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REVIEW

Serum albumin concentration and the risk of cardiovascular disease and acute coronary syndrome — a narrative review

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ABSTRACT

Cardiovascular diseases are the primary cause of global health decline. Conditions that cause inflammation and excessive oxidation are present in the early development of the majority of cardiovascular diseases, including coronary artery disease and heart failure. Among the many physiological functions of albumin, its antioxidant, anti-inflammatory, anticoagulant, and anti-aggregant properties are the most important. Low serum albumin levels are associated with the occurence of various cardiovascular diseases such as coronary artery disease, stroke, heart failure, and atrial fibrillation. Several recent meta-analyses support the idea that hypoalbuminemia may act as a modifiable risk factor that increases oxidative stress and inflammation, contributing to the development and progression of cardiovascular diseases. However, it is unclear whether correcting hypoalbuminemia can improve outcomes for patients with cardiovascular diseases and reduce mortality rates. In this regard, further research is crucial.

Keywords: acute coronary syndrome, serum albumin, prognosis, inflammation

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INTRODUCTION

Cardiovascular disease is the primary cause of death in industrialized nations.[1,2] Strong evidence from longitudinal research suggests that lower serum albumin levels are associated with an increased risk of heart failure and other cardiovascular diseases.[3] Albumin, a protein that constitutes over half of the body's serum proteins, has a crucial role in various physiological functions. Multiple clinical studies have shown that hypoalbuminemia is a strong predictor in a wide range of diseases.[4,5]

Low serum albumin levels are associated with the development of cardiovascular conditions such as coronary heart disease, stroke, heart failure, and atrial fibrilla-

tion.[5] Moreover, hypoalbuminemia has become a highly significant predictor in these diseases, independent of other prognostic markers.[6] Its predictive value reflects both the severity of comorbidities and the likelihood of malnutrition-inflammation.[5,7] In cases of acute coronary syndrome, hypoalbuminemia has been associated with increased disease severity, long-term mortality, and progression toward heart failure.[8]

The studies included in this review were identified through a comprehensive search of PubMed, Medline, Scopus, Cochrane Library, Google Academics and Web of Science databases. To refine the selection of relevant articles, we used the following keywords: "hypopalbuminemia", "inflammation", "cardiovascular disease", "prognosis", "heart failure", "stroke", "albumin", "arrhythmias", and "atrial fibrillation".

After a thorough review of the literature, we identified 285 articles, of which 60 were removed due to duplication. A further 189 studies were excluded based on insufficient data, variations in interventions, outcomes, or an inadequate sample size. Of the 36 remaining studies, only 6 m*et al*l inclusion criteria and were included in the qualitative analysis.

PHYSIOLOGICAL AND BIOCHEMICAL PROPERTIES OF SERUM ALBUMIN

Albumin is synthesized in the liver in approximately 17 days.[5] There are continual schisms between intravascular and interstitial compartments, with more than one-third of the total albumin found in the intravascular compartment.[5,9] Several factors promote albumin production, including reduced colloid pressure osmosis, insulin, and amino acid intake. Conversely, high colloid osmotic pressure, starvation, inflammation, diabetes, liver disease, and sepsis can reduce its synthesis.[5] The normal serum albumin level ranges from 3.5 to 5.0 g/dl, although the threshold for concerning levels may vary depending on the analytical method used.[5] Women typically have slightly lower levels than men, and these levels gradually decrease with age. Albumin has several important physiological roles, including particle and drug transport, anti-inflammatory, antioxidant, and antiplatelet activity, as well as regulating fluid exchange between intravascular and interstitial spaces.[5,10]

In addition to transporting a wide range of endogenous and exogenous substances, such as ions, bilirubin, vitamin B12, hormones, steroids, and drugs,[5] albumin also has anti-inflammatory properties. Although not fully understood, one key mechanism involves its ability to prevent monocytes from adhering to endothelial cells, thereby reducing inflammation and atherosclerosis.[10–12]

In an experimental rat model of endotoxemia, albumin reduced both the messenger RNA and protein expression of cardiac nitric oxide synthase II, which regulates nitric oxide production and myocardial inflammation.[10] Serum albumin is considered the most important antioxidant in the circulatory system.[11,12] At normal concentrations, albumin prevents the accumulation of histones in arterial plaques; however, a decrease in serum albumin levels reduces its ability to prevent plaque formation. Additionally, biological data indicate that serum albumin has a key role in anticoagulation.[5,13]

