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The Role of High Sensitivity C-Reactive Protein as an Inflammation Predictor in Cardiovascular Diseases

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ABSTRACT

Inflammation can be measured by analyzing the levels of inflammatory markers, such as High Sensitivity C-reactive Protein (hs-CRP). This protein plays a crucial role as a strong independent predictor indicating the risk of cardiovascular. The hs-CRP can measure the levels of C-reactive protein with high sensitivity, making it a highly responsive marker to acute-phase inflammation. The presence of hs-CRP serves as an inflammation indicator that can predict the potential occurrence of heart attacks, strokes, peripheral artery diseases, and sudden death due to Acute Coronary Syndrome (ACS). Produced by the liver in response to inflammation, hs-CRP is nonspecific and can elevate various types of inflammation, including infections and chronic inflammatory conditions in cardiovascular. This study is a literature review using secondary data from related research. The hs-CRP has a very high sensitivity and specificity level compared to CRP as an inflammation marker. Therefore, hs-CRP serves not only as a diagnostic tool but also as a strong predictor of inflammation, capable of predicting cardiovascular risk.

1. Introduction

As per the findings of the World Health Organization (WHO) in 2023, cardiovascular disease (CVD) stands out as a primary contributor to worldwide mortality rates. This disease results in approximately 17.9 million deaths each year, accounting for about 44% of total global deaths.¹ Cardiovascular disease, often referred to as heart disease, encompasses a range of conditions impacting the heart and blood vessels. Cardiovascular disease comprises four entities: Coronary artery disease (CAD) is a condition marked by the narrowing or blockage of blood vessels that play a crucial role in supplying blood to the heart, specifically the coronary arteries, leading to angina (chest pain) or myocardial infarction

(heart attack); Peripheral artery disease (PAD) refers to the narrowing or obstruction of arteries beyond the heart and brain, especially in the extremities (such as the legs); Cerebrovascular disease, a term referring to various conditions or disorders affecting the blood vessels that carry blood to the brain, leading to strokes; and atherosclerosis of the aorta, a disease resulting from the accumulation of fatty plaques, cholesterol, and other substances on the arterial walls. The causes of cardiovascular disease can vary, including genetic factors, unhealthy lifestyle choices (such as smoking, consuming unhealthy foods, and lack of exercise), high blood pressure, diabetes, and other risk factors.²

Cardiovascular risk refers to diseases involving the heart and blood vessels, one of which, if it occurs, can lead to inflammation. Inflammation in the cardiovascular system involves the body's response to damage or irritation to blood vessel tissues, including arteries, veins, and the heart. This process can occur in response to various risk factors that may damage the integrity of blood vessels. It can harm the inner layer of arteries, triggering an inflammatory response. White blood cells, especially monocytes, may migrate to the affected area to repair damage, but this interaction can also intensify inflammation. Other immune cells, such as monocytes and macrophages, are involved in the cardiovascular inflammatory response, playing a role in clearing the affected area and responding to foreign materials or dead cells. During the inflammation process, other inflammatory markers also play a role, such as C-reactive protein (CRP) and proinflammatory cytokines (e.g., interleukin-6), which may increase.³

C-reactive protein (CRP), found in the bloodstream, rises as a response to bodily inflammation and is categorized as an acute phase reactant (APR). The high-sensitivity C-reactive protein (hs-CRP) assay shows improved sensitivity compared to the standard CRP test, capable of detecting even minor increases in CRP levels within the typical range of values. Its increased sensitivity, the hs-CRP test can evaluate the likelihood of cardiovascular disease (CVD). The liver produces the hs-CRP in response to inflammation within the body's tissues.

The high-sensitivity C-reactive protein (hs-CRP) serves as a general indicator of inflammation without specificity, meaning its levels can increase in response to various types of inflammation, including infections or chronic inflammatory conditions. The hs-CRP, a crucial protein in the innate immune system, hs-CRP reacts to elevated concentrations of proinflammatory cytokines, particularly during the transcription stage of interleukin (IL)-6. The signaling of IL-6 can also be heightened by TNF and IL-1 β , as both cytokines stimulate an elevated transcription rate of hs-CRP. Proinflammatory cytokines released by visceral

