European Journal of Internal Medicine 102 (2022) 24–39

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Low serum albumin: A neglected predictor in patients with cardiovascular disease

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ARTICLE INFO

Keywords:
Serum albumin
Hypoalbuminemia
Cardiovascular disease
Coronary artery disease
Atherosclerosis
Myocardial infarction
Heart failure
Hypertension
Stroke
Atrial fibrillation
Congenital heart disease

ABSTRACT

Albumin, the most abundant circulating protein in blood, is an essential protein which binds and transports various drugs and substances, maintains the oncotic pressure of blood and influences the physiological function of the circulatory system. Albumin also has anti-inflammatory, antioxidant, and antithrombotic properties. Evidence supports albumin's role as a strong predictor of cardiovascular (CV) risk in several patient groups. Its protective role extends to those with coronary artery disease, heart failure, hypertension, atrial fibrillation, peripheral artery disease or ischemic stroke, as well as those undergoing revascularization procedures or with aortic stenosis undergoing transcatheter aortic valve replacement, and patients with congenital heart disease and/or endocarditis. Hypoalbuminemia is a strong prognosticator of increased all-cause and CV mortality according to several cohort studies and meta-analyses in hospitalized and non-hospitalized patients with or without comorbidities. Normalization of albumin levels before discharge lowers mortality risk, compared with hypoalbuminemia before discharge. Modified forms of albumin, such as ischemia modified albumin, also has prognostic value in patients with coronary or peripheral artery disease. When albumin is combined with other risk factors, such as uric acid or C-reactive protein, the prognostic value is enhanced. Although albumin supplementation may be a plausible approach, its efficacy has not been established and in patients with hypoalbuminemia, priority is focused on diagnosing and managing the underlying condition. The CV effects of hypoalbuminemia and relevant issues are considered in this review. Large cohort studies and meta-analyses are tabulated and the physiologic effects of albumin and the deleterious effects of low albumin are pictorially illustrated.

1. Introduction

Albumin, the most abundant circulating protein in blood (accounting for 50% of the plasma proteins), composed of 585 amino acids with a molecular weight of 66 kDa, binds and transports various drugs and substances in plasma, and most importantly, it maintains the oncotic (colloid-osmotic) pressure of blood and influences the physiological function of the circulatory system (Fig. 1) [1–4]. It opposes the effect of hydrostatic blood pressure, which, if unopposed, would push water and small molecules out of circulation into the interstitial space and produce edema. Furthermore, albumin contains one free thiol group, highly reactive against oxidant species, which accounts for 80% of free thiols in plasma and gives albumin important antioxidant properties [5]. In addition, albumin exerts anticoagulant and antiplatelet activity [6,7].

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CHD, congenital heart disease; CKD, chronic kidney disease; COVID-19, corona virus disease 2019; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICU, intensive care unit; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TAVI, transcatheter aortic valve implantation.

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https://doi.org/10.1016/j.ejim.2022.05.004
Received 13 April 2022; Received in revised form 29 April 2022; Accepted 3 May 2022
Available online 7 May 2022

Low serum albumin concentrations can be caused by liver impairment during acute phase inflammatory processes, or by increased excretion through the kidney, by malnutrition, increased catabolism, enteral loss, severe volume overload and via escape into the interstitial space [8]. Decreased levels of serum albumin (hypoalbuminemia) are reported in patients with severe forms of myocardial infarction (MI) or injury, heart failure (HF), stroke, hip fracture, malignancy, and renal disease [9–11]. Hypoalbuminemia has been associated with morbidity and mortality in hospitalized patients with or without comorbidities [10], including patients with coronavirus disease 2019 (COVID-19) where low serum albumin on presentation is associated with a higher incidence of serious outcomes including cardiac injury among other organ damages [11].

We herein review the literature on the role of serum albumin in vascular and cardiovascular (CV) disease (CVD) and related mortality. Indeed, there is robust evidence accumulated over the years regarding albumin's important role as a strong predictor of CV risk.

2. Etiology of hypoalbuminemia / pathogenetic mechansims leading to cardiovascular disease

Factors influencing the serum levels of albumin include the intake of protein, rate of synthesis in the liver and the amount secreted from the liver cell, protein loss via the gastrointestinal tract and/or the kidneys, the distribution in body fluids, and the degree of degradation and catabolism (Table 1). A low serum concentration of albumin can be caused by reduced albumin production due to a decrease in energy or deficient amino acid supply and intake (fasting/malnutrition), impaired liver synthesis as in hepatocyte damage (cirrhosis), increased loss via the gastrointestinal tract (e.g., protein-losing enteropathy) or the kidneys (e.g., nephrotic syndrome), increased or accelerated tissue catabolism or distributional problems, most commonly due to acute or chronic inflammation [12–14]. Although hypoalbuminemia may be considered as the result of inadequate nutritional intake, in most cases it is caused by inflammatory states and conditions which increase capillary permeability and escape of serum albumin leading to expansion of interstitial space and increasing the distribution volume of albumin [14]. Other causes include a poor nutritional status where albumin might serve as a nutritional marker.

Table 1
Etiology of Hypoalbuminemia.

I. Decreased/Deficient Protein Intake
● Fasting
● Malnutrition
● Advanced stage chronic disease
● Malabsorption
II. Decreased/Defective Hepatic Synthesis
● Liver failure/cirrhosis
● Inflammation / Malnutrition
● Genetic abnormalities
III. Increased Loss
● Hemorrhage
● Nephrotic syndrome
● Protein-losing enteropathy (*lymphatic blockage*, e.g., constrictive pericarditis, ataxia telangiectasia, mesenteric blockage due to tumor; *mucosal disease*, e.g., IBD, sprue, bacterial overgrowth/blind loop syndrome)
● Extensive burns
IV. Increased Catabolism
● Infection / Sepsis
● Critical illness
● Cancer
V. Increased Volume of Distribution / Redistribution/ Hemodilution
● Heart failure
● Ascites
● Sepsis
● Renal failure
VI. Acute and Chronic Inflammation
● Cytokine-induced hypoalbuminemia (TNF, IL-6): Increased vascular permeability Increased degradation Decreased synthesis (e.g., by activating TNF-α, which decreases transcription of the albumin gene)

IBD = inflammatory bowel disease; IL = interleukin; TNF = tumor necrosis factor.

The potential role of low serum albumin levels in CVD may relate mostly to its oncotic, anti-inflammatory, antioxidant, and antithrombotic activities (Fig. 2) [2,4,15-17]. The anti-inflammatory properties of serum albumin may not be well understood in the clinical setting; however, its antioxidant effects have been well established in CVD [4]. Other pathophysiological mechanisms may be involved including the fact that hypoalbuminemia can promote pulmonary edema and fluid