HYPOALBUMINEMIA IN ACUTE CORONARY SYNDROME

The prevalence of hypoalbuminemia in patients with acute coronary syndrome remains poorly defined, with reported rates varying across studies, being influenced by age, disease severity, and the acuity of the underlying condition.[5] The most common parameters associated with hypoalbuminemia in acute coronary syndrome include advanced age, anemia, inflammatory mediators, and low cholesterol.[5,14,15]

Hypoalbuminemia occurs in approximately 14% of patients with congenital cardiac disease and is independently linked to functional class, liver failure, and renal impairment.[5] In addition, both the Framingham Offspring Study and the Multiple Risk Factor Intervention Trial have identified a significant inverse relationship between serum albumin levels and the risk of coronary heart disease.[16]

A recent retrospective study by Polat *et al.* involving 403 patients with unstable angina pectoris or non-ST elevation myocardial infarction (NSTEMI) found that those with hypoalbuminemia were at a higher risk of long-term mortality than those without hypoalbuminemia. Based on these findings, the authors considered albumin to be a simple and easily measurable biomarker for predicting mortality risk in patients with NSTEMI.[17]

THE PREDICTIVE VALUE OF HYPOALBUMINEMIA IN CARDIOVASCULAR DISEASES

Hypoalbuminemia is a strong independent predictor for all cardiovascular diseases and their causes.[18,19] In a study by Chien *et al.*, patients with low albumin levels had significantly higher risk of all-cause mortality than those with normal albumin levels (10.2% vs. 0.5%; p <

0.001).[19] In a study involving 546 elderly patients admitted for acute non-ischemic heart failure, Ancion *et al.* found that a serum albumin level of ≤34 g/L was an independent predictor of hospital mortality.[20] Another study examining the altered nutritional status, inflammation, and systemic vulnerability of patients with myocardial infarction after percutaneous coronary revascularization revealed that patients with malnutrition had significantly higher serum urea levels and significantly lower total cholesterol and albumin levels than patients with normal nutritional status, calculated in accordance with the CONUT guidelines.[21,22]

The predictive value of hipoalbuminemiea has been well-established in patients with heart failure, and it has emerged as a time-independent predictor of worsening outcomes in both acute and chronic heart failure.[23,24] This suggests that hypoalbuminemia may play a role in the progression of these conditions. According to Starling's law, severe hypoalbuminemia is associated with pulmonary congestion, which can destabilize both latent and active heart failure. Albuminuric acid maintains the hydrostatic balance of the heart through its osmotic action.[25] Furthermore, because serum albumin has antioxidant properties, hypoalbuminemia may aggravate oxidative stress and accelerate the progression of heart failure.[26,27]

In the Atherosclerosis Risk in Communities (ARIC) study, which followed 14,506 individuals, a significant correlation was found between serum albumin levels and the incidence of ischemic cardiopathy in smokers, independent of other known risk factors.[5,28] This suggests an interdependent relationship between albumin levels and smoking. The median albumin level, adjusted for age and sex, was significantly lower in participants who experienced a cardiovascular event compared to those who did not ($p < 0.0001$).[28]

Another prospective study, which followed 2,986 participants over a period of 12 years, identified low albumin levels as a predictor of first stroke, alongside factors such as body mass index and inflammatory status.[29,30] In a prospective study by Arques *et al.*, involving 52 elderly patients with acute diastolic heart failure, hypoalbuminemia was found to be the strongest predictor of in-hospital mortality (odds ratio, 0.57; $p < 0.005$) after adjustments for age and type B natriuretic peptide levels.[31]

Serum albumin plays a major role in the prognosis of cardiovascular disease, influencing inflammation, malnutrition, and the severity of comorbidities. This raises the question of whether could be an unrecognized, potentially modifiable risk factor. Recent meta-analyses examining the role of low serum albumin levels in the onset of cardiovascular disease, heart failure, and acute coronary syndrome have provided compelling evidence in favor of this theory.[5] The potential impact of low serum albumin levels on the development and progression of cardiovascular diseases is likely related to the anti-inflammatory, antioxidant, anticoagulant, and antiaggregative properties of serum albumin, particularly in the case of coronary artery disease, heart failure, atrial fibrillation, stroke, and venous thromboembolism.[30,32–36] Additionally, there is evidence that hypoalbuminemia contributes to pulmonary edema and sodium retention, both of which are key factors in the progression of heart failure.[37]