adipose tissue during the inflammation process contribute to the rise in serum hs-CRP levels by amplifying signals. Elevated serum leptin levels and reduced adiponectin levels commonly associated with obesity and insulin resistance are linked to disruptions in adipokine levels, leading to increased hs-CRP synthesis in the liver. Similarly, hyperleptinemia is also correlated with heightened hs-CRP production in vascular endothelial cells. People with high levels of hs-CRP have a higher risk of developing cardiovascular. Approximately half of all individuals who experience a heart attack have high CRP, whereas high CRP is much less common in those without heart disease. Measurement of hs-CRP levels can provide crucial information in the field of medical diagnostics as it can serve as an inflammation predictor and indicate ongoing inflammation in the body, especially related to cardiovascular diseases and other inflammatory conditions. One of the advantages of measuring hs-CRP is its ability to measure CRP levels at very low concentrations with high sensitivity, making it an indicator of cardiovascular disease risk and assessing an individual's risk of heart attack or stroke.⁴

Numerous inflammatory biomarkers contribute to cardiovascular diseases, with hs-CRP standing out as a pivotal predictor of inflammation. Carrero and colleagues' investigation underscores the independent and notably influential role of hs-CRP as a risk factor in the onset of ischemic cardiovascular diseases.⁵ Additionally, Gholoobi et al.'s research reinforces the significance of hs-CRP as a crucial inflammatory indicator in non-ST-segment elevation myocardial infarction, alongside its association with cardiovascular diseases.⁶ This study underscores the need for additional exploration into hs-CRP's role in cardiovascular disease. Understanding that elevated hs-CRP levels may indicate inflammation and pose a heightened risk of cardiovascular conditions such as atherosclerosis, coronary heart disease, and stroke, measuring hs-CRP can aid in predicting an individual's cardiovascular disease risk.

2. Methods

This article was written initially by secondary data from searching the recent publications in PubMed NCBI database, Portal Garuda, and Google Scholar with the keywords “high sensitivity C-reactive protein, “inflammatory predictor, and “cardiovascular”. The references utilized were limited to the years 2015 through 2023, and sourced from a pool of 32 articles. The writing of this article started from January to May 2024. The criteria for excluding sources during secondary data collection encompass those that do not align with the inclusion criteria, and there are several sources for which full-text access is unavailable.

Inflammation pathophysiology in the cardiovascular system

The pathophysiology of inflammation entails an intricate sequence of events within the cardiovascular system, involving the heart, blood vessels, and blood itself. When acute coronary syndrome (ACS) occurs during an ongoing cardiovascular disease, there will be inflammation, either local or systemic, involving the activation of the complement system that results in the release of C3a and C5a, which are anaphylatoxins that stimulate the inflammatory response, including the migration and activation of immune cells such as leukocytes.⁷

Additionally, there is activation of the immune system, playing a role in the inflammatory response, namely the early immune system known as the innate immune system, triggering early inflammation in response to stimuli. This system involves cells and early defense mechanisms such as neutrophils, macrophages, dendritic cells, and NK cells. Conversely, the adaptive immune system is also involved in the inflammatory reaction, encompassing T cells and B cells capable of recognizing and responding to inflammation with greater specificity. In both local and systemic inflammation, there will be the release of several inflammatory cytokines, including cytokines (anti-inflammatory and pro-inflammatory), and other inflammatory markers such as an increase in hs-CRP.⁸ In cardiovascular diseases, one example

of an inflammatory pathway involved in atherosclerosis is the activation of T lymphocyte cells and early defense mechanism cells to recognize and respond to inflammation more accurately, contributing to the regulation of inflammation. T lymphocyte cells include T helper cells (Th1 cells play a role in helping recognize peptides on APC, activating T cells, and producing cytokine molecules) and regulatory T cells (function in regulating the immune response when it is no longer required). These cytokines will produce several interleukins (cytokines produced by one leukocyte and act on other leukocytes). Focusing on IL-6 produced by endometrial stroma and epithelial cells due to estrogen induction by IL-1 β , it will stimulate the liver to produce specific proteins, including acute-phase proteins such as hs-CRP, so that acute-phase inflammatory markers in the cardiovascular system can be observed by monitoring hs-CRP levels (Figure 1).⁹

