may result in the omission of significant insights published in other languages.

The research question was developed using the PICO framework. The "Population(P)" consisted coronary artery disease (CAD) or undergoing coronary angiography, both stable and unstable presentations, "Intervention (I)" defined as elevated serum levels of inflammatory biomarkers: Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and C-reactive protein (CRP), healthy individuals or patients without CAD, or those with lower levels of IL-6, TNF-α, and CRP are defined as "Comparison (C)". "Outcome (O)" was association between inflammatory marker and presence, severity or extent of CAD (e.g. gensini or SYNTAX score) on coronary angiography also comparison between different types of CAD (NSTEMI VS STEMI, obstructive vs non-obstructive, SAP vs USAP vs ACS). Hence, the formulated question was as follows: Is there an association between elevated levels of inflammatory biomarkers- IL-6, TNF-alpha and CRP and CAD and the severity based on angiography?

### 2.2. Information sources

Therefore, we conducted a comprehensive review of the titles and abstracts within the two chosen databases PubMed, Scopus and Medline which are recognized for indexing a wide range of high-impact, peer-reviewed publications in English. The key words used for literature search in the database are "inflammatory marker", "coronary artery disease" or IL-6, TNF-alpha, CRP in coronary artery disease and "association of inflammatory markers with severity". Further articles were discovered by examining cross-references to enhance the search. The systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Nonetheless, future reviews could be improved through multilingual collaboration to foster inclusivity and comprehensiveness. Both qualitative and quantitative studies were reviewed. Qualitative research included literature reviews, systematic reviews, meta-analyses and scoping reviews. For quantitative studies case-control, prospective and retrospective cohort, and experimental studies were included.

### 2.3. Search strategy

For the analysis of the inflammatory biomarker profile in patients with CAD, a systematic review search was done in the databases of PubMed, Scopus, and Medline.

The key words used for literature search in the database are "inflammatory marker", "coronary artery disease" or IL-6, TNF-alpha, and CRP in coronary artery disease. Further articles were discovered by examining cross-references to enhance the search. The systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

### 2.4. Selection Process

Relevant citations and references extracted from all recognised studies were reviewed to make sure of full-scale reporting. The screening and selection were done through Mendeley version 1.19.4 reference management software through which all the citations were imported. Selection process included 3 stages in which first stage was to identify the duplicate study and these duplicates were automatically and manually identified and removed. In 2nd stage titles of and abstracts were screened and in the final 3rd stage all the full text articles included were thoroughly reviewed. In addition, relevant citations and references from all identified studies were assessed to ensure complete coverage. The screening and selection process was performed utilizing Mendeley version 1.19.4 reference management software, following a systematic three-phase approach. During Phase I, duplicate records were discarded. Phase II included the screening of article titles and abstracts, whereas Phase III comprised a thorough review of the full-text articles selected from the earlier phase.

**Figure 1** shows a schematic representation of the steps associated with the literature search of our systematic review. During the preliminary search, a total of 1860 articles were identified (PubMed-848, Scopus-803, Medline-208). After elimination of 1225 replicate studies, 635 studies were selected for further review. Then we excluded 526 non-relevant studies (such as CAD associated with some other disease and studies that did not fulfil the selection criteria and exclusion criteria), studies published in non-English languages, lack of full-text access, and availability of only abstract. Then 109 studies were screened for the eligibility to be enrolled in this review and 24 research studies were excluded because of not relevant to aim and objective of our systematic review. A total of 85 full-text articles were evaluated for eligibility based on the established inclusion and exclusion criteria. 19 full text articles which do not met the inclusion and exclusion criteria were excluded. Also 9 studies containing narrative review were excluded. Remaining 57 studies are included in this systematic review. Two independent reviewers (PUK and PA) evaluated the titles and abstracts of all identified studies. To guarantee reliability and reduce bias, they adhered to a standardized protocol for selection and data extraction. Any discrepancies that arose during the selection or extraction phases were addressed through discussions among the reviewers. If disagreements persisted, a third reviewer (JH) was brought in to help reach a consensus. In instances where immediate consensus was not achievable, the study was collectively re-evaluated prior to making a final decision. This approach ensured consistency, minimized bias, and upheld the integrity of the review.

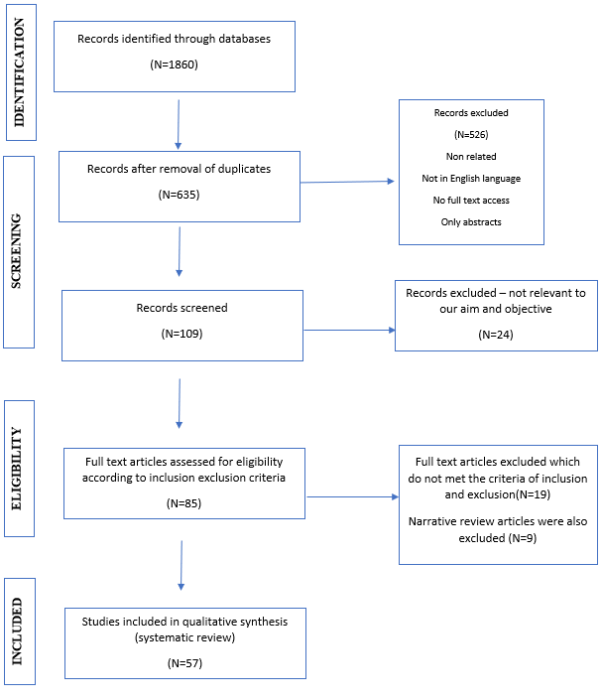


**Figure 1. Study selection flowchart. From 1,860 records identified, 635 remained after removing duplicates. After screening titles and abstracts, 109 articles were reviewed, with 85 full texts assessed. In total, 57 studies were included.**

### 2.5. Data extraction and analysis

For every study included, a systematic data extraction method was utilized to gather essential information which encompassed the author, year of publication, country, type of study, sample size and findings of each study. To guarantee precision and uniformity, the reviewers worked together to scrutinize the extracted data, thereby reducing discrepancies in interpretation.

This review showcases its findings by employing a narrative synthesis strategy, adhering to the PRISMA guidelines to comprehensively recognize all available evidence and accentuate essential characteristics.