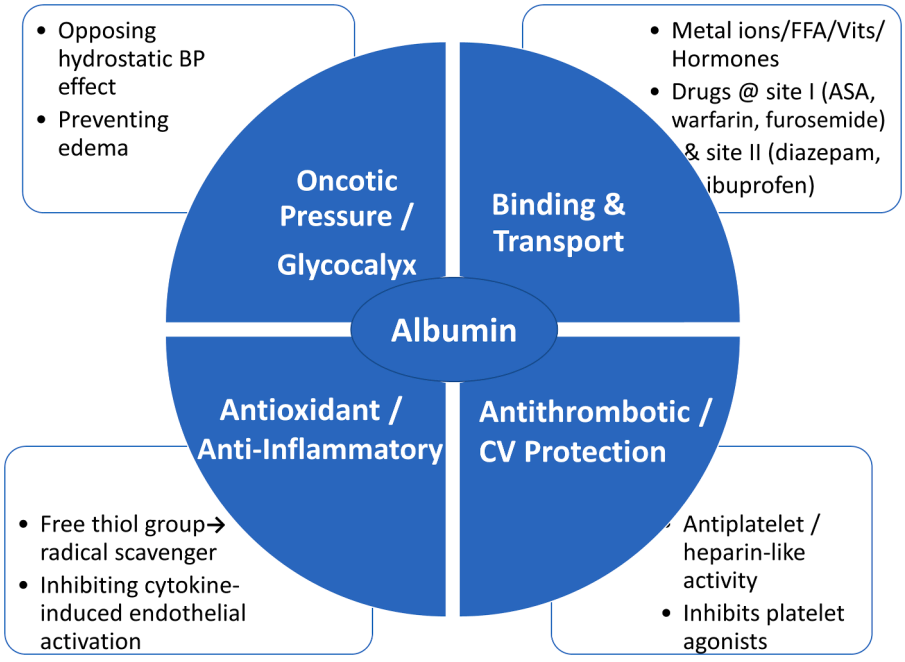

Fig. 1. The schema illustrates the physiologic effects and properties of circulating albumin.
ASA = acetyl-salicylic acid (aspirin); BP = blood pressure; CV = cardiovascular; FFA = free fatty acids; Vits = vitamins.

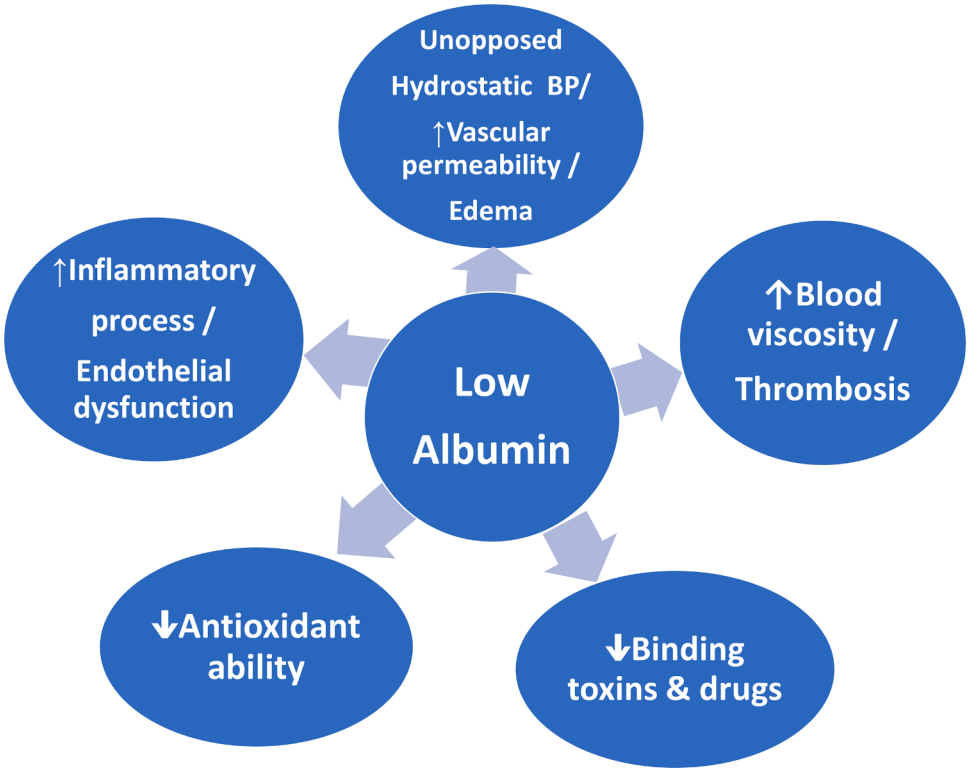

Fig. 2. The schema illustrates the pathophysiological mechanisms via which hypoalbuminemia may lead to cardiovascular diseases. BP = blood pressure.

retention, with its attendant adverse outcome in patients with established or at risk for HF, and also contributing to the worsening of ischemic heart disease by promoting myocardial edema and thus, aggravating myocardial dysfunction [4]. Via its colloid-osmotic effect and interaction with the glycocalyx, serum albumin also has an important role in maintaining capillary membrane stability and fluid balance across the capillary wall averting fluid extravasation [17]. According to the Starling's law, hydrostatic capillary pressure, the force responsible for the fluid transfer from the intravascular to the interstitial space, is opposed by the plasma colloid-osmotic pressure, of which ~80% of the effect results from serum albumin [17]. An imbalance of Starling's forces produced by hypoalbuminemia leads to a net extravasation of fluid to

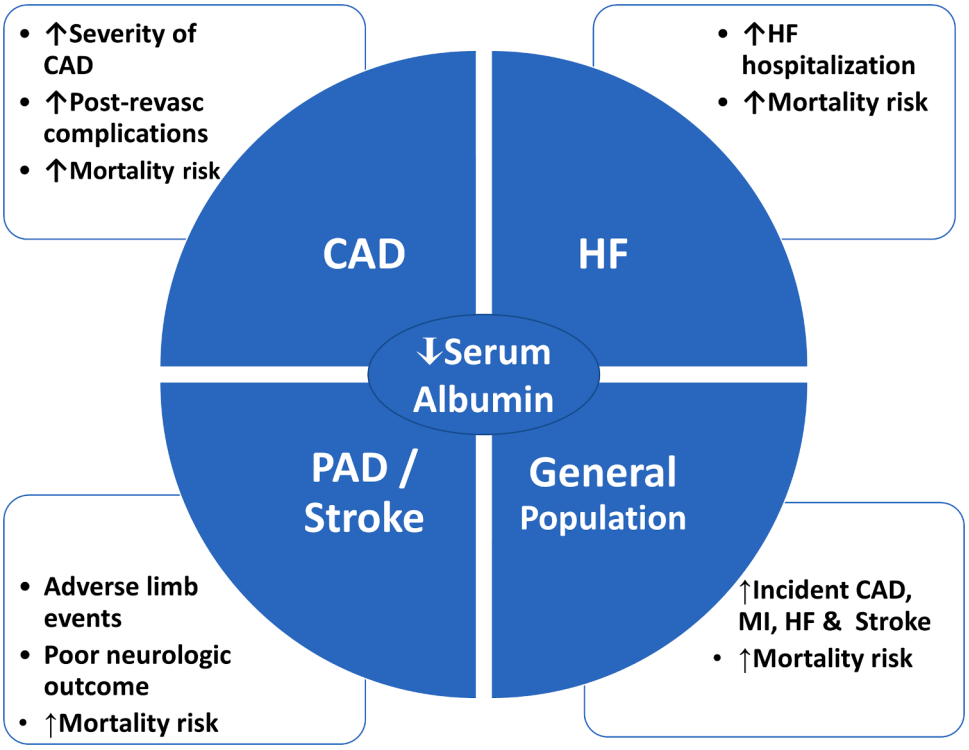

Fig. 3. The schema illustrates the deleterious consequences (rectangles) of hypoalbuminemia in various groups of persons and patients (quadrants). AF = atrial fibrillation; AS = aortic stenosis; BP = blood pressure; CAD = coronary artery disease; CHD = congenital heart disease; HF = heart failure; HTN = hypertension; MI = myocardial infarction; PAD = peripheral artery disease; PAF = paroxysmal atrial fibrillation; revasc = revascularization; SBE = subacute bacterial endocarditis; TAVI = transcatheter aortic valve implantation.

the interstitial space, with ensuing interstitial edema, hypovolemia and fluid retention; when this happens in the pulmonary circulation, pulmonary edema will develop [4,17]. Beyond its oncotic properties, the binding ability of albumin for several endogenous and exogenous particles (e.g., inorganic ions, fatty acids, bilirubin, vitamins, hormones, steroids, etc.) and drugs might also be implicated in some CV diseases [18]. Serum albumin may also have a protective effect against endothelial dysfunction related to inflammation and oxidative stress in sepsis, and hypoalbuminemia might exacerbate such pathophysiological mechanisms [2]. Importantly, serum albumin also exerts anticoagulant and antithrombotic/antiplatelet aggregation activity that contributes to circulatory homeostasis [7,16].