Biomarker for cardiovascular inflammation

The measurement of cardiovascular inflammatory biomarkers can provide additional information in evaluating an individual's cardiovascular risk. The presence or high concentration of these biomarkers can indicate inflammation at the vascular level. During both local and systemic inflammation, the release of inflammatory mediators, such as cytokines, occurs. Cytokines refer to small-sized proteins (<40 kDa) secreted by nearly every cell in the body to regulate and influence the immune response. When inflammation occurs, various pro-inflammatory and anti-inflammatory cytokines are released simultaneously as part of the immune response.¹⁰

Pro-inflammatory cytokines drive the immune response or reinforce the inflammatory response in the body. These cytokines stimulate the destruction and clearance of pathogens such as bacteria and viruses and promote tissue healing processes. Pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF- α , exemplify molecules that promote inflammation. Conversely, anti-inflammatory cytokines are those that counteract exaggerated

inflammatory reactions and mitigate unbridled immune responses. These cytokines are produced to help regulate and maintain the balance of inflammatory responses in the body to prevent excess damage to normal tissues. Thus, they support the healing process and reduce inflammatory symptoms such as pain and swelling. Instances of anti-inflammatory cytokines comprise IL-4, IL-6, IL-10, IL-13, and TGF- β . In IL-6, it is produced by endometrial

stroma and epithelial cells due to estrogen induction by IL-1 β , which then stimulates the liver to produce specific proteins, including acute-phase proteins like hs-CRP. Therefore, the acute-phase inflammatory marker in cardiovascular health can also be observed by monitoring hs-CRP levels.¹¹ However, there are several cardiovascular inflammatory biomarkers most commonly used as predictors of inflammation, including hs-CRP, IL-6, TNF- α , and procalcitonin.

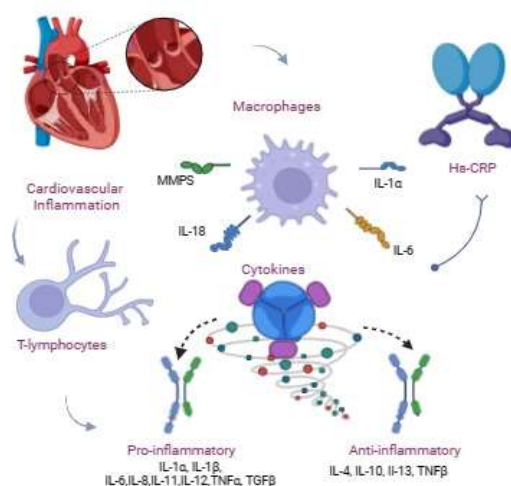


Figure 1. Inflammatory pathways involved in cardiovascular inflammation (modified from Nguyen et al).⁹ In cardiovascular diseases, one example of an inflammatory pathway involved in atherosclerosis is the activation of T lymphocyte cells and early defense mechanism cells to recognize and respond to inflammation more accurately, contributing to the regulation of inflammation. These cytokines as marker inflammation will produce several interleukins (cytokines produced by one leukocyte and act on other leukocytes), such as pro-inflammatory and anti-inflammatory cytokines. Other immune cells, such as monocytes and macrophages, are involved in the cardiovascular inflammatory response, playing a role in clearing the affected area and responding to foreign materials or dead cells. During the inflammation process, other inflammatory markers also play a role, focusing on IL-6 produced by endometrial stroma and epithelial cells due to estrogen induction by IL-1 β , it will stimulate the liver to produce specific proteins, including acute-phase proteins such as hs-CRP, so that acute-phase inflammatory markers in the cardiovascular system can be observed by monitoring hs-CRP levels. (Figure created with BioRender.com)

Differences between hs-CRP and CRP

C-reactive protein (CRP) is a polypeptide molecule from the pentraxin group, which is an acute-phase protein. CRP production occurs in the liver and is controlled by cytokines, primarily interleukin-6.¹² A notable rise in serum CRP levels is observed 6-8 hours following the initiation of the inflammatory process, which stimulates its production and subsequent release into the bloodstream. The peak concentrations are typically reached within 24-48 hours, with a half-life of approximately 19 hours. The concentration of CRP in circulation is primarily determined by the rate of its synthesis.¹³ Although it is an acute-phase

protein, CRP levels also change during chronic inflammatory processes.¹⁴ CRP is involved in the innate immune response to an infection. CRP also attaches to C1q and can thereby activate the complement system or function as an opsonin through its interaction with C1q receptors on phagocytes.¹⁵ Meanwhile, HS-CRP is a more sensitive and specific form of CRP used to measure inflammation in the body. Hs-CRP can measure CRP protein levels with very high sensitivity, thus being able to detect very low levels of CRP in the blood. The following table presents the significant differences between hs-CRP and CRP.