### 2.6. Risk of bias assessment

Three independent reviewers (PA, UK, and JH) performed assessments of the risk of bias in the selected articles. The Newcastle–Ottawa Scale (NOS) was employed to thoroughly evaluate the quality of risk of bias for each article (23). In the case of cohort and cross-sectional studies the NOS assessed the selection of study groups (both exposed and non-exposed), their comparability, and the evaluation of

outcomes. Conversely, for case–control studies, the NOS examined the selection of study groups (cases and controls), their comparability, and the determination of exposure for both cases and controls. A total of eight items across the three domains could receive a star rating, with each item being assigned a minimum of one star and a maximum of two stars. Studies that achieved a total score of seven to nine stars were classified as high quality, those scoring four to six stars were deemed fair quality, and those with one to three stars were categorized as low quality. NOS assessment for risk of bias of cohort, cross-sectional and case-control studies are shown in **Table 2**, **Table 3** and **Table 4** respectively. Cochrane scale (24) for randomized controlled trial is shown in **Table 5** and for animal model SYRCLE (25) was used shown in **Table 6**.

## 3. RESULTS

A total of 57 studies were reviewed that satisfied the inclusion criteria., 34 studies showed a relationship between IL-6 and coronary artery disease (CAD) summarized in **Table 7**. Furthermore, **Table 8** shows 12 studies reflecting relationship of TNF-α with CAD and 21 studies of CRP and CAD are shown in **Table 9**. The results indicated that the levels of the inflammatory markers IL-6, TNF-α, and CRP were elevated in patients with coronary artery disease in comparison to the control group, and these markers demonstrated a correlation with the severity of the disease. 15 studies demonstrated a correlation between C-reactive protein, TNF-α, and IL-6 with coronary artery disease (CAD) and its severity, as illustrated in **Table 10**.

## 4. DISCUSSIONS

The current research systematically explores the connection between inflammatory markers and the incidence of coronary artery disease. The inflammatory parameters that were studied include Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF-alpha) and C-reactive protein (CRP). Elevated levels of these inflammatory markers are commonly linked to adverse outcomes of coronary artery disease leading to a increased chance of cardiac failure, myocardial infarction leading to death.

### 4.1. Inflammatory Markers and CAD Association

Inflammatory markers and CAD were strongly correlated in nearly all of the studies reviewed. The majority of the studies showed an association between IL-6 and coronary artery disease and fewer studies showed an association of TNF-alpha with coronary artery disease. Among 57 studies reviewed for this systematic review, finding from 34 studies have revealed a link between interleukin-6 (IL-6) and the development of coronary artery disease, and 12 studies reflected a relationship between TNF-alpha and CAD. 21 studies mentioned in **Table 9** showed the relationship between serum levels of CRP and CAD. But very few studies compared all three inflammatory parameters IL-6, TNF-alpha, and CRP together. Studies such as those done by Bouzidi N et al. (26), Fadhil Jaafar A. et al. (27), Shen L et al.(34), Zhou M et al.(35), Schlitt A. et al. (45), Luc G. et al. (48) showed that concentration of IL-6 in serum were elevated in the group having patients of coronary artery disease than the healthy control group. Studies such as those done by Fadhil Jaafar A. et al. (27), Shen L. et al. (34), and Schlitt A. et al. (42) observed that serum TNF-alpha was elevated in patients of CAD than healthy control (patients without CAD). CRP contributes in the formation of atherosclerotic plaque. Some of the prior studies done by Mahajan N et al. (68), Sharma S B et al. (69), and Zhu M. et al. (66) demonstrated that hs-CRP were elevated in group of subjects with coronary artery disease than controls (group free of CAD) and Luc G. et al. (48) stated The CAD group exhibited higher CRP levels in comparison to the non-CAD group. Sharma S B et al. (69) also showed that hs-CRP was 4.5 times raised than control.

### 4.2. Inflammatory Markers and Obstructive vs. Non-Obstructive CAD

Of the 57 studies analyzed, only one focused on comparing the serum levels of IL-6 and TNF-alpha in cases of obstructive coronary artery disease versus non-obstructive CAD. Mohammad-Rezaei M et al. (32) concluded in their study that serum concentration of interleukin-6 and TNF-α were more elevated in obstructive than non-obstructive CAD. It was also found that circulating levels of IL-6 in coronary heart disease patients with obstruction in their coronary arteries were 3.32 times that of the subjects with coronary artery patients without obstruction and TNF-alpha levels were 2.25 times in CAD with obstruction that of CAD without obstruction. A characteristic feature of occlusive CAD is the substantial accumulation of atherosclerotic plaque that constricts the coronary arteries and stimulates a heightened inflammatory reaction. IL-6 is generated by stimulated macrophages along with endothelial and SMCs (smooth muscle cells) found in atherosclerotic plaques. Therefore, the larger the burden of plaque, the more IL-6 is produced. (83) Moreover, in obstructive coronary artery disease (CAD), plaques are more likely to become unstable and break apart, initiating acute inflammatory responses. During this process, levels of interleukin-6 (IL-6) increase

Table 2. The Newcastle–Ottawa Scale (NOS) for assessment of cohort studies.