3. CV effects of hypoalbuminemia

Several adverse CV effects have been demonstrated in individuals with hypoalbuminemia, including outcomes in patients with coronary artery disease (CAD), heart failure, congenital heart disease, infective endocarditis, peripheral arterial disease, or stroke, and in the general population [2] (Fig. 3). Hypoalbuminemia is a strong, reliable and independent prognostic marker in these populations [5]. Low serum albumin functions independently from confounders such as malnutrition, inflammation and liver dysfunction that may be a causative factor. Importantly, this is a potentially modifiable risk factor [9]. Its involvement in the physiopathogenesis of CV disease relates mostly to the antioxidant, anti-inflammatory, and antithrombotic/anticoagulant capabilities, and plasma oncotic properties of serum albumin (Fig. 1).

4. Clinical studies

4.1. Hypoalbuminemia and mortality in general populations

An early cohort study demonstrated a strong inverse association between serum albumin and mortality in a large patient cohort [19]. The predictive value of low albumin was remarkably higher in men than in women. Specifically, among 285,930 patients, who attended an Austrian hospital over a decade (1992-2002) (median observation period 7.4 ±4.0 years; death rate 16.8%), hazard ratios (HRs) for all-cause-mortality increased linearly with decreasing albumin levels from 1.05 in the 9th to 2.98 in the 1st decile [19]. Compared with women, men had an average 50% increased risk of death in almost every decile. In critically ill patients, HRs for all-cause-mortality ranged from 4.5 in the 9th decile to 9.5 in the lowest albumin category.

A more recent study investigating the association of albumin levels on admission and change in levels during hospitalization with hospitalization outcomes in a cohort of 30,732 patients (mean age 67±18 years, 51% male) showed that low albumin levels on admission were associated with increased short- and long-term mortality [10]. In this study, most patients had normal albumin levels (3.5-4.5 mg/dL) on admission (n=20,124, 65%), 29% of patients had hypoalbuminemia, mostly mild (2.5-3.5 mg/dL) (n=7,334, 24%), and 5% of patients had marked (<2.5 mg/dL) hypoalbuminemia (n=1436). Hyperalbuminemia (>4.5 mg/dL) on admission was evident in 6% of the patients (n=1838). During a median follow-up of 4.6 years, compared with in-hospital mortality with normal albumin on admission (2%), mortality was higher with mild (12%) and marked hypoalbuminemia (34%) and lower with hyperalbuminemia (0.3%). Mortality rate at the end of follow-up was 29% with normal albumin levels, 67% with mild and 83% with marked hypoalbuminemia. After adjustment for several variables, adjusted HRs were 6.1 for marked hypoalbuminemia, compared with patients with normal albumin levels on admission, 2.7 for mild hypoalbuminemia and 0.5 for hyperalbuminemia. Patients with hyperalbuminemia on admission and before discharge had the best short- and long-term survival. This pattern was similar when analyzed separately in different age groups. In patients with hypoalbuminemia on admission, normalization of albumin levels before discharge conferred better short- and long-term survival, compared with patients with hypoalbuminemia before discharge. The authors concluded that low albumin levels on admission are associated with increased short- and long-term mortality. Normalization of albumin levels before discharge confers lower mortality risk, compared with hypoalbuminemia before discharge.

An early retrospective study of 13,473 adult patients with end-stage renal disease who were receiving chronic hemodialysis indicated that the serum albumin concentration was a powerful predictor of death with 60% of the patients having serum albumin concentrations predictive of an increased risk of death (values <4.0 g/dl) [20]. The odds ratio for death was 1.48 for serum albumin concentrations of 3.5 to 3.9 g/dl and 3.13 for concentrations of 3.0 to 3.4 g/dl. Diabetic patients had lower serum albumin concentrations.

A study investigated the association between serum albumin levels and cause-specific mortality among 77,531 community-dwelling older adults with a mean albumin level of 4.3 g/dL, which significantly decreased by age [21]. Compared with albumin levels ≥4.4 g/dL, over an average of 3.3 years of follow-up, mildly low albumin levels (4.2-4.3 g/dL) were associated with an increased mortality risk (HR: 1.16, for all-cause mortality), and albumin levels <4.2 g/dL were associated with significantly higher rates of all-cause, cancer, cardiovascular, and respiratory mortalities. Albumin levels <3.6 g/dL conferred an HR of 5.12 for all-cause mortality and 3.81 for CV mortality. In the spline regression, the curve of mortality risk was relatively flat at an albumin level ≥4.4 g/dL, and the mortality risk gradually increased as the albumin level declined. Albumin levels ≥4.4 g/dL were associated with better survival among community-dwelling older adults, and mortality risk increased as the albumin level decreased. The mortality risks were attenuated after adjusting for several variables (age, sex, demographic characteristics and comorbidities), but remained significant (adjusted HR 2.84 for all-cause mortality and 2.31 for CV mortality when albumin was <3.6 g/dL).

A study reviewing 2,680 patients admitted to a cardiac care unit (median age 68; 39% women) with various diagnoses (acute coronary syndrome, HF, cardiac arrest, and cardiogenic shock) indicated that hospital mortality was 16%, and patients with hypoalbuminemia (<3.5 g/dL) had higher hospital mortality (21% vs. 9%, adjusted OR 2.64, p<0.001) [22]. Albumin level was inversely associated with hospital mortality (adjusted OR 0.60 per 1 g/dL higher albumin level, p<0.001), with a stepwise increase in the hospital mortality at lower albumin levels. Post-discharge death rate was higher in hospital survivors with hypoalbuminemia, and increased as a function of lower albumin levels.

4.2. Coronary artery disease and cardiovascular outcomes

Early data from 45 to 64 year-old adults in the Atherosclerosis Risk in Communities (ARIC) Study (n=15,725) showed a mean albumin concentration 0.04-0.12 g/L lower in patients with diabetes (n=1527) and 0.02-0.06 g/L lower in those with CV disease (n=2313), compared with participants free of these conditions [23]. However, lower serum albumin level was also correlated with most traditional risk factors and hemostatic variables. On adjustment for these, there was essentially no association between serum albumin and prevalent CV disease. The authors concluded that hypoalbuminemia may be a marker for chronic disease and perhaps renal loss of albumin, however, it seems unlikely that it is an important cause of atherosclerosis.

Nevertheless, more recent data from 4947 persons participating in the ARIC study (mean age 75.5±5.12 years and mean baseline serum albumin level at 4.05±0.30 g/dL), showed an association of hypoalbuminemia with adverse CV outcomes [24]. Over a median of 4.42 years, 553 participants (11.2%) died and 2457 participants (49.7%) were hospitalized at least once. The total number of hospitalizations was 5725. In analyses adjusted for various parameters, 1 g/dL lower baseline serum albumin level was associated with higher risk of both hospitalization (incidence rate ratio - IRR: 1.58; p<0.001) and death (HR: 1.67; p<0.001). Associations were weaker with older age but not different by

frailty status or level of high-sensitivity C-reactive protein (hsCRP). Associations between serum albumin, hospitalizations, and death were also similar in a real-world cohort of primary care patients.