In a study by González-Pacheco *et al.* involving 8,848 patients with acute coronary syndrome, mortality rates were highest in the group with the lowest serum albumin levels and lowest in the group with the highest levels, with a significant difference ($p < 0.0001$) observed across all groups. The main finding of the study was that a serum albumin level below 3.5 g/dl at admission was an independent predictor of new-onset heart failure and in-hospital mortality. The authors also concluded that, in this particular clinical situation, the inflammatory state may be a mechanism underlying hypoalbuminemia.[39]

Another study, involving 2,886 patients with congenital heart disease, showed that the prevalence of hypoalbuminemia was significantly higher in patients with congenital heart disease of high complexity (18.2%) compared to patients with mild disease (11.3 %) or uncomplicated disease (12.1 %; $p < 0.001$). In the univariable regression analysis, hypoalbuminemia was a strong predictor of the outcome (hazard ratio, 3.37; $p < 0.0001$) and also remained a significant predictor of decline in the multivariable regression analysis.[40]

In a study involving 8,750 patients with acute myocardial infarction, Plakht *et al.* found that serum albumin levels were an independent marker for all-cause mortality in hospitalized survivors.[14] In a study that analyzed 2,794 patients who underwent isolated coronary artery bypass grafting, Bhamidipati *et al.* found that the patients with the highest adjusted mortality rate had serum albumin levels of 2–3 g/dl ($p = 0.02$), the lowest body mass index ($p < 0.05$), lower LVEF, and higher intra-aortic balloon pump use ($p < 0.001$). In addition, an increase in albuminemia was associated with a lower rate of severe complications ($p = 0.001$) and a lower risk of mortality (adjusted odds ratio, 0.61; 95% CI 0.42–0.90). The study found that albumin is more closely linked to mortality and morbidity than the body mass index in patients undergoing coronary artery bypass grafting.[41]

ALBUMIN AND INFLAMMATION

Albumin is a major mediator of coronary ischemia-reperfusion injury and a significant inhibitor of plaque formation and aggregation. Fibrinogen, a plasma protein involved in inflammatory and thrombotic processes, can also serve as a marker for trombotic states[42] and predict cardiovascular events in the general population.[43] Additionally, a recent study has shown a correlation between elevated fibrinogen levels and the presence and severity of coronary heart disease.[44]

Albumin is not just a basal protein responsible for maintaining the oncotic pressure of plasma; it is also a transporter of various substances and is involved in both acute and chronic inflammatory processes. Hypoalbuminemia can result from malnutrition, malabsorption, increased renal loss, decreased hepatic function, acute or chronic inflammation processes, and increased plasma volume. Inflammatory processes have been linked to an increase in albumin catabolization.[45] In a recent study, Çetin *et al.* found that patients with slow coronary flow had lower albumin levels than those with normal coronary arteries.[46]

Total albumin reserves are 4–5 g/kg body weight, of which 40–45% are found in the intravascular space and the remaining 55–60% in the interstitial space.[47] Due to its relatively low molecular weight compared to other major intravascular proteins, such as immunoglobulins, albumin contributes to 75–80% of the body's colloid osmotic pressure. Another important function of albumin is its ability to bind to various ligands, including free fatty acids, calcium, steroid hormone analogues, bilirubin, thyroxine, and tryptophan.[47]

Given that albumin is a negative acute-phase protein, its serum concentration is influenced by both inflammation and nutritional status.[47] Inflammation alters the structure of lipoproteins, contributing to the morbidity and mortality associated with hypoalbuminemia.[47]

ALBUMIN AND HEART FAILURE

Heart failure is becoming one of the most important cardiovascular diseases owing to its increasing prevalence, high mortality, and rising costs of care. The inflammatory process that accompanies heart failure is an important prothrombotic factor.[48]

Hypoalbuminemia is common in patients with heart failure and appears to be a reliable indicator of mortality and morbidity among individuals with low ejection fraction (<40%).[49,50] In addition, it has been observed that hypoalbuminemia is significantly associated with the incidence of heart failure in elderly patients.[50]