| Author | Year | Type of study | Representatives of the Exposed Cohort | Selection of the Non-Exposed Cohort | Ascertainment of Exposure | Demonstration that Outcome of Interest Was Not Present at Start of Study | Comparability of Cohorts on the Basis of the Design or Analysis | Assessment of Outcome | Was Follow-Up Long Enough for Outcomes to Occur | Adequacy of Follow-Up of Cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gager G. M. et al.[31] | 2020 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Fanola C et al.[34] | 2017 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Su D et al.[40] | 2013 | Cohort | * | * | * | * | * | * | * | | 7 |
| Saremi A et al.[43] | 2009 | Cohort | * | * | * | * | ** | * | * | | 8 |
| Brueckmann M et al.[46] | 2004 | Cohort | * | * | * | * | * | * | * | * | 8 |
| Cesari M et al.[47] | 2003 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Luc G et al.[48] | 2003 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| van der Meer IM et al.[49] | 2002 | Cohort | * | * | * | * | ** | * | * | | 8 |
| Jenny NS et al.[50] | 2002 | Cohort | * | * | * | * | ** | * | * | | 8 |
| Koukonnen H et al.[52] | 2001 | Cohort | * | | * | * | * | * | * | * | 8 |
| Lindmark E et al.[53] | 2001 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Biasucci L. M. et al.[59] | 1999 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Khandelwal V et al. [67] | 2022 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Pan H. C. et al. [71] | 2015 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Mahajan N et al. [72] | 2009 | Cohort | * | * | * | * | ** | * | * | | 8 |
| Sharma S B et al. [73] | 2008 | Cohort | * | * | * | * | ** | * | * | | 8 |
| Zacho J et al. [74] | 2008 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Mora S et al. [76] | 2006 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Ishikawa T et al. [78] | 2003 | Cohort | * | * | * | * | * | * | * | * | 8 |
| Heeschen C et al. [81] | 2000 | Cohort | * | * | * | * | ** | * | * | * | 9 |
| Haverkate F et al. [83] | 1997 | Cohort | * | * | * | * | ** | * | * | * | 8 |
| Liuzzo G et al. [84] | 1994 | Cohort | * | * | * | * | * | | * | | 6 |

**Table 3.** The Newcastle–Ottawa Scale (NOS) for assessment of cross-sectional studies

| Author | Year | Type of study | SELECTION (MAX-*****) | | | COMPARABILITY (MAX-**) | OUTCOMES (MAX-***) | | TOTAL SCORE |
|---|---|---|---|---|---|---|---|---|---|
| | | | Representativeness of the Sample | Sample Size Justification | Non-Respondents Ascertainment of Exposure (Biomarkers) | | Assessment of Outcome | Statistical Test Appropriateness | |
| Ling Y et al.[29] | 2021 | cross-sectional | * | | * | * | * | * | 5 |
| Tang J et al.[36] | 2015 | cross-sectional | * | | * | * | | * | 4 |
| Anderson DR et al.[39] | 2013 | Cross-sectional observational | * | | * | * | * | * | 5 |
| Tanindi A et al.[42] | 2011 | cross-sectional | * | | * | * | * | * | 5 |
| Gotsman I et al.[44] | 2008 | Cross-sectional observational | * | * | ** | * | * | * | 7 |
| Schieffer B et al.[57] | 2000 | cross-sectional | * | * | ** | | * | * | 6 |
| H.G. Rus et al.[61] | 1996 | cross-sectional | * | * | ** | | * | * | 6 |
| Jianbo Z et al. [68] | 2022 | cross-sectional | * | * | ** | | * | * | 6 |
| Li X. Y. et al. [85] | 2018 | cross-sectional | * | | ** | ** | * | ** | 8 |
| Min X et al. [86] | 2017 | cross-sectional | * | * | ** | ** | * | ** | 9 |
| Al-Tu'maa FJ et al. [87] | 2016 | cross-sectional | * | * | ** | | * | ** | 7 |
| Zebrack JS et al. [88] | 2002 | cross-sectional | * | * | ** | ** | * | ** | 9 |

**Table 4.** The Newcastle–Ottawa Scale (NOS) for assessment of case-control studies.

| Author | Year | Type of Study | Case Definition Adequate | Representativeness of Cases | Selection of Controls | Definition of Controls | Comparability (Max-2) | Ascertainment of Exposure | Same Method of Ascertainment | Non-Response Rate | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bouzidi N et al. [24] | 2023 | Case-Control | * | * | * | * | * | * | * | * | 8 |
| Fadhil Jaafar A et al. [25] | 2023 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Heinisch RH et al. [27] | 2022 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Douskami H et al. [28] | 2021 | Case-Control | * | | * | * | * | * | * | * | 7 |
| Mohammad-Rezaei M et al.[30] | 2021 | Case-Control | * | * | * | * | * | * | * | * | 8 |
| Shen L et al. [32] | 2019 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Zhou M et al. [33] | 2019 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Schlitt A et al. [45] | 2004 | Case-Control | * | * | * | | * | * | * | | 6 |
| Ridker PM et al. [55] | 2000 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Ridker PM et al. [56] | 2000 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Biasiussi L. M. et al. [60] | 1996 | Case-Control | * | * | * | * | ** | * | * | | 8 |
| Ridker PM et al. [65] | 1999 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Maury CPJ et al. [66] | 1989 | Case-Control | * | * | * | | | * | * | * | 6 |
| Tajfard M et al. [69] | 2018 | Case-Control | * | * | * | * | ** | * | * | | 8 |
| Zhu M et al. [70] | 2018 | Case-Control | * | * | * | * | ** | * | * | | 8 |
| Haidari M et al. [79] | 2001 | Case-Control | * | * | * | * | ** | * | * | * | 8 |
| Danesh J et al. [80] | 2000 | Case-Control | * | * | * | * | ** | * | * | * | 9 |
| Tataru MC et al. [82] | 1999 | Case-Control | * | * | * | * | ** | * | * | | 8 |

**Table 5.** The Cochrane scale for assessment of randomized controlled trial.

| Author | Year | Type of study | Bias arising from the randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result |
|---|---|---|---|---|---|---|---|
| Lindmark E et al.[53] | 2001 | | LOW RISK | LOW RISK | LOW RISK | LOW RISK | MODERATE RISK |

**Table 6.** The SYRCLE scale for assessment of animal model study.

| | Selection Bias (randomization) | Baseline Characteristics | Performance Bias (blinding) | Detection Bias (blinding of assessors) | Attrition Bias | Reporting Bias |
|---|---|---|---|---|---|---|
| Huber SA et al.[58] | 1999 Unclear | Low Risk | High Risk/Unclear | High Risk/Unclear | Low Risk | Moderate Risk |