Table 1. Significant differences between hs-CRP and CRP:¹⁶

Criteria	Hs-CRP	CRP
Measurement	Usually quantified in milligrams per liter (mg/L).	Usually quantified in milligrams per liter (mg/L).
Sensitivity	More sensitive in detecting changes in CRP levels in the body.	Less sensitive than hs-CRP in detecting small changes in CRP levels.
Purpose of measurement	Used to detect mild chronic inflammation or the risk of cardiovascular disease.	Commonly used to measure acute inflammation in the body.
Normal levels	<1 mg/L (Low Risk) 1-3 mg/L (Moderate Risk) >3 mg/L (High Risk)	<10 mg/L (Normal)
Triggering factors	Hs-CRP can increase in response to chronic inflammation in the body, which may be related to cardiovascular disease and other risk factors.	CRP can increase during bacterial infection or acute inflammation.
Clinical use	Employed for evaluating the risk of cardiovascular disease, particularly in individuals with cardiovascular risk factors.	Used in the diagnosis of infection and monitoring acute inflammation.

Structure and biological activities of Hs-CRP

Apart from its involvement in inflammation processes, hs-CRP plays a vital role in the body's immune response to infection by activating the complement pathway, generating cytokines like Interleukin-6 and TNF- α , promoting apoptosis, releasing nitric oxide (NO), and facilitating

phagocytosis. Two CRP isoforms, Native C-reactive protein (nCRP) and Monomer C-reactive protein (mCRP), differ in structure, molecular weight, antigenic characteristics, binding affinities with different types of Fc gamma receptors, and thus exhibit distinct biological functions.¹⁷

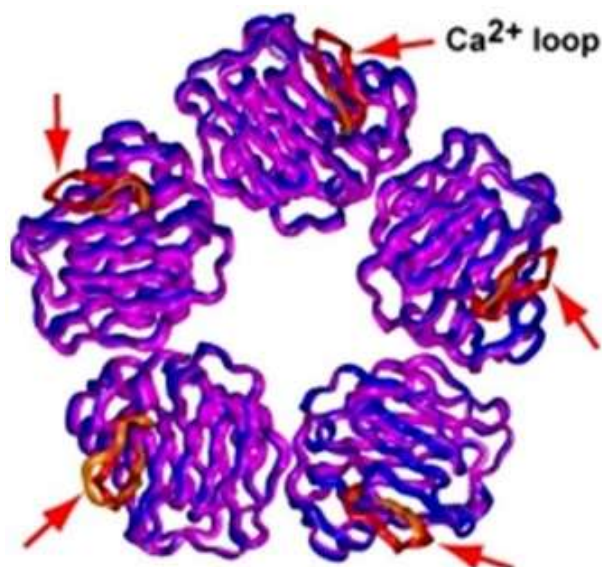


Figure 2. The structure of pentameric native C-reactive protein (nCRP).¹⁷

Native C-reactive protein (nCRP) is the form of CRP found in the blood as a pentamer (consisting of five identical protein units). NCRP is the original form of CRP without additional structural changes. In nCRP, CRP acts as a major component in the acute inflammatory response and dissociates into five monomer C-reactive protein (mCRP) molecules irreversibly at the site of inflammation. nCRP binds to bacteria, pathogens, and infected cells, facilitating phagocytosis by white blood cells. nCRP can also bind to cellular components such as phospholipid membranes on injured cells. Additionally, nCRP can activate the classical complement pathway, promote apoptosis, induce phagocytosis, suppress platelet adhesion to neutrophils, and exhibit stronger anti-inflammatory properties compared to mCRP.¹⁷

On the contrary, monomer C-reactive protein (mCRP) is a form of CRP that has undergone structural changes, becoming a monomeric form consisting of a single protein unit. This change can occur in certain pathological conditions, such as chronic inflammation. mCRP has different biological activities compared to nCRP. MCRP has been associated with stronger pro-inflammatory effects than nCRP. It may play a role in atherosclerosis, cardiovascular diseases, and other chronic inflammations. Conversely, mCRP can inhibit apoptosis by enhancing chemotaxis and recruiting circulating leukocytes to inflamed areas.¹⁷ The main differences between them lie in their structure and biological activities. NCRP is the original pentameric form of CRP involved in acute inflammatory responses and the body's defense against infections. In contrast, mCRP is a monomeric form formed as a result of structural modifications in certain pathological conditions and may have stronger pro-inflammatory effects.