Studies have shown that hypoalbuminemia occurs both in heart failure with impaired and preserved function.[51–53] In acute heart failure, it is a reliable predictor of mortality.[53] The Cardiovascular Health Study, which included 5,450 healthy individuals aged 65 and older, found that hypoalbuminemia was significantly associated with the risk of developing heart failure within 10 years.[50] The causes of hypoalbuminemia have not been specifically studied in patients with heart failure; nevertheless, it may result from malnutrition and hepatic dysfunction.[52] It has to be noted that systemic inflammation can lower serum albumin concentrations without causing malnutrition.[54]

The inflammatory response results in significant changes to plasmatic, cytokine, and complement proteins. Serum albumin levels decrease in response to inflammation, being common in clinical scenarios linked to oxidative stress and chronic inflammation.[55–57] According to Ancion *et al.*, hypoalbuminemia is common in hospitalized patients with acute heart failure and is linked to a higher risk of in-hospital mortality.[58] In addition to traditional risk markers such as age, hemodynamic and biological parameters (leukocyte count), low serum albumin levels can also predict an in-hospital outcome.[58,59] Studies suggest that older patients with heart failure are more likely to have hypoalbuminemia, and the prevalence of this condition rises with increasing frailty,[60] ranging from 20–25% among patients with cronic heart failure to about 90% among elderly individuals with severe acute heart failure.[61]

ALBUMIN AND STROKE

Stroke is an acute neurological injury resulting from cerebral ischemia, especially acute ischemic stroke, and cerebral hemorrhage secondary to intracerebral hemorrhage. Acute stroke, internal cerebral hemorrhage, and severe cerebral hemorrhage account for 62%, 28%, and 10%, respectively, of strokes worldwide.[62] One of the most abundant proteins in the blood, albumin, goes through chemical changes to its N-terminal strand in ischemia, which results in the production of ischemia-modified albumin.[63]

Studies have shown a favorable relationship between albumin levels and the outcome of stroke.[64,65] Additionally, a low serum albumin level is one of the predictors of a first non-embolic stroke in the elderly.[65,66] Experimental studies also suggest that albumin has a neuroprotective effect, either by reducing cerebral edema or due to its antioxidant and antiapoptotic properties.[65,67]

Albumin increases microcirculatory flow, plasmin velocity, and oxygen transport capacity.[68] Additionally, serum albumin has a positive effect on the immune system.[69,70] After an ischemic episode, albumin treatment increases collateral fiber density, which has a significant therapeutic effect.[69]

Several studies have shown that hypoalbuminemia is associated with a poor prognosis for patients with heart failure,[36] stroke,[69] renal failure needing hemodialysis, and infections.[71] Further research has revealed that hypoalbuminemia increases the risk of a new myocardial infarction in patients with coronary artery disease.[72]

ALBUMIN AND ARRHYTHMIAS

Although albumin itself does not directly cause arrhythmias, alterations in its levels may reflect underlying physiological changes that can contribute to the development of arrhythmias. Monitoring albumin levels in clinical practice can provide valuable information about a patient's overall health status and help identify individuals who are more susceptible to cardiovascular complications, including diabetes.

Atrial fibrillation, the most common arrhythmia, is accompanied by the infiltration of immune cells and inflammatory proteins into the heart valves. Inflammatory mediators can alter atrial electrophysiology and structural substrates, increasing the heart's vulnerability to atrial fibrillation. Inflammation in patients with atrial fibrillation may originate from various sources, including underlying inflammatory mechanisms. Numerous systemic conditions, such as coronary heart disease, hypertension, and obesity, are associated with decreased anti-inflammatory markers and elevated levels of pro-inflammatory cytokines.[73,74]

Guo *et al.* examined multiple inflammatory markers associated with atrial fibrillation, such as C-reactive protein, tumor necrosis factor, interleukin (IL)-2, and IL-6. They proposed several mechanisms to explain the link between inflammation and AF, such as increased platelet activation, endothelial activation or damage, monocyte factor production, and elevated fibrinogen expression.[75]

Zhang *et al.* reported a direct correlation between atrial fibrillation and inflammation, validating the role of myocardial infarction and inflammatory biomarkers in predicting the recurrence of atrial fibrillation.[76] Fibrinogen and albumin levels are particularly important biomarkers that can help predict the risk of atrial fibrillation.[77,78]

In a study by Mukamal *et al.*, higher fibrinogen and lower albumin levels were associated with an increased risk of atrial fibrillation and a higher risk of cardiovascular disease.[77,78]