**Table 7.** Showing the studies of IL-6 in coronary artery disease.

| Sl.no | Author's name | Year | Place | Type of Study | Sample size | Findings |
|---|---|---|---|---|---|---|
| 1. | Bouzidi N et al. (26) | 2023 | Tunisia | Case-control | 310-CAD, 210-Controls | The concentration of IL-6 in coronary artery disease patients was elevated in comparison to the control group. |
| 2. | Fadhil Jaafar A et al. (27) | 2023 | Tehran, Iran | Case-control | 176 | The levels of IL-6 were markedly elevated in the CAD group compared to the control group. |
| 3. | Djahanpour N et al. (28) | 2023 | Canada | Systematic review | 17 articles | IL-6 levels were closely linked with peripheral artery disease (PAD).<br>IL-6 has the potential to act as a biomarker for the diagnosis and prognosis of peripheral artery disease (PAD). |
| 4. | Heinisch RH et al. (29) | 2022 | Brazil | Case-control | 20- ACS, 20-SA, 20-control | IL-6 increased in ACS patients as compared with stable angina or control subjects.<br>IL-6 levels were elevated in patients with acute coronary syndrome when compared to those with stable angina or control subjects. |
| 5. | Doustkami H et al. (30) | 2021 | Iran | Case-control | N=90<br>AMI-30<br>SAP-30<br>Control-30 | Interleukin (IL)-6 levels were significantly increased in patients with AMI compared with SAP and control groups ($P < 0.05$ to $P < 0.001$).<br>Interleukin-6 concentrations were markedly elevated in patients diagnosed with acute myocardial infarction (AMI) when compared to those in the stable angina pectoris (SAP) and control groups. |
| 6. | Ling Y et al.(31) | 2021 | China | Cross-sectional Observational Study. | 346<br>ACS-201<br>SAP-145 | IL-6 levels are closely linked to the extent of coronary artery disease in ACS patients undergoing percutaneous coronary intervention<br>IL-6 levels were significantly higher in the ACS group than SAP with p value<0.001<br>The levels of IL-6 are strongly associated with the severity of CAD in patients with ACS who are receiving percutaneous coronary intervention. Furthermore, IL-6 levels were markedly elevated in the ACS compared to those with SAP, with a p-value of less than 0.001. |
| 7. | Mohammad-Rezaei M et al. (32) | 2021 | Iran | Case-control | 42-non obstructive CAD (control)<br>42- obstructive CAD (cases) | IL-6 levels in Coronary artery obstruction increased to 3.32 times that of the subjects with non-obstructive CAD. |
| 8. | Gager G. M. et al. (33) | 2020 | Austria | Prospective | N=322 | Elevated serum IL-6 concentrations are associated with an increased risk of long-term cardiovascular mortality when assessed at the time point of ACS.<br>Elevated levels of serum IL-6 are linked to a heightened risk of long-term cardiovascular mortality when evaluated at the time of acute coronary syndrome (ACS). |
| 9. | Shen L et al. (34) | 2019 | China | Case-control | 138 | IL-6 levels were markedly elevated in the CAD group compared to the control group. |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10. | Zhou M et al. (35) | 2019 | Wuhan, China | Case-control | 155-CAD 181-Control | Compared to the control subjects, individuals with CAD exhibited significantly higher circulating levels of IL-6. |
| 11. | Fanola C et al. (36) | 2017 | USA | Cohort | N=4939 | The ACS group exhibited a substantial increase in IL-6 levels relative to the control group |
| 12. | Akita K et al. (37) | 2017 | Japan | Clinical trial | ~~ | IL-6 plays a significant role in the progression of atherosclerosis. Its signalling pathways have been associated with the initiation and destabilization of plaques, as well as negative outcomes during episodes of acute ischemia. |
| 13. | Tang J et al. (38) | 2015 | China | Cross-sectional | N=81 | There was a notable increase in IL-6 expression in the ACS and SAP groups relative to the control group, with a statistically significant p-value of less than 0.01. |
| 14. | Anderson DR et al. (39) | 2013 | USA | Case-control | 73 | IL-6 was elevated in AMI compared to CAD and controls. |
| 15. | Su D et al. (40) | 2013 | China | cohort | N=718 | Among hospitalized individuals suffering from coronary artery disease, there is a notable association between serum IL-6 levels and the rates of all-cause and cardiovascular mortality. |
| 16. | Sarwar N et al. (41) | 2012 | UK | Metanalysis | 82 studies | There is a significant cross-sectional link between circulating IL-6 and the likelihood of coronary heart disease occurrence in those without any previous cardiovascular disease history |
| 17. | Tanindi A et al. (42) | 2011 | Turkey | Cross-sectional | 134 | IL-6 levels were found to be higher in patients with CAD compared to control subjects, and individuals experiencing acute coronary syndromes exhibited an even more significant rise in IL-6 levels.<br><br>individuals with STEMI and NSTEMI exhibited markedly elevated levels of IL-6 in contrast to those in the SAP group. |
| 18. | Saremi A et al. (43) | 2009 | Chicago | Cohort | N=306 | A significant correlation was observed between the inflammatory marker IL-6 and coronary atherosclerosis, particularly in subjects who demonstrated less evidence of systemic atherosclerosis. |
| 19. | Gotsman I et al. (44) | 2008 | Israel | Cross-sectional | 201 | Patients suffering from acute coronary syndrome exhibited increased levels of IL-6 in contrast to stable patients. |
| 20. | Schlitt A et al. (45) | 2004 | Germany | Case-control | 247-cad, 61-controls | In comparison to the control group, the CAD group exhibited significantly increased levels of IL-6 |
| 21. | Brueckmann M et al. (46) | 2004 | Germany | Cohort study | 26 | A significant elevation in IL-6 levels was noted in ACS patients compared to the control group, and these levels showed a decline after three months. |
| 22. | Cesari M et al. (47) | 2003 | USA | Cohort study | N=2225 | In patients with coronary heart disease events, stroke events, and coronary heart failure, IL-6 levels were found to be significantly higher than in those who did not have any cardiac events. |
| 23. | Luc G et al. (48) | 2003 | France | Cohort study | 317 | Levels of IL-6 were remarkably higher in cases (CHD) than control. With p-value<0.05 |