Metabolism of Hs-CRP

Hs-CRP functions as an acute-phase protein and is a pivotal component of innate immunity synthesized by the liver in response to heightened levels of proinflammatory cytokines, particularly during the interleukin (IL)-6 transcription phase. The signaling of

IL-6 may be further intensified by Tumor Necrosis Factor (TNF) and IL-1 β , which enhance the transcription rate of hs-CRP. Visceral adipose tissue also releases proinflammatory cytokines during inflammation, thereby contributing to increased serum hs-CRP levels by amplifying signaling pathways. Elevated serum levels of leptin and reduced adiponectin levels are commonly associated with obesity and insulin resistance. These disruptions in adipokines are linked to heightened hs-CRP production from the liver, with hyperleptinemia additionally correlating with increased hs-CRP production in vascular endothelial cells.¹⁸

In this context, adipose tissue, functioning as an endocrine tissue, plays a significant role in immune modulation. Adipose tissue releases inflammatory cytokines with pleiotropic effects, such as IL-6, IL-1 β , and resistin, indicating that chronic inflammation may be a fundamental component of obesity. As lipid storage increases within adipocytes, hypertrophy, hyperplasia, and adipocyte dysfunction occur, which are central phenomena in obesity development. These structural and metabolic alterations make adipocytes susceptible to hypoxic damage and more likely to rupture, leading to the secretion of proinflammatory adipokines from adipose tissue. Studies have indicated that hs-CRP is probably expressed in adipocytes in response to various proinflammatory mediators. This expression of hs-CRP signifies the relationship between chronic inflammation and obesity.¹⁹

The synthesis of CRP or hs-CRP outside the liver occurs because CRP messenger ribonucleic acid (mRNA) has been identified in lymphocytes, lungs, adipose tissue, epithelial tubular cells in the kidney cortex, smooth muscle cells, and macrophages within atherosclerotic plaques. This local level of hs-CRP also aids in predicting the risk of developing cardiovascular disease, including evidence of hs-CRP production in smooth muscle cells within coronary arteries in response to inflammatory cytokines. Endothelial cell activation resulting from local hs-CRP plays a critical role in the development of various non-communicable

diseases. When hs-CRP levels rise, there is an increase in erythrocyte sedimentation rate (ESR). Hs-CRP serves as a direct indicator of inflammation, whereas ESR is an indirect indicator that can be influenced by conditions or factors not related to acute or chronic inflammation, such as advanced age, female sex, anemia, end-stage kidney disease, and obesity.²¹ Elevated hs-CRP levels are valuable for detecting different degrees of low-grade systemic inflammation in the body. With advancements in hs-CRP testing methods, levels can be accurately assessed from both frozen and fresh plasma samples. Hs-CRP has the potential to serve as a predictor and biological marker for assessing the risk of vascular and cardiovascular diseases.²²

Hs-CRP as an inflammation predictor

The assessment of inflammation can be conducted by analyzing the levels of the inflammatory marker hs-CRP. This particular protein serves as a vital independent predictor, signaling the likelihood of cardiovascular diseases. Hs-CRP can measure C-reactive protein levels very sensitively, making it a highly responsive marker to acute inflammation. The

presence of hs-CRP serves as an inflammation indicator that can predict the potential occurrence of heart attacks, strokes, peripheral artery diseases, and sudden death due to acute coronary syndrome (ACS).³ While numerous biomarkers associated with inflammation contribute to cardiovascular diseases, hs-CRP stands out as a crucial predictor of inflammation. Carrero et al.'s study emphasizes that hs-CRP, functioning independently, serves as a significant and remarkable risk element for the onset of ischemic CVD.⁵ The likelihood of cardiovascular disease development across different levels of serum hs-CRP. The normal range for hs-CRP is typically below 1.0 mg/L. Elevated levels exceeding this threshold are linked to heightened susceptibility to cardiovascular disease. Levels surpassing 2.0 mg/L are indicative of an unfavorable prognosis, heightened complication rates, and elevated mortality. To anticipate the potential onset of cardiovascular diseases, it is recommended to incorporate hs-CRP with other atherogenic markers, including LDL-C, heightened total cholesterol, reduced levels of high-density lipoprotein (HDL), elevated triglycerides, and higher blood glucose levels (Table 2).