A study investigating the impact of low serum albumin levels (n=35) among 82 patients with acute coronary syndrome (ACS) (in-hospital mortality 10%, 8 patients) indicated that in-hospital adverse outcomes (death, acute HF, cardiogenic shock, and re-infarction occurring in 43%) occurred more frequently in patients presenting with hypoalbuminemia, whereas mortality did not differ significantly [25]. Univariate analysis showed that hypoalbuminemia was associated with a 2.8-fold greater risk of developing adverse outcomes. This risk was greater in the subgroup of non-ST elevation ACS (5.4-fold increased risk), but not in those with ST-elevation MI (STEMI). Adjustment with other covariates revealed that hypoalbuminemia did not independently predict in-hospital adverse outcomes, as it interacted with other predictors, especially Killip class II-IV, which was consistently an independent predictor of in-hospital adverse outcomes.

A prospective cohort study (n=734) stratified patients with stable coronary artery disease (CAD) into low serum albumin group (baseline albumin concentration <3.5 g/dL, n=98) and normal albumin group (baseline albumin concentration ≥3.5 g/dL, n=636) [26]. Low serum albumin concentration (<3.5 g/dL) conferred a worse prognosis, with increased risk of all-cause mortality (10.2 *vs* 0.5%, p<0.001) and hard CV events (7.1 *vs* 1.4%, P<0.001). The association remained significant after adjustments for confounders (all-cause mortality, HR 6.81, 95% CI 1.01-45.62; hard CV events, HR 3.68, 95% CI 1.03-13.19).

A longitudinal study investigated 3-year change in serum albumin level as a determinant of incident cardiovascular disease (CVD) and all-cause mortality in 713 participants in the Longitudinal Aging Study Amsterdam (LASA) initially aged 55-85 years [27]. At the 6-year follow-up, overall, 18.9% developed CVD and 10.9% died. After adjustment for potential confounders, a higher level of serum albumin at the 3-year follow-up was linked with a lower risk for incident CVD (relative risk-RR 0.88). The risk of incident CVD was 0.88 per unit (g/l) increase in change in albumin between 3-year follow-up and baseline. Chronic low serum albumin (≤43 g/l at baseline and 3-year follow-up) was not linked with incident CVD (p=0.22). A clinically relevant decrease in serum albumin (≥standard deviation (2.5 g/l) between baseline and 3-year follow-up) tended to confer a twofold risk (RR 2.00). For all-cause mortality, no associations were noted. The authors concluded that older persons with a decrease in serum albumin concentration, even within the normal range, might be at higher risk of incident CVD and proposed change in serum albumin as an early marker for CVD risk.

Another cohort study enrolling 2305 patients with first-onset acute myocardial infarction (MI) indicated that over a median 3 years, low serum albumin level (≤3.62 g/dl) on admission was an independent predictor of long-term all-cause, cardiovascular, and cardiac mortality [28]. There was a dose-response relationship between low serum albumin levels and increased long-term all-cause, cardiovascular, and cardiac mortality. Similarly, a retrospective study of 1424 patients admitted for acute MI indicated that over a median of 4.1 years, the primary endpoint (composite of hospitalization for HF and CV death) occurred in 19% of patients with low (<3.8 g/dL) albumin at a remote phase of acute MI (1 year after discharge) and 3.3% of patients with normal albumin (adjusted HR 2.76; P=0.007) [29]. The all-cause death rate was 29.7% vs 4.3% (adjusted HR, 4.02; P<0.001). The prognostic impact of remote low serum albumin was consistent across albumin status in the acute phase of MI. The authors concluded that regardless of albumin status in the acute phase of MI, low albumin in the remote phase after MI was significantly associated with long-term adverse outcomes.

The Copenhagen General Population Study that included 100,520 individuals without prior CVD reported 8247 incident CVD events that developed during a median follow-up of 8.5 years [30]. The association of plasma albumin and CVD was almost linear and confounder adjustment had little influence on the effect estimates, except for some attenuation after CRP adjustment. In analyses according to subtypes of CV events, the HRs for each 10 g/L lower plasma albumin were 1.17 for CAD, 1.25 for MI, 1.37 for any stroke, and 1.46 for ischemic stroke. Exploratory analyses of the mechanism of the association indicated that it was probably not due to fatty acid binding but may be due to the regulation of plasma albumin by inflammation; nevertheless, the predictive value was independent of inflammatory markers, suggesting a role of other physiological functions of serum albumin (adverse pleiotropic effects of decline in serum albumin).

An observational retrospective cohort study of 2860 all-comer patients with CAD who underwent a first percutaneous coronary intervention (PCI), with a mean albumin level of 4.0±0.5 g/dL, showed that after adjusting for traditional CV risk factors including age, ACS, body mass index and chronic kidney disease, serum albumin levels were significantly associated with incidence of major adverse cardiac events (MACE) (HR 1.74 per 1 g/dl decrease, 95% CI 1.34-2.26, p<0.0001) and all-cause mortality (HR 1.74, 95% CI 1.30-2.33, p=0.0002) [31]. Pre-PCI low serum albumin level was associated with worse long-term outcomes, independent of traditional risk factors. The authors concluded that assessing albumin levels may allow risk stratification in patients with CAD undergoing PCI.

The same investigators in a similar study comprising 1316 patients with CAD and preserved renal function undergoing PCI, with mean albumin concentration of 4.1±0.4 g/dL, showed that over a median of 7.5 years, 181 MACE, defined as the first event of non-fatal MI or all-cause mortality, occurred (13.8%) [32]. Kaplan-Meier curves revealed that patients with decreased serum albumin concentrations showed a higher event rate for MACE (log-rank, p<0.0001). Using the highest tertiles (>4.3 g/dL) as reference, adjusted hazard ratios were 1.97 (95% CI, 1.12-3.55), 1.77 (95% CI, 0.99-3.25), and 1.19 (95% CI, 0.68-2.15) for serum albumin concentrations of <3.9, 3.9-4.0, and 4.1-4.3 g/dL, respectively. Decreased serum albumin concentration was associated with MACE even after adjusting for other independent variables (HR, 2.21 per 1-g/dL decrease; 95% CI, 1.37-3.56, p=0.001). The authors concluded that decreased serum albumin concentration independently predicted worse long-term prognosis in non-CKD patients after PCI.

In keeping with these results, a multivariate analysis in a retrospective cohort study of 220 STEMI patients undergoing primary PCI within 12 h from the onset of symptoms, showed that low serum albumin levels were associated with worse in-hospital adverse events, irrespective of troponin and CRP plasma levels; probably contributing to the pro-thrombotic phenotype of these patients, as shown in a subgroup of 132 patients, where serum albumin inversely correlated with D-Dimer levels (rS 0.31, p<0.001) [33].

A study evaluated the prognostic significance of changes in serum albumin in 5449 patients undergoing PCI (age 66.8±12 years; 26% women) [34]. Patients with greater changes in albumin (Δalbumin) (albumin before PCI minus lowest albumin within the 5 years following the PCI) were older with a higher prevalence of most CV risk factors and comorbidity. Over a median of 7 years, the cumulative rate of MACE including all-cause mortality, non-fatal MI, target vessel re-vascularization, and coronary artery bypass surgery, was 49.5%. MACE rates and the rates of all the MACE components increased progressively with the increase in Δalbumin. Multivariate analysis showed that Δalbumin was an independent predictor of long-term MACE following PCI (HR = 1.4 for Δalbumin of 0-0.5 g/dL; HR=2.2 for Δalbumin of 0.5-1 g/dL, and; HR =3.8 for Δalbumin of ≥1 g/dL; P<0.001 for all). The authors concluded that decrease in albumin levels following PCI is an independent prognostic marker of worse long-term outcomes.