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| 24. | van der Meer IM et al. (49) | 2002 | Netherland | Cohort study | 7983 | Interleukin-6 has been linked to the development of atherosclerosis. |
| 25. | Jenny NS et al. (50) | 2002 | USA | cohort | 5201 | An association was found between IL-6 and elevated atherosclerosis when contrasting the control group with individuals who were free of subclinical cardiovascular disease. |
| 26. | Koukonnen H et al. (51) | 2001 | Finland | Cohort study | 263 | Elevated levels of IL-6 were linked to a heightened risk of coronary mortality among patients diagnosed with unstable angina pectoris |
| 27. | Lindmark E et al. (52) | 2001 | Sweden | Prospective Randomized trial | 3269 | Circulating IL-6 is a robust independent marker of elevated mortality risk in patients suffering from unstable coronary artery disease (CAD), and it can be utilized to identify those individuals who would derive the greatest benefit from an early invasive treatment approach. |
| 28. | Ridker PM et al. (53) | 2000 | Boston | Case-control study | 122- cases<br>244-control | Il-6 was substantially increased in female with cardiovascular episodes than in women without cardiovascular events with a p-value of 0.003 |
| 29. | Ridker PM et al. (54) | 2000 | Boston | Case-control | Cases-202<br>Control-202 | In the myocardial infarction group, IL-6 levels were significantly greater than those observed in the control group, yielding a p-value of 0.002. |
| 30. | Schieffer B et al. (55) | 2000 | Finland | Cross-sectional | N=33 | Atherectomy samples exhibited a more significant level of IL-6 in comparison to stable coronary segments. |
| 31. | Huber SA et al. (56) | 1999 | United Kingdom | Cross-sectional | 48 | IL-6 enhances fatty lesion development in atherosclerosis-prone mice. |
| 32. | Biasucci L. M. et al. (57) | 1999 | Italy | Cohort | N=43<br>uneventful course=17<br>complicated in-hospital course=26 | Elevated levels of IL-6 were linked to poor in-hospital outcomes in patients with acute coronary syndrome (ACS).<br>IL-6 was higher in unstable angina and with worsening disease than in patients with an uneventful course. |
| 33. | Biasucci L. M. et al. (58) | 1996 | America | Case-control | 38 | Cytokine IL-6 levels were detectable in group with stable and unstable angina than non-diseased control in which IL-6 was not detectable ($p<0.01$). |
| 34. | H.G. Rus et al. (59) | 1996 | USA | Cross-sectional | 34 | IL-6 levels were remarkably increased in normal intima than fibrous plaque with $p<0.05$ and IL-6 contributes to the atherosclerotic process. |

**Table 8. Showing the studies of TNF-alpha in coronary artery disease.**

| Sl.no | Author's name | year | place | Type of study | Sample size | Findings |
|---|---|---|---|---|---|---|
| **1.** | Fadhil Jaafar A et al. (27) | 2023 | Tehran, Iran | Case-control | 176 | TNF-alpha levels were notably increased in the coronary artery disease group than those in control group. |
| **2.** | Heinisch RH et al. (29) | 2022 | Brazil | Case-control | 20- ACS<br>20-SA<br>20-control | Compared to individuals with stable angina or control subjects, patients suffering from acute coronary syndrome (ACS) exhibited an increase in TNF-alpha levels. . |
| **3.** | Mohammad-Rezaei M et al. (32) | 2021 | Iran | Cross-sectional | 84<br>42-non obstructive CAD (control)<br>42- obstructive CAD (cases) | In patients with obstructive coronary artery disease (CAD), serum levels of TNF-alpha were elevated to 2.25 times the levels observed in non-obstructive CAD. |
| **4.** | Shen L et al. (34) | 2019 | China | Case-control | N=138 | TNF-alpha levels were markedly elevated in the coronary heart disease group than control group. |
| **5.** | Schlitt A et al. (45) | 2004 | Germany | Case-control | 247-CAD<br>61-controls | TNF-alpha levels were elevated in the group with coronary heart disease than control. |
| **6.** | Lei L et al. (60) | 2009 | China | Clinical trial | ~~~ | In the early phase of lesion development, TNF-alpha contributes to the progression of atherosclerosis. |
| **7.** | Gotsman I et al. (44) | 2008 | Israel | Cross-sectional | N=201 | Compared to stable patients, individuals with acute coronary syndrome exhibited elevated levels of TNF-alpha. |
| **8.** | Brueckmann M et al. (46) | 2004 | Germany | Case-control | N=26 | The levels of TNF-alpha were markedly elevated in both central and peripheral blood of patients with ACS on days 0 and 1 (p-value < 0.01) when compared to the control group, returning to baseline levels by day 120. |
| **9.** | Cesari M et al. (47) | 2003 | USA | Cohort study | N=2225 | TNF-alpha was significantly elevated in subjects with CHD events, stroke events and heart failure than patients with no cardiac events. |
| **10.** | Koukonnen H et al. (51) | 2001 | Finland | Cohort study | N=263 | Elevated levels of TNF-alpha were linked to a heightened risk of coronary mortality among patients diagnosed with unstable angina pectoris (UAP). |
| **11.** | Ridker PM et al. (61) | 1999 | Boston, United states | Case-control | Cases-272<br>Control-272 | Systemic TNF-alpha concentration was higher in cases (subjects Who developed recurrent coronary event than control (subjects free of recurrent coronary disease) |
| **12.** | Maury CPJ et al. (62) | 1989 | Finland | Case-control study | N=22 | Circulating TNF-alpha levels were elevated in patients with myocardial infarction than healthy control. |

Table 9. Showing the studies of CRP in coronary artery disease.