Table 2. The standard range of hs-CRP:¹⁶

No	Cardiovascular risk level	Hs-CRP level
1	Low	<1 mg/L
2	Moderate	1-2 mg/L
3	High	>2 mg/L

Elevated hs-CRP levels elevate the vulnerability to cardiovascular diseases, as they possess the capacity to enlarge the zone of ischemic necrosis by activating the complement system, thereby exacerbating the severity of diseases.²³ In ischemic conditions, arterial damage occurs as a result of white blood cells and various inflammatory mechanisms present within the vessel wall, positioning hs-CRP as a broad indicator for both acute infection and inflammation, as well as a marker for the risk of cardiovascular diseases, albeit

not being an exceedingly specific prognostic indicator. Potential mechanisms elucidating the involvement of hs-CRP in the pathogenesis of CVD involve multiple stages within physiological processes such as endothelial and macrophage cell activation, inhibition of neutrophil apoptosis and endothelial NO synthase expression, complement cascade stimulation, increased PAI-1 activity and LDL absorption, lipid accumulation, and blood clotting, as well as increased pro-inflammatory cytokine expression (Figure 3).²⁴

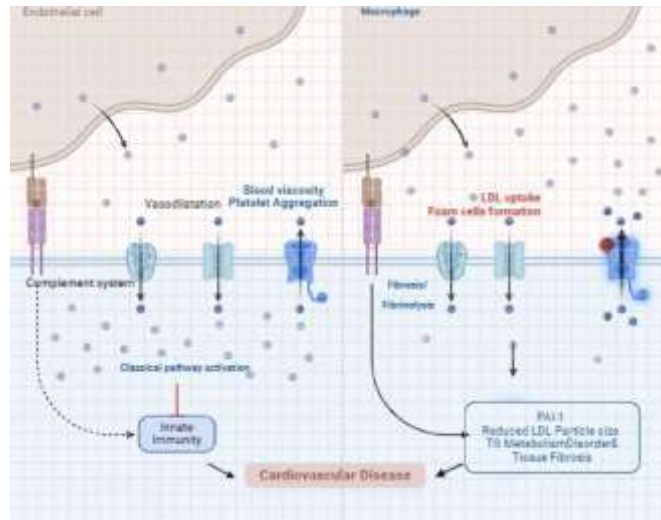


Figure 3. Mechanisms underlying the role of hs-CRP in cardiovascular (modified from Luan et al).²⁴ hs-CRP inhibits the expression of endothelial cells, a pivotal signaling molecule closely linked to the regulation of vasodilation, blood rheology, platelet aggregation, and various physiological and pathological processes. Furthermore, hs-CRP triggers the activation of macrophages, resulting in the release of tissue factor, an intensely procoagulant substance that can result in disseminated intravascular coagulation and the formation of blood clots during inflammatory conditions. Hs-CRP has the potential to induce tissue fibrosis in cardiovascular diseases by activating the Transforming Growth Factor- β (TGF- β)/Smad signaling pathway through mechanisms that are both TGF- β -dependent and TGF- β -independent. Additionally, hs-CRP enhances the absorption of LDL into macrophages, augments the macrophages' ability to bind to phosphocholine on oxidized LDL, and triggers the classical complement pathway, directly activating and enhancing the innate immunity of the complement system. (Figure created with BioRender.com)

While the mechanisms of chronic and sustained inflammation remain incompletely understood, certain vascular mediators such as IL-1, IL-6, and TNF- α are thought to exert a substantial influence on the chronic inflammatory process. Consequently, due to

its heightened sensitivity to vascular inflammation, hs-CRP is extensively utilized as an ideal biomarker for predicting overall CVD.²⁵ Here are some studies related to hs-CRP and cardiovascular (Table 3).