A study comprising 536 patients with ST elevation MI (STEMI) (aged 60 ± 13 years; 74% men) who underwent primary PCI, indicated that admission serum albumin levels were significantly lower in the no-reflow group than in the normal-reflow group (3.55±0.44 *vs* 4.01 ±0.32 mg/dL, p<0.001) (no-reflow was defined as thrombolysis in

myocardial infarction ≤2 flow) [35]. In multivariate analysis, serum albumin level remained an independent predictor of angiographic no-reflow (odds ratio-OR 0.114, p=0.001) together with left ventricular ejection fraction (LVEF), hsCRP, and baseline culprit artery patency.

Contrast-induced acute kidney injury is a serious complication among patients undergoing PCI [36], and lower serum albumin, compared to controls, has been suggested as a potential independent biomarker for such complication [37,38].

Finally, a recent analysis of registry data in 1,724 patients with MI who underwent primary PCI indicated that the cumulative 3-year incidence of moderate/severe bleeding was significantly higher in the low serum albumin group (<3.8 g/100 ml) than in the middle serum albumin (3.8 to 4.1 g/100 ml) and normal serum albumin (≥4.2 g/100 ml) groups (30.8% and 11.9% vs 7.7%; P<0.001) [39]. After adjusting for confounders, the low serum albumin group showed excess risk of bleeding events relative to normal serum albumin (HR 1.56; P=0.026), whereas risk of bleeding was neutral in middle serum albumin relative to normal serum albumin (HR 0.94; P=0.752). The authors concluded that low serum albumin at admission was independently associated with higher risk for bleeding events in patients with MI undergoing PCI.

4.3. Heart failure and CV outcomes

A medical record review of 1726 patents with HF with reduced ejection fraction (HFrEF) (age 52±13 years, LVEF 23±7%) indicated that hypoalbuminemia (≤3.4 g/dL), present in 25% of patients, was associated with higher New York Heart Association (NYHA) class, higher serum urea nitrogen, creatinine level, C-reactive protein, and B-type natriuretic peptide but lower levels of sodium, hemoglobin, and cholesterol [40]. One-year survival was 66% in patients with *vs* 83% in those without hypoalbuminemia (p<0.0001). Risk-adjusted HR was 2.2 for 1-year mortality and the same for 5-year mortality. The authors concluded that hypoalbuminemia is common in HF and is independently associated with increased risk of death in HF.

Another medical record review comprising 576 consecutive patients with HF with preserved ejection fraction (HFpEF) showed that hypoalbuminemia (≤34 g/L) was detected in 160 (28%) at admission [41]. Over 1 year of follow-up, patients with hypoalbuminemia had a significantly lower survival rate (53 *vs* 84%, p<0.001) and a higher rate of CV death (21.8 *vs* 8.9%, p<0.001) when compared with those without hypoalbuminemia. Cox regression further revealed that hypoalbuminemia, a history of cerebrovascular disease, and older age were the most powerful independent predictors of all-cause mortality in HFpEF patients at 1 year.

According to a more recent study of 118 patients with HFpEF, a low serum albumin was associated with higher myocardial extracellular volume (52.3 *vs* 57.4 *vs* 39.3 mL in lowest to highest albumin tertile, respectively; p=0.0023) and greater N-terminal pro B-type natriuretic peptide (NTproBNP) levels, but not with a higher myocardial cellular volume (123 *vs* 114 *vs* 102 mL; p=0.13) [42]. Lower serum albumin was also associated with an increased forward wave amplitude and markedly increased pulsatile power in the aorta. Serum albumin was a strong predictor of death or HF hospitalization even after adjustment for NTproBNP levels and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (adjusted standardized HR=0.56; p<0.0001). The authors concluded that serum albumin is associated with myocardial fibrosis, adverse pulsatile aortic hemodynamics, and prognosis in HFpEF.

A cohort study of 438 patients with acutely decompensated HF (mean age 75±13 years, mean LVEF 41±20%) indicated that quintile analysis demonstrated an increased mortality risk below a serum albumin level of 3.4 g/dL [43]. Patients with hypoalbuminemia (<3.4 g/dL; n=236, 54% overall) were more likely to have prior HF, more severe HF symptoms, more likely to be edematous, and a higher frequency of renal dysfunction and elevated B-type natriuretic peptide. In Cox proportional hazards analysis, hypoalbuminemia predicted 1-year mortality (HR adjusted=2.05, P=0.001). Hypoalbuminemia was mainly predictive of outcomes among those with systolic HF (HR adjusted=5.00, P<0.001). The authors concluded that hypoalbuminemia is common among patients with acute HF and is independently associated with increased one year mortality.

Data from a more recent cohort study, the Kyoto Congestive Heart Failure registry, on 3160 patients who were discharged alive after acute HF hospitalization indicated that patients with increased albumin levels (n=1083, 34%) had a lower 1-year risk for a composite of all-cause death and hospitalization compared to those with no increase in albumin levels (n=2077, 66%) (HR 0.78, P=0.0004, after adjusting for confounders including baseline albumin levels) [44]. Another cohort study comprising 5779 HF patients, with 12% of them having hypoalbuminemia (<3.5 g/dL), indicated that decreasing quartiles of albumin was significantly associated with mortality (HR 5.74 for lowest quartile compared to highest; P<0.001) [45]. Cox regression analysis demonstrated that reduced albumin levels conferred higher mortality (P<0.001 for the adjusted model). Decreasing quartiles of albumin were also a significant predictor of increased cardiac-related hospitalizations. A decrease in albumin on follow-up was an independent predictor of increased mortality (HR 2.58, P<0.001).

In contrast, baseline serum albumin levels were not associated with short-term clinical outcomes for acute HF among 456 patients undergoing decongestive therapies (with mean baseline albumin level at 3.5 ±0.5 g/dL) [46]. Albumin was not associated with worsening renal function, worsening HF, or clinical decongestion by 72 h. Furthermore, there was no association between continuous albumin levels and symptom change according to visual analog scale or weight change by 72 h. Albumin was not associated with 60-day mortality, rehospitalization, or unscheduled emergency room visits.

A meta-analysis of 9 studies comprising 16,763 HF patients indicated that hypoalbuminemia was associated with an increased in-hospital mortality (risk ratio - RR 4.90) and long-term all-cause mortality (RR 1.75) in acute HF patients. Chronic HF patients with hypoalbuminemia exhibited a 3.5-fold higher risk for long-term all-cause mortality [47]. The authors concluded that hypoalbuminemia is possibly an independent predictor of all-cause mortality in patients with acute or chronic HF.

Finally, a more recent and larger meta-analysis of 48 studies comprising 44,048 patients with HF indicated that hypoalbuminemia was found in 32% of HF patients with marked heterogeneity ($I^2 = 98\%$). In 10 studies evaluating acute HF, in-hospital mortality was ~4-fold higher in patients with hypoalbuminemia (odds ratio - OR 3.77) [48]. Hypoalbuminemia also conferred a significant increase in long-term mortality (OR: 1.5) especially at 1-year post-discharge (OR: 2.44; $I^2 = 11\%$). Pooled area under the curve (AUC 0.73) was comparable to serum brain natriuretic peptide (BNP) in predicting mortality in HF patients.

4.4. Hypertension

A retrospective observational study comprising 1,385 normotensive men and 855 normotensive women without CVD at baseline, of whom 242 men (17.5%) and 89 women (10.4%) developed hypertension over a mean of 3.1 years, showed that the incidence of hypertension significantly decreased through the quartiles of albumin (P for trend=0.012) [49]. The HR of hypertension for each one SD increase in the serum albumin level was 0.779 (P<0.001). Compared with the lowest quartile of serum albumin, the HRs of hypertension for the second, third and fourth quartiles were 0.765, 0.628 and 0.520, respectively (all P<0.001). The authors concluded that a decreased serum albumin level was a significant predictor of hypertension in a Japanese health screening population. Interestingly, recent data have indicated that genetically determined hypoalbuminemia is a significant predictor of incipient hypertension [50]. It has been suggested that serum albumin may prevent hypertension in a concentration-dependent manner by inhibiting intravascular and extravascular angiotensin converting

enzyme (ACE) [51].