| Sl.no | Author's name | year | place | Type of Study | Sample size | Findings |
|---|---|---|---|---|---|---|
| 1. | Khandelwal V et al. (63) | 2022 | India | Cross-sectional | N=284 | Patients with STEMI showed considerably higher CRP levels relative to patients with unstable angina and chronic stable angina. |
| 2. | Jianbo Z et al. (64) | 2022 | China | Cross-sectional | N=65 | A notable positive correlation (P = 0.03) was observed between the volume of the infarct core and the levels of serum hs-CRP.<br>Elevated serum hs-CRP levels can be indicative of the infarct core volume in individuals experiencing acute ischemic syndrome. |
| 3. | Tajfard M et al. (65) | 2018 | Iran | Case-control | N=2346<br>Cases-1187<br>Control-1159 | Serum levels of hs-CRP were raised in advanced ischemic heart disease (stenosis ≥ 50% stenosis of at least one coronary artery) than in healthy control ($p < 0.001$) |
| 4. | Zhu M. et al. (66) | 2018 | China | Case-control | N=579<br>Cases-492<br>control-87 | In the CAD group, hs-CRP levels were significantly greater than those observed in the non-CAD group.<br>Within the CAD group, there was a notable increase in hs-CRP levels corresponding to the number of affected coronary artery branches, whether it was 1, 2, or 3 or more, with statistical significance indicated by $P < 0.01$. |
| 5. | Tang J et al. (38) | 2015 | China | Cross-sectional | N=81 | The ACS group had a significantly greater hs-CRP than SAP and the control group (p-value<0.01). |
| 6. | Pan H. C. et al. (67) | 2015 | China | Cross-sectional | 181<br>Without MACE-142<br>With MACE-39 | Patients with major adverse cardiovascular events (MACE) have significantly higher hs-CRP than those without MACE<br>(p-value = 0.025) |
| 7. | Sarwar N et al. (41) | 2012 | UK | Meta-analysis | 82 studies | There is an association of circulating levels of C-reactive protein with an occurrence of CHD risk with no known history of cardiovascular disease. |
| 8. | Mahajan N et al. (68) | 2009 | India | Case-control | N=140<br>Cases-100<br>Control-40 | The CAD group exhibited significantly elevated levels of hs-CRP in comparison to the healthy control group. |
| 9. | Sharma S B et al. (69) | 2008 | India | Case-control | N=30 | A significant increase in hs-CRP levels ($p< 0.001$) was observed in young patients suffering from coronary artery disease (CAD).<br>hs-CRP was 4.5 times raised than the control. |
| 10. | Zacho J et al. (70) | 2008 | Copenhagen | Cross-sectional study | N=10276 | Genetic polymorphisms within the CRP gene are correlated with a substantial rise in CRP levels, thereby suggesting a potential increase in the risk of ischemic vascular disease. |

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| **11.** | Mora S et al. (71) | 2006 | USA | Prospective study | N=27742 | The levels of hs-CRP exhibited a positive correlation with the risk of cardiovascular disease. |
| **12.** | Luc G. et al. (48) | 2003 | France | case-control | 317-cases Control-607 | CRP levels were substantially higher in patients (CHD) group compared to controls with p-value < 0.05. |
| **13.** | Ishikawa T et al. (72) | 2003 | Japan | Cross-sectional | N=27 | C-reactive protein (CRP) within atheromatous plaques contributes to the pathogenesis and/or progression of unstable angina pectoris and restenosis following directional coronary atherectomy (DCA) |
| **14.** | Haidari M et al. (73) | 2001 | Canada | Case-control | 284-CAD 166-control | C-reactive protein (CRP) is significantly linked to stable coronary artery disease (CAD), and assessing CRP levels could enhance the evaluation of coronary risk in patients with CAD. |
| **15.** | Danesh J et al. (74) | 2000 | London | Nested Case-control | Cases-507 Control-1026 | The baseline measurements of C-reactive protein demonstrated a correlation with the future likelihood of coronary heart disease. |
| **16.** | Ridker PM et al. (53) | 2000 | England | Prospective nested case-control | N=28263 | hs-CRP concentration were elevated in category having cardiovascular disease than the group free of cardiovascular disease in women. |
| **17.** | Heeschen C et al. (75) | 2000 | USA | Cross-sectional study | N=447 | C-reactive protein (CRP) served as an independent predictor for both cardiac risk and the likelihood of undergoing repeated coronary revascularization procedures, including coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty, over the 6-month follow-up period. |
| **18.** | Tataru MC et al. (76) | 1999 | Germany | Case-control | 1411-CAD 464-Control | The mean C-reactive protein levels during the early stages of generalized atherosclerosis were greater than those recorded in patients experiencing coronary heart disease |
| **19.** | Haverkate F et al. (77) | 1997 | London, UK | Cross-sectional study | N=2121 | Elevated levels of C-reactive protein (CRP) were linked to coronary events in individuals experiencing either stable or unstable angina. Patients exhibiting CRP concentrations in the highest quintile (>3.6 mg/L) faced approximately double the risk of experiencing a coronary event. |
| **20.** | Biasucci L M. et al. (58) | 1996 | USA | Case-control | N=38 | CRP concentration were increased (i.e. >3 mg/L) in the subjects with unstable angina than stable angina pectoris. |
| **21.** | Liuzzo G et al. (78) | 1994 | Italy | Cross-sectional study | N=92 | C-reactive protein (CRP) serves as an inflammatory marker in the development of CHD, as elevated levels of CRP upon hospital admission are associated with unfavourable outcomes in patients experiencing unstable angina |

**Table 10.** Studies showing association of IL-6, TNF-alpha, and CRP with severity of coronary artery disease.

| Sl.no | Author's name | S | place | Type of Study | Sample size | Findings |
|---|---|---|---|---|---|---|
| 1. | Bouzidi N et al. (26) | 2023 | Tunisia | Case-control | 310-CAD 210-Controls | The levels of IL-6 were found to be correlated with Gensini scores in patients with coronary artery disease (CAD). The levels of IL-6 were found to be correlated with Gensini scores in patients with coronary artery disease (CAD). |
| 2. | Heinisch RH et al. (29) | 2022 | Brazil | Case-control | 20- ACS 20-SA 20-control | Inflammatory markers are linked to the severity of ischaemic disease, exhibiting higher levels in acute coronary syndrome (ACS) compared to stable angina or control subjects. |
| 3. | Zhu M. et al. (66) | 2018 | China | Case-control | N=579 Cases-492 Cases-87 | The Gensini score exhibited a positive correlation with hs-CRP levels, (with a correlation coefficient of r = 0.361 and a significance level of P < 0.01.) |
| 4. | Tajfard M et al. (65) | 2018 | Iran | Case-control | N=2346 Cases-1187 Control-1159 | The hs-CRP exhibited a significant correlation with the score associated with coronary artery disease (p < 0.01). |
| 5. | Li X. Y. et al. (79) | 2018 | China | Cross-sectional | N=77 CAD-40 Non-CAD-37 | Serum concentration of TNF-like cytokine 1A (TL1A), a component of the TNF superfamily are positively correlated with SYNTAX scores in patients having cardiac surgery. |
| 6. | Min X et al. (80) | 2017 | China | Cross-sectional | N=149 | IL-6 and TNF- alpha significantly increase on increasing severity of ischemic events with p<0.005 |
| 7. | Al-Tu'maa FJ et al. (81) | 2016 | Iraq | Cross-sectional | N=76 | A notable and robust positive correlation was observed between the severity of coronary artery disease (CAD) and the serum concentrations of high-sensitivity C-reactive protein (hs-CRP). |
| 8. | Tang J et al. (38) | 2015 | China | Cross-sectional | N=81 | The levels of IL-6 were markedly elevated in the groups with one-vessel, two-vessel, and three-vessel disease when compared to the control group. The levels of IL-6 were markedly reduced in the one-vessel disease group compared to both the two-vessel disease group (p-value<0.05) and the three-vessel disease group (p-value<0.01). |
| 9. | Cesari M et al. (47) | 2013 | USA | Cohort study | N=2225 | The levels of TNF-alpha and IL-6 were correlated with the severity of left ventricular dysfunction. |
| 10 | Tanindi A et al. (42) | 2011 | Turkey | Cross-sectional | N=134 | IL-6 demonstrated a significant correlation with the Gensini score, which serves as an objective measure of the severity and extent of coronary artery disease (CAD). |