IMPLICATIONS FOR CLINICAL PRACTICE

The measurement of serum albumin levels is an affordable, easy-to-use laboratory test that provides vital information for the prognosis of cardiovascular diseases.[5,30] Consequently, it should be considered in the evaluation of any patient who has a cardiovascular risk. The first sign of a subclinical infection could be hypoalbuminemia, malnourishment, associated inflammatory bowel disease, enteral or urinary loss, and hypervolemia.[5] Additionally, a dietetic study should be conducted to identify inappropriate behavior and improve eating habits. A clinical study revealed an improvement in the functional status of patients with suspected heart surgery during parenteral nutrition.[79,80]

The management of malnutrition was reported to be favorable in a recent study. In a randomized clinical trial involving 120 patients with malnutrition and heart failure, the management of malnutrition was associated with a significant reduction in all-cause mortality during a 12-month follow-up ($p < 0.01$).[5,51] However, it is unclear whether correcting hypoalbuminemia can improve survival among patients with heart failure. The Saline versus Albumin Fluid Evaluation (SAFE) study, which examined the use of albumine in critically ill patients, showed that the mortality rate of patients receiving albumin was equal to that of patients receiving salinized solutions.[80] Another meta-analysis concluded that a serum albumin level of >3 g/dl may slow down the rate at which deleterious effects manifest in critically ill patients with severe hypoalbuminemia.[81]

Inflammation is associated with reduced albumin levels, increased levels of acute-phase proteins such as hs-CRP, and increased expression of mRNA, IL-6, IL-1, and tumor necrosis factor.[82] Studies indicate that inflammatory activity, as reflected by elevated hs-CRP, is a key factor contributing to lower serum albumin levels in acute coronary syndrome.[82]

Patients with hypoalbuminemia should be considered at higher risk of mortality, and the underlying causes should be investigated. In this context, hypoalbuminemia is as a crucial marker with a strong physiological basis, and should be regarded as an essential component in the clinical decision-making process for managing this complex patient population.[83]

The characteristics and results of the studies included in this analysis are presented in Table 1.

TABLE 1. General characteristics and findings of the studies included in the analysis

Study	Disease	Year	No. of patients	Mean age (years)	Male sex (%)	Outcome
Nihat *et al.*[17]	Unstable angina pectoris/ NSTEMI	2020	403	64 ± 12	60.0	Patients with unstable angina pectoris or NSTEMI and hypoalbuminemia are more likely to die over the long term than those without hypoalbuminemia.
Chien *et al.*[19]	Coronary heart disease	2017	734	62.1 ± 12.4	84.1	Reduced serum albumin concentration (<3.5 g/dl) impairs patients' chances of having stable congestive heart failure.
Ancion *et al.*[20]	Acute non-ischemic heart failure	2017	546	72 ± 12	59.0	Serum albumin level is a simple predictive factor in non-ischemic heart failure.
Northern Manhattan Study[29]	Incident stroke	2014	2,986	69 ± 10	37.2	There is a relationship between low serum albumin levels and stroke.
González-Pacheco *et al.*[39]	Acute coronary syndrome	2017	8,848	62 ± 13	74.9	A serum albumin level <3.5 g/dl is an independent predictor of newly-diagnosed heart failure in patients with acute coronary syndrome.
Kempny *et al.*[40]	Adult congenital heart disease	2015	2,886	33.3 ± 12.9	50.1	Hypoalbuminemia is a robust, independent predictor of mortality in patients with adult congenital heart disease.
Bhamidipati *et al.*[41]	Coronary artery bypass grafting	2011	2,794	64.6 ± 12.9	30.1	In isolated coronary artery bypass grafting recipients, albumin is more closely linked to mortality and morbidity than the body mass index.

CONCLUSIONS

Serum albumin level is a significant predictive indicator in coronary heart disease and its measurement should be part of the routine evaluation of patients with coronary artery disease even after they are admitted to the hospital. This should lead to more attentive monitoring and measures that improve a potentially unfavorable prognosis. Hypoalbuminemia is an independent predictor of in-hospital mortality, particularly in older patients with acute myocardial infarction. Further well-designed studies evaluating functional capacity, particularly over the long term, and the causes of hypoalbuminemia in coronary artery disease are still needed.

CONFLICT OF INTEREST

Nothing to declare.

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