4.5. Cardiac arrhythmias

A recent retrospective case-control study examined the association between serum albumin levels and atrial fibrillation (AF) in 950 patients in comparison with 963 age- and sex-matched non-AF patients who were in sinus rhythm [52]. Albumin levels of AF patients were significantly lower in both men and women (P<0.05), especially of paroxysmal AF. After adjusting for confounders, an independent negative association between albumin levels and AF was found in men (OR=0.89, P<0.05). There was a positive correlation of albumin with total cholesterol (r=0.359, P<0.05), low-density lipoprotein cholesterol (r=0.283, P<0.05), and serum apolipoprotein A1 (r=0.429, P<0.05); a negative correlation was observed with serum creatinine (r=0.129, P<0.05) in patients with AF. The authors concluded that low serum albumin in men was significantly associated with AF.

4.6. Aortic valve disease and CV outcomes

A study investigating 2608 patients with aortic valve stenosis undergoing transcatheter aortic valve implantation (TAVI) demonstrated by multivariable analysis that each increase in stage, as determined by a new scoring system dividing patients into 5 stages (0-4) based on extent of cardiac damage, was associated with significant increased risk of 1-year mortality (HR 1.37, 95%CI 1.23-1.54, p<0.001) [53]. Among patients at increased stage (3-4), incorporation of baseline of album, considered an index of frailty, identified the highest risk group, such that each 1 decrement in albumin levels was associated with more than 3-fold increase in mortality among patients at stage 3 and 4 (HR 2.77, 95% CI 1.48-5.18, p=0.001). The authors concluded that in a real-world cohort of patients undergoing TAVI, incorporation of low baseline albumin may identify patients in the highest risk group. In keeping with these findings, a large cohort study evaluating TAVI patients ≥65 years of age in a US registry (n=36,242) indicated that frailty indices of anemia, albumin level, and 5-min walk speed were independently associated with mortality at 30 days and 1 year, with low albumin providing the best value (HR: 1.52) [54].

A meta-analysis of 11 studies (n=6456) evaluating the prognostic value of serum albumin level in patients undergoing TAVI indicated that lower serum albumin level was associated with a lower survival rate at follow-up [55]. A sub-group analysis of 8 studies reporting adjusted HRs indicated that low serum albumin was independently correlated with increased post-operative mortality [55]. The HR of mortality risk associated with each 1 g/dL increment in serum albumin level was 0.46, suggesting a potential dose-response relationship between increased serum albumin level and increased survival rate in patients undergoing TAVI.

Finally, a meta-analysis of 10 studies (n=8,236) of patients undergoing TAVI (mean age of 83 years, 49% men) showed that low albumin was significantly associated with an about two-fold increase in 30-day all-cause mortality (HR, 2.09) and a 61% increased risk for one-year mortality (HR, 1.61) [56].

4.7. Congenital heart disease

Data from a retrospective cross-sectional study comprising 2,886 adult patients (mean age 33.3 years; 50% men) with congenital heart disease (CHD) indicated that hypoalbuminemia, present in 14% of patients, was a strong predictor of outcome (HR 3.37, P<0.0001). On multivariate analysis, after adjusting for several variables, hypoalbuminemia remained a significant predictor of death [57]. A retrospective study using US registry data on 1,290 patients with CHD awaiting heart transplantation indicated that hypoalbuminemia (<3.2 g/dl) was one of the strongest predictors of death and delisting for aggravation (HR 2.0; P<0.001), after adjusting for several variables [58].

4.8. Endocarditis

According to a retrospective study of 192 patients with infective endocarditis, an abnormal (<30 g/l) serum albumin concentration (n=59) predicted a higher mortality rate at discharge (36%) vs a normal serum albumin (9%) [59]. This difference was also observed at 6 months (P=0.0007). A retrospective observational cohort study of 336 patients referred for surgical management of infective endocarditis reported that albumin level independently predicted early mortality (OR 0.94, P=0.04), after adjusting for other variables [60]. Similarly, another retrospective study evaluated the value of preoperative serum albumin in predicting early mortality after surgery in 276 patients with infective endocarditis, whereby 20 (7.2%) died in hospital or within 30 days of surgery [61]. Multivariate analysis showed that hypoalbuminemia (<3.5 g/dL), present in 109 (39.5%) patients, was inversely associated with early mortality after full adjustment (adjusted odds ratio – OR 0.22 per 1 g/dL, P=0.006).

4.9. Pulmonary artery hypertension and CV outcomes

A retrospective study of 163 out of 273 patients with World Health Organization group 1 pulmonary artery hypertension who had a documented serum albumin level, indicated that hypoalbuminemia was present in 41 (25.2%) patients and serum albumin ≤3.3 g/dL represented the lowest quartile of serum albumin [62]. Patients with hypoalbuminemia had higher rates of renal dysfunction (26.8 *vs* 9.8%, P=0.0069) and hepatic dysfunction (29.3 *vs* 6.6%, P<0.001), and lower hemoglobin levels (11.6 *vs* 13.4 g/dL, P<0.001). Hemodynamic and functional capacity assessments were comparable between groups. Among other risk factors, low albumin level was an independent predictor of mortality (HR 0.485, P=0.008). Patients with hypoalbuminemia demonstrated a significantly lower survival rate at latest follow-up (P=0.01) (mean of 4.3 ±2.6 years).

4.10. Peripheral artery disease (PAD) and CV outcomes

A very large study in 35,383 patients with PAD undergoing major lower extremity amputation, indicated that hypoalbuminemia was associated with an increased risk of postoperative mortality in a dose-response manner, specifically in above knee amputations, being highest in patients with very low albumin levels (11%) as compared with low (6.8%) and normal levels (3.9%) [63]. On multivariable analysis, lower albumin levels emerged as a risk-adjusted independent predictor of mortality.

Another large study of 5,110 PAD patients undergoing lower extremity bypass showed that low albumin was independently associated with increased mortality (odds ratio - OR 1.8, P=0.001), repeat procedure (OR 1.4, P<0.001), and increased length of stay (P<0.001) [64]. When compared with patients with normal albumin, patients with more severe hypoalbuminemia (<2.8 g/dL), showed further increased risk of mortality (OR: 2.5), repeat surgery (OR: 1.6), and prolonged hospital stay (means ratio - MR 1.2).

C-reactive protein (CRP) and albumin representing biomarkers of inflammation and malnutrition, respectively, have been assessed as a combined marker, the CRP-to-albumin ratio (CAR), in patients with PAD. A study of 149 patients with PAD undergoing endovascular therapy (EVT) indicated that all-cause mortality and amputation rates of patients in the high CAR group were significantly higher than those in the low CAR group (21.3 *vs* 6.8% and 18.7 *vs* 5.4%, respectively) [65]. Survival curve analysis showed significantly better survival for patients in the low CAR group (log-rank P=0.0058). Multivariate analysis showed CAR as an independent predictor of amputation and all-cause mortality even after adjusting for other confounding factors.