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| 11 | Gotsman I et al. (44) | 2008 | Israel | Cross-sectional | N=201 | There was a higher prevalence of coronary vessel disease, characterized by over 70% stenosis, among patients as the levels of serum TNFα and IL-6 increased across tertiles.<br><br>The severity of coronary heart disease, evaluated using the Gensini score, demonstrated independent associations with the inflammatory markers TNFα and IL-6 in patients with both stable and unstable forms of the condition |
| 12 | Zebrack JS et al. (82) | 2002 | USA | Cross-sectional | N=2554 | Elevated C-reactive protein (CRP) levels are observed in individuals suffering from mild, moderate, and severe coronary artery disease (CAD) in contrast to patients who present with normal angiograms.<br>CRP – minimal CAD< intermediate CAD < advanced CAD |
| 13 | Van Der Meer I M et al. (49) | 2002 | Netherland | Cohort study | N=7983 | IL-6 increases on increasing the size and severity of the lesion. |
| 14 | Mahajan N et al. (68) | 2009 | India | Case-control | N=140 Cases-100 Control-40 | Within the CAD group, there is a notable and positive association between the levels of hs-CRP and the severity of coronary artery disease. |
| 15 | Biasucci L. M et al. (58) | 1996 | America | Case-control | N=38 | The levels of IL-6 were found to be higher in cases of unstable angina pectoris compared to those with chronic stable angina pectoris.<br><br>Higher levels of IL-6 are typically present in unstable angina and have a significant association with prognostic implications.<br><br>There is a positive relationship between the severity of angina and the levels of CRP, with higher levels observed in more severe cases. |

significantly, which contributes to systemic inflammation. In contrast, non-obstructive CAD is related to early atherosclerosis consisting of smaller and more stable plaques that are associated with less active inflammation, resulting in lower levels of IL-6. (84)

### 4.3. Inflammatory Markers in Stable vs. Unstable Angina and ACS

Some of the studies compared serum IL-6, CRP and TNF-alpha levels between stable angina and unstable angina. A study done by Heinisch RH et al. (29) indicated that baseline levels of CRP, IL-6, and TNF were elevated in patients with acute coronary syndrome (ACS) when compared to those with stable angina (SA) or control subjects. In a study done by Doustkami H et al. (30) it was found that cytokine interleukin-6 levels were elevated in the acute myocardial infarction group than stable angina pectoris group and non-CAD category. Also, Ling Y et al. (31) revealed that the ACS group exhibited elevated levels of IL-6 and hs-CRP in contrast to the SAP group. Unlimited death rates common diet Hence, the findings of these studies exhibited the importance of TNF-alpha, IL-6 and CRP in the pathophysiology of unstable angina and acute coronary syndrome. It has been demonstrated that CRP, TNF-α and interleukin-6 have a strong association with the likelihood of cardiac events and is a significant predictive indicator of inflammatory status.

### 4.4. Inflammatory Markers and Myocardial Infarction

Anderson DR et al. (39) compared serum concentrations of IL-6 between AMI, CAD, & healthy control subjects. They found that serum levels of inteleukin-6 were more raised in group with AMI than in CAD as well as control. Additionally, Doustkami H et al. (30) showed that IL-6 levels were significantly increased in patients with AMI compared with SAP and groups with healthy control. (IL-6 levels-AMI>SAP> healthy control). Maury CPJ et al. (62) found in their study that in individuals having AMI, TNF-alpha levels were significantly greater than those having prolonged chest pain but no myocardial infarction. Patients having MI and prolonged chest pain have higher TNF-alpha levels than healthy control subjects. The rise in myocardial injury and inflammation was associated with heightened TNF-α levels, suggesting that it could worsen heart damage and hinder recovery following an infarction. Blake GJ et al. (85) found that higher levels of CRP were observed in patients with acute myocardial infarction and unstable angina in comparison to those diagnosed with stable angina. Also, Tang J et al. (38) showed ACS group had a significantly greater hs-CRP than SAP and the control group (p-value<0.01).

### 4.5. Inflammatory Markers and CAD Severity

Less number of studies showed a link between IL-6, TNF-alpha & CRP with the extent of coronary artery disease. Fifteen studies mentioned in **Table 9** showed that there is a relationship between the levels of TNF-alpha, CRP and IL-6 in serum and the severity of coronary artery disease. Bouzidi N et al. (26) concluded in their study that serum IL-6 levels were substantially raised in group with high Gensini scores against low Gensini scores. Gotsman I et al. (44) also stated patients having more coronary vessel stenosis (> 70% stenosis) also have elevated tertiles of IL-6 and TNFα has a substantial correlation with the number of vessels affected. Furthermore, it was found that patients with stable and unstable CHD showed independent associations between the intensity of coronary disorder (based on the Gensini scoring system) and IL-6. Also, TNF-alpha levels were found to be remarkably linked with CAD in patients with stable angina and acute coronary syndromes. They concluded that IL-6 circulating levels were associated with the Gensini severity score and the count of obstructed coronary vessels, indicating that IL-6 is an important predictor of the severity of CAD.