Table 3. Studies related to hs-CRP and cardiovascular.

No	References	Type or study	Findings
1	Gholoobi et al (2021) ⁶	Randomized clinical trial, placebo control, double-blind	High-sensitivity C-reactive protein (hs-CRP) is a critical inflammatory marker in non-ST-segment elevation myocardial infarction and is closely linked to cardiovascular diseases.
2	Carrero et al (2019) ⁵	Randomized control trial	The majority of patients experiencing myocardial infarction typically show elevated hs-CRP levels, with hs-CRP levels ≥ 2 mg/L correlating with an increased risk of adverse cardiovascular events. The rise in hs-CRP serves as a prognostic indicator with validity as a biomarker in real-world healthcare settings, extending beyond evidence from clinical trials.
3	Li et al (2017) ²⁶	Meta-analysis	Subjects in research with the highest levels of hs-CRP experience a 2.03-fold increase in the risk of cardiovascular death. hs-CRP can effectively stratify the risk of both all-cause mortality and cardiovascular death in the general population.
4.	Wang et al (2017) ²⁷	Cross-sectional	The cumulative exposure to hs-CRP is linked to a gradual, dose-dependent elevation in the risk of cardiovascular disease (CVD) and myocardial infarction. Cumulative measurement of hs-CRP is superior to single measurements.

Inflammatory cytokines such as IL-1 β , IL-6, and TNF- α stimulate hepatocytes to produce acute-phase proteins and induce bone marrow endothelial cells to release neutrophils. Acute-phase proteins serve as enhancers for pathogen clearance, facilitated by increased neutrophil recruitment from the bone marrow. Additionally, IL-1 β , IL-6, and TNF- α act as endogenous pyrogens, elevating body temperature, which is thought to facilitate the clearance of infections. These cytokines primarily impact the hypothalamus, affecting temperature regulation, and muscle and fat cells, influencing energy mobilization to raise body temperature. Increased temperatures are linked to decreased efficiency of bacterial and viral replication, while also enhancing the effectiveness of adaptive immune responses.²⁸

One of the pivotal impacts of these cytokines is observed in the liver, where they instigate a reaction termed the acute-phase response. Acting on hepatocytes, these cytokines prompt alterations in the array of proteins synthesized and released into the bloodstream. During the acute-phase response, certain protein levels in the blood decrease while others undergo significant elevation. These proteins induced by TNF- α , IL-1 β , and IL-6 are termed acute-phase proteins. Among these, some hold particular significance as they emulate the functions of antibodies. Unlike antibodies, however, they exhibit broad specificity towards molecular pathogen patterns and rely solely on cytokine presence for their production.²³

Because of its high sensitivity in detecting CRP protein levels, Hs-CRP enables the measurement of extremely low CRP levels in the bloodstream. After inflammation begins, serum CRP levels significantly rise within 6-8 hours, initiating its synthesis and subsequent release into the circulation. Peak levels are typically reached between 24-48 hours, given its half-life of approximately 19 hours. The concentration of CRP in circulation is primarily dictated by the rate of synthesis.²⁹ Despite being an acute-phase protein, CRP levels undergo changes during chronic inflammatory processes.³⁰ CRP plays a role in the

innate immune response to infection and also binds to C1q, potentially activating complement pathways or functioning as an opsonin through interaction with C1q receptors on phagocytes.¹⁵

Research findings on hs-CRP as a predictor of cardiovascular inflammation

The findings of studies on hs-CRP have established it as a reliable predictor of cardiovascular inflammation. Elevated levels of hs-CRP have been consistently associated with an increased risk of cardiovascular events, including heart attacks and strokes. The research highlights several key points:²²

- 1) Correlation with cardiovascular events: Elevated hs-CRP levels are strongly correlated with the occurrence of cardiovascular events. Individuals with elevated hs-CRP levels face a substantially increased risk of developing heart disease compared to those with lower levels.
- 2) Predictive value: hs-CRP serves as an independent predictor of cardiovascular risk. It provides additional prognostic information beyond traditional risk factors such as cholesterol levels, blood pressure, and smoking status.
- 3) Risk stratification: hs-CRP levels help in stratifying patients into different risk categories. This stratification aids clinicians in identifying individuals who may benefit from more aggressive preventive measures or therapeutic interventions.
- 4) Inflammation marker: as a marker of systemic inflammation, hs-CRP reflects the underlying inflammatory processes that contribute to atherosclerosis and other cardiovascular conditions. Its levels can indicate the severity of inflammation and the potential for plaque rupture in arteries.
- 5) Impact of lifestyle and therapies: Lifestyle interventions such as exercise, weight loss, and smoking cessation, as well as pharmacological treatments like statins, have been shown to reduce hs-CRP levels. This reduction is often accompanied by a decreased risk of cardiovascular events,

underscoring the importance of managing inflammation in cardiovascular disease prevention.