A registry study indicated that the CAR was associated with mortality

in 172 patients with chronic limb-threatening ischemia undergoing EVT for below-the-knee lesions [66]. Another recent study also investigated the predictive value of the CAR, categorized according to CAR tertiles, on the severity of PAD and outcomes after EVT in 307 patients [67]. The rates of complex lesions and multilevel involvement increased with increasing CAR tertiles (all P<0.001). The third *vs* the second and first CAR tertile showed a significantly higher incidence of MACE and major adverse limb events (log-rank P<0.001). A higher CAR as a continuous variable was also independently associated with the 4-year rate of MACE (HR, 1.20; P=0.015).

4.11. Stroke

According to the results of a study, the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, focusing on variables associated with risk of stroke in 2141 adults who had started hemodialysis the previous year and were receiving an erythropoiesis-stimulating agent and intravenous iron, among other factors, low serum albumin was independently associated with stroke events during follow-up (median 2.1 years) [68].

Serum albumin level has been found to be a predictor of all-cause and cerebro-cardiovascular death in a general population [69]. Specifically, according to a periodic epidemiological survey over a 15-year period in a population of 1,905 healthy Japanese individuals (783 males, 1,122 females) older than 40 years of age, and after adjusting for confounders, regression analysis demonstrated that a low serum albumin level was an independent predictor of all-cause death (HR 0.39], cancer death (HR 0.43), death from infection (HR 0.21) and cerebro-cardiovascular death (HR 0.19) [69]. The HRs for all-cause and cerebro-cardiovascular death in the highest quartile *vs* the lowest quartile of albumin after adjusting for confounders were 0.59 and 0.15, respectively.

Data from the Third China National Stroke Registry (CNSR-III) comprising 13,618 patients with acute ischemic stroke or transient ischemic attack (TIA), indicated that over a 3-month follow-up period, patients with serum albumin <35 g/L had an increased risk of poor functional outcome and mortality (adjusted OR 1.37 and adjusted HR 2.13) compared with those with albumin levels at 40-44.9 g/L [70]. The relationship in per 10 g/L decreased serum albumin and prognosis was consistently inversed (adjusted OR 1.17; adjusted HR 1.86). Also, low serum albumin levels were independently correlated with clinical outcomes at 1 year. The authors concluded that low serum albumin levels predict poor functional outcome and mortality in patients with ischemic stroke or TIA.

4.12. Longevity

A study reported associations between CV disease-related biomarkers and survival to the highest ages among 1,427 oldest individuals (ages 85 to ≥110 years) from three longitudinal cohort studies [71]. Overall, NT-proBNP, interleukin-6, cystatin C and cholinesterase were associated with all-cause mortality independent of traditional CV risk factors and plasma albumin. Of these, low NT-proBNP level was statistically associated with a survival advantage to supercentenarian age. Only low albumin was associated with high mortality across age groups.

4.13. Microalbuminuria

Microalbuminuria in type 2 diabetes (T2D) reflects both the existence of diabetic nephropathy and PAD which is often associated with the insulin resistance syndrome [72]. A study comprising 444 patients with T2D showed that albuminuria was a prognostic factor for vascular morbidity and death in T2D patients treated with insulin but not in patients treated with diet or oral agents [73].

Dysfunction of vascular endothelium may be a link between albuminuria and atherosclerotic CV disease in T2D according with the results in 94 patients with T2D [74]. In this group of patients, where plasma concentration of von Willebrand factor (vWF), an indicator of endothelial dysfunction, was determined, raised baseline urinary albumin excretion was associated with an increased risk of new CV events only in patients with vWF concentrations above the median (relative risk - RR 3.66) and not in patients with lower vWF (RR 0.19). In addition, the CV risk associated with increased urinary albumin excretion was modified by low compared with high concentrations of serum high density lipoprotein (HDL) cholesterol (RR 2.86 *vs* 0.15)

Microalbuminuria is considered a major risk factor predisposing to CV morbidity and mortality. A study evaluating the effects of microalbuminuria on coronary blood flow and prognosis in 247 ST-segment elevation myocardial infarction (STEMI) patients undergoing primary PCI, indicated that microalbuminuria (urinary albumin extraction rate 20-200 μg/min) on admission, present in 108 patients, was an independent predictor of poor myocardial perfusion (adjusted relative risk -RR 3.14) and a higher rate of 6-month mortality (adjusted RR 1.58) [75]. Furthermore, Thrombolysis In Myocardial Infarction (TIMI) flow grades 0-2 in the microalbuminuria group were more frequent (9.4 *vs* 21.2%, P<0.05) than in the normoalbuminuria group (<20 μg/min), and corrected TIMI frame count was higher (23.9 ± 18.5 *vs* 29.8 ± 23.5, P<0.05).

4.14. Drug efficacy

Hypoalbuminemia may affect the binding of antibacterial drugs and thus may produce significant variations in the pharmacokinetics of many highly protein-bound antibiotics [76]. In the same context, this may also occur with other drugs. In patients receiving the non-vitamin K oral anticoagulant, rivaroxaban, an almost 4.5-fold higher risk of bleeding (adjusted odds ratio - OR 4.405) was reported with any 1 g/dL reduction in albumin [77].

A study investigating the impact of albumin levels on the efficacy of aspirin (100 mg/d) in 612 patients with T2D, followed-up for 54.4±7.3 months, of whom 250 (41%) patients had serum albumin <3.5 g/dL, indicated that of 86 CV events, more (49 events) occurred in patients with serum albumin <3.5 g/dL vs patients (37 events) with albumin ≥3.5 g/dL (*P*=0.001) [78]. At multivariable analysis, serum albumin <3.5 g/dL (HR 1.89, *P*=0.014), among other factors, was associated with CV events. In keeping with this, serum thromboxane B2 levels were higher (0.32±0.12 vs 0.24±0.12 ng/ml) in patients with albumin <3.5 g/dL vs ≥ 3.5 g/dL (*P*<0.001). The authors concluded that in patients with T2D, the efficacy of aspirin varies according to albumin levels; hypoalbuminemia associated with impaired thromboxane B2 inhibition and an increased risk of long-term CV events.

In contrast, the efficacy of loop diuretics, although they are 95%–99% albumin-bound, has not been found compromised in patients with hypoalbuminemia [79]. On the other hand, altered albumin, e.g., oxidized albumin, encountered in renal or hepatic disease or in T2D, may offer increasing binding capacity for drugs, like verapamil [18].

4.15. Coronavirus disease 2019 (COVID-19)

Albumin down-regulates the expression of angiotensin converting enzyme 2 (ACE2) that is the target receptor of COVID-19 [80,81]. In this context, hypoalbuminemia on admission in patients with COVID-19 infection appears to influence outcomes independent of age and morbidity, associated with a higher incidence of cardiac injury and hypercoagulability, among other ailments, contributing to higher mortality [11]. In contrast, a retrospective review of 181 COVID-19 patients, of whom 60% had hypoalbuminemia (albumin level <3.3 g/dL), found that higher albumin levels on admission were associated with significantly fewer adverse outcomes, including fewer venous thromboembolic events, less acute respiratory distress syndrome (ARDS) development, and fewer admissions and readmissions within 90 days [82]. Finally, a recent cohort observational study of 840 COVID-19 patients admitted to the hospital indicated that severe hypoalbuminemia (≤3 g/dL) was an

independent risk factor for mortality (OR 2.18; *P*=0.039) among older adults with a consistent correlation between albumin levels and inflammatory biomarkers [83]. These findings are in keeping with prior data indicating that among critically ill patients in the intensive care unit (ICU), lower serum albumin was independently associated with increased risk of ARDS after controlling for severity of illness and potential confounders [84].