TNF-alpha was found to be an independent predictor of overall atherosclerotic burden, as evidenced by the count of arteries that were occluded by more than 50% or 70%. Additionally, Zhou et al. (35) noted a considerable association between higher Gensini scores and increased levels of interleukin-6 in postmenopausal women, reinforcing the connection between inflammatory cytokine IL-6 and the extent of CAD. Similarly, Gerin et al. found that interleukin-6 concentrations were noticeably raised in individuals diagnosed with coronary heart disease, showing a correlation with both Gensini and SYNTAX scores, which suggests a connection between plasma interleukin-6 levels and the degree of pathology of the disease. (86) Min X et al. (80) unveiled the association of serum TNF-alpha and the severity of CAD. They stated that TNF- alpha significantly increases increasing severity of ischemic events with p<0.005. Additionally, Li X. Y. et al. (79) revealed that the levels of TNF- alpha-like cytokine 1A (TL1A) is positively correlated with SYNTAX scores in patients having cardiac surgery. To summarize this, the increased inflammatory condition associated with more advanced coronary artery disease is indicated by the increase in IL-6 levels corresponding to higher Gensini scores and syntax scores.

This association underscores the significance of inflammation in the mechanisms of atherosclerosis and

indicates its viability as a target for therapeutic intervention in the management of coronary artery disease (CAD). As atherosclerosis progresses, the inflammatory load intensifies, leading to elevated levels of inflammatory cytokine interleukin-6 and tumor necrosis factor-alpha in circulation. As a result, individuals with more significant coronary artery narrowing, indicated by elevated Gensini scores, are likely to show higher IL-6 levels. Increased levels of IL-6 have been consistently linked to both the occurrence and intensity of CAD, with numerous studies showing that high IL-6 and TNF-alpha concentrations correlate with increased arterial stiffness, endothelial dysfunction, and atheromatous plaque formation. Similar to IL-6, elevated serum TNF-alpha is also linked to the pathogenesis of CAD and its severity. This reinforces the concept that IL-6 may serve as a useful biomarker for assessing the inflammatory burden in CAD. A relationship was observed between IL-6 levels and Gensini scores among individuals suffering from coronary heart disease.

Zhu M. et al. (66), Al-Tu'maa FJ et al. (81), Mahajan N et al. (68), Biasucci L. M et al. (58) showed a strong positive association between the severity of CAD and serum levels of hs-CRP. Additionally, Zebrack JS et al. (82) found that elevated C-reactive protein levels are observed in patients diagnosed with mild, moderate, and severe coronary artery disease when contrasted with those who have normal and are free of CAD. (CRP levels- mild CAD<moderate CAD<severe CAD). It is concluded that CRP indicates ongoing inflammation, which contributes to atherosclerosis and the risk of plaque rupture, it serves as a valuable indicator for predicting CAD progression and potential cardiac events. Considering that elevated CRP levels reflect an enhanced inflammatory condition associated with a greater risk, their application in assessing cardiovascular risk and targeting inflammation therapeutically is warranted. Therefore, CRP may serve as a predictor of the progression of CAD or cardiac events as well as a prognostic marker for CAD. (87) Therefore, CRP may serve as a predictor of the progression of CAD or cardiac events. (87) CRP, an acute-phase protein, is produced in reaction to inflammatory cytokines, including IL-6, so, Atherosclerosis is marked by persistent inflammation in the blood vessels, and both systemic and vascular inflammation are indicated by elevated CRP levels. It is concluded that CRP indicates ongoing inflammation, which contributes to atherosclerosis and the risk of plaque rupture, it serves as a valuable indicator for predicting CAD progression and potential cardiac events. Considering that elevated CRP levels reflect an enhanced inflammatory condition associated with a greater risk, their application in assessing cardiovascular risk and targeting inflammation therapeutically is warranted.

Recent clinical trials, including the CANTOS trial, have yielded strong evidence that directly addressing inflammation particularly the IL-1β/ IL-6/CRP pathway can markedly decrease cardiovascular events irrespective of lipid reduction. These results highlight the clinical significance of IL-6 and CRP not only as biomarkers but also as potential therapeutic targets. Incorporating these findings into clinical practice may transform the management of coronary artery disease from a solely risk-factor oriented model to a more inflammatory focussed strategy, thereby facilitating personalized therapies that integrates anti-inflammatory agent with conventional treatment.

## 5. CONCLUSIONS

Elevated levels of inflammatory markers TNFα and IL-6 have been connected to the severity of coronary artery disease in individuals presenting with both stable and unstable coronary conditions. This correlation might reflect a chronic inflammatory load and could act as a marker indicating a heightened risk for serious coronary disease. These provisional observations suggest that the baseline concentration of CRP may serve as a more effective marker for inflammation compared to cytokines in individuals with CAD. IL-6 serves as an effective biomarker indicating the extent of coronary stenosis and significantly contributes to advancement of atherosclerosis. These inflammatory markers can serve as predictors of the progression of CAD as well as prognostic markers. IL-6 has been identified as both a reliable biomarker and a potential therapeutic target. Subsequent research should prioritize interventional studies and mechanistic trials to clarify causality and examine IL-6 modulation as a strategy for lowering cardiovascular risk.

## 6. LIMITATIONS

The systematic review encompassed a limited selection of articles, and it was possible to include only a few prospective and follow-up studies in the analysis.

There are many inflammatory markers involved in the mechanism of pathogenesis of CAD but only few markers were considered for review in this study.

The majority of the research incorporated in our study was carried out at a single institution. Therefore, it is essential to further assess high-quality prospective multi-centre studies.

Differences in study design, populations, interventions, and outcomes might result in heterogeneity, complicating data synthesis and limiting results comparability.

## 7. FUTURE IMPLICATIONS

These biomarkers contributed significantly in risk assessment of CAD which helps in guiding the extent of preventive strategies. This can lead to the addition of supportive tools for better target treatment and to make more precise interventions. As there are a smaller number of studies linking concentration of inflammatory biomarkers IL-6, TNF-alpha, and CRP with the extent of CAD, it can be considered for future research topics.

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### Conflict of interest

The authors do not have any conflict of interest.

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### Ethical statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

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