Interventions to lower hs-CRP levels

a) Lifestyle interventions

Exercise has been shown to have a positive impact on serum hs-CRP levels by reducing its concentration. Several studies indicate that individuals with elevated hs-CRP levels or dyslipidemia prior to initiating exercise experience greater reductions in hs-CRP. Previous intervention studies have demonstrated that smoking cessation, regular exercise, and weight loss can decrease hs-CRP levels among participants at high risk for developing non-communicable diseases such as diabetes mellitus, cerebrovascular events, and ischemic cardiovascular disease.³¹

b) Statin therapy

Lipid-lowering medications like statins (HMG-CoA reductase inhibitors) can effectively treat elevated hs-CRP levels. Numerous studies have confirmed that statins can lower hs-CRP levels due to their anti-inflammatory and lipid-lowering properties. Statins are the preferred treatment for managing hypercholesterolemia in patients with high hs-CRP levels.³²

3. Results and Discussion

These concepts are subsequently comprehended and enhanced to enable precise delineation and practical implementation. The purpose of this research is to examine the function of hs-CRP as an inflammation predictor in cardiovascular diseases, with the aim of serving as a reference for assessing the healing progress of patient. The potential mechanisms underlying the association between hs-CRP and cardiovascular risk include several interconnected biological processes. Hs-CRP, as a robust marker of inflammation, reflects chronic inflammation in the body that can damage blood vessel endothelium, influence endothelial activation, and enhance thrombogenic responses. Continuous endothelial activation by hs-CRP can trigger atherosclerosis and plaque deposition within blood vessels, while

increased thrombogenic response elevates the risk of potentially fatal clot formation. Furthermore, hs-CRP also contributes to endothelial dysfunction and promotes inflammatory processes through interactions with receptors on inflammatory cells and increased production of pro-inflammatory cytokines. A thorough understanding of these mechanisms provides a crucial foundation for exploring more effective intervention strategies in managing cardiovascular risk, focusing on controlling chronic inflammation and protecting endothelial function.

4. Conclusion

The increase in serum hs-CRP levels is observed in various instances, serving as a marker for both acute and chronic inflammation. Previous experimental and clinical studies consistently highlight a strong correlation between elevated serum hs-CRP levels and the risk of cardiovascular diseases. Hs-CRP functions as an indicator of chronic inflammatory states and holds promise as an inflammation predictor, offering valuable insights into cardiovascular diseases. A comprehensive understanding of hs-CRP synthesis throughout the inflammatory process, its activation, intricate mechanisms, and its role in inflammation during acute coronary syndrome (ACS) within cardiovascular diseases is essential.

Therefore, the assessment of hs-CRP is a valuable diagnostic tool as it can assist in monitoring cardiovascular risk, planning treatment strategies, and providing more targeted care. However, it is important to understand that hs-CRP is just one of many predictive factors that must be considered in the evaluation of cardiovascular risk, and its results should be interpreted in a broader clinical context. Therefore, for future purposes, further studies on other inflammatory markers that play a role as predictors of cardiovascular inflammation are needed.

Future research could focus on elucidating the specific pathways through which hs-CRP contributes to cardiovascular risk, including its interactions with inflammatory cytokines, endothelial dysfunction, and lipid metabolism. Investigating how hs-CRP influences

the progression of cardiovascular risk, atherosclerosis, plaque instability, and thrombosis formation could provide deeper insights into its role as a predictor of cardiovascular events. Additionally, exploring genetic variations and epigenetic modifications that impact hs-CRP levels and their cardiovascular implications may uncover novel therapeutic targets for mitigating cardiovascular risk associated with elevated hs-CRP.

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