5. Meta-analyses

The results of large studies and meta-analyses that evaluated the relationship of serum albumin levels with mortality and CV outcomes are summarized in Table 2. An early (2003) meta-analysis of 90 cohort studies (N=291,433) evaluated hypoalbuminemia as an outcome predictor by multivariate analysis and of an additional 9 prospective controlled trials (N=535) on correcting hypoalbuminemia [85]. Hypoalbuminemia was a potent, dose-dependent independent predictor of poor outcome (independent of nutritional status and inflammation). Each 10-g/L decline in serum albumin concentration significantly raised the odds of mortality by 137%, morbidity by 89%, prolonged ICU and hospital stay respectively by 28% and 71%, and increased resource utilization by 66%. There was a suggestion that complication rates may be reduced at a serum albumin level of >30 g/L, achieved during albumin administration.

Another early meta-analysis of 33 studies comprising 91,160 elderly persons (82,066 elderly individuals in the community, 662 in chronic care homes, 8432 in hospital; mean age 71.5-84 years) indicated that in the elderly living in the community there was a clear association between albumin levels and long-term mortality (3-12 years) [86]. However, in the elderly living in chronic care homes, albumin was associated with short-term mortality (1 year) but not with long-term mortality. Importantly, this analysis also showed that healthy elderly had normal albumin values, indicating that age in itself is not a pathophysiological mechanism of hypoalbuminemia. The authors concluded that hypoalbuminemia, regardless of its cause, is an adverse prognostic indicator in the elderly, which should not go unnoticed.

A meta-analysis of 48 observational cohort studies comprising of 1,492,237 participants (initially healthy persons or general populations with both healthy and prevalent cases of cardiometabolic disease at baseline) indicated that multivariable adjusted RRs (95% CIs) comparing the top *vs* bottom third of serum albumin levels were: 1.03 (0.86-1.22) for T2D; 0.60 (0.53-0.67) for CVD; 0.74 (0.66-0.84) for CAD; 0.57 (0.36-0.91) for CAD death; 0.76 (0.65-0.87) for MI; 0.66 (0.55-0.77) for all-cause mortality; 0.71 (0.61-0.83) for venous thromboembolism; 0.65 (0.48-0.88) for cancer mortality; and 0.62 (0.46-0.84) for fractures [87]. The authors concluded that elevated levels of serum albumin are associated with reduced risk of vascular outcomes, all-cause mortality, certain cancers, and fracture with inconsistent findings for T2D attributable to selective reporting by studies.

A meta-analysis of 8 studies comprising 21667 patients with ACS indicated that ACS patients with low serum albumin level had an increased risk of all-cause mortality (risk ratio - RR 2.15) after adjusting for important covariates [88]. Subgroup analysis showed that the impact of low serum albumin level was stronger in hospital mortality (RR 3.09) than long-term all-cause mortality (RR 1.75).

As mentioned, a meta-analysis of 9 studies comprising 16,763 HF patients indicated that hypoalbuminemia was linked with an increased in-hospital mortality (RR 4.90) and long-term all-cause mortality (RR 1.75) in acute HF patients and an increased long-term all-cause mortality in chronic HF patients (RR 3.5) [47]. As also mentioned, a meta-analysis of 48 studies comprising 44,048 patients with HF indicated that hypoalbuminemia, found in 32% of HF patients, conferred a significant increase in long-term mortality (OR 1.5) especially at 1-year post-discharge (OR 2.44; OR 3.77 in acute HF) [48].

A meta-analysis of 14 studies (n=150 652) assessing the association between plasma albumin and CV events indicated an RR_{pooled} of 1.96 for CVD per 10 g/L lower plasma albumin [30]. Results of analyses using CV mortality as an outcome were similar.

Another meta-analysis of 15 studies of serum albumin and CV events involving 65,077 individuals (mean age 57.89±6.05 years) indicated that over 9.4±5.56 years, persons with serum albumin <3.8 g/dL had a combined HR for CV events of 2.16 [89]. An increased risk for CV events was also evident using serum albumin as a continuous variable (HR = 1.89). Females and males had a raised risk for CV events (HR 2.46 and 1.46, respectively). A raised risk of CV events was found between primary and secondary prevention studies (HR 1.79 and HR 2.47, respectively). The authors concluded that low albumin levels confer an increased risk of CV events, not only in subjects free from prior CV events, but also in patients who already experienced a CV event.

6. Ischemia modified albumin (IMA)

Ischemia-modified albumin (IMA), first discovered in the early 1990s, is a form of human serum albumin modified by reactive oxygen species (ROS) generated by hypoxia, free-radical injury or membrane disruption, whereby the amino (N)-terminal end of albumin is unable to bind to transition metals [90]. In ischemia, the structure of albumin is modified due to the generation of free radicals and subsequent release of free iron and copper. Altered albumin (IMA) is unable or has a decreased binding capacity (in the presence of ischemia) to bind divalent metals and leave bound copper [91]. IMA has been proposed as a reflection of oxidative stress and has been found to be a useful and sensitive serum biomarker of myocardial ischemia and CVD in peritoneal dialysis patients, in patients after PCI, but also in patients with ACS and a negative ECG and negative cardiac troponin [90–93]. IMA has also been suggested to be a better independent predictor of MACE than NT-proBNP or hs-cTnT in patients with PAD [94].

7. Uric acid to albumin ratio

As mentioned, several studies have shown that low serum albumin values increase the risk of CVD and mortality. Other studies have shown that high uric acid is also a CV marker and prognosticator, especially in people with suspected or definite CAD [95,96]. A recent study assessed whether the uric acid/albumin ratio (UAR) is a predictor of mortality in 4599 STEMI patients who underwent PCI (median age 58 years; 78% male) [97]. The incidence of mortality in the entire patient group was 11.9%. Multivariate Cox proportional regression analysis showed that over a median of 42 months, age (increase 50 to 67 years; HR 1.34) and UAR (increase 1.15-1.73; HR 1.33) were associated with mortality. The authors concluded that UAR is a prognostic factor for mortality in STEMI patients and an easily accessible parameter to identify high-risk patients.

8. C-reactive protein-to-serum albumin ratio (CAR)

C-reactive protein (CRP) has been suggested as a contributor to or a marker of the pathogenesis of CAD and inflammatory reactions and/or a therapeutic target for CVD [98–101]. On the other hand, high CRP levels and hypoalbuminemia have been shown to be independently and jointly associated with long-term mortality among CAD patients; CAD patients with high CRP levels (>3 mg/L) and with hypoalbuminemia (<35 g/L) seem to have the highest mortality risk vs a reference group with normal values of these indices (HR 3.79) [102].

Interestingly, a retrospective analysis of 1011 patients with predominantly ischemic cardiomyopathy fitted with an implantable cardioverter defibrillator (ICD) (mean LVEF 30%) reported that a CRP-to-albumin ratio (CAR) value of >0.270 predicted all-cause mortality with 70% sensitivity and 72% specificity and an area under curve (AUC) of 0.75 (P<0.001) [103]. CAR had higher predictive value for all-cause mortality compared with CRP and albumin alone. The AUCs for CRP and albumin separately were 0.71 (p<0.001) and 0.65 (p<0.001), respectively.

Table 2
Large Studies with >1000 Participants and Meta-Analyses Examining the Relationship of Serum Albumin Levels with Mortality and Cardiovascular (CV) Outcomes.

First Author/ Year	Type of Study	No of Participants	Results	Comments
Owen et al. / 1993 [20]	Retrospective cohort	13,473 pts on hemodialysis	● Serum albumin level was a powerful predictor of **death** / 60% of pts had serum albumin levels predictive of an increased risk of death (<4 g/dl) ● OR for death: 1.48 for serum albumin levels of 3.5-3.9 g/dl and 3.13 for levels of 3.0-3.4 g/dl	Diabetic pts had lower serum albumin levels than nondiabetic pts
Folsom et al. / 1995 [23]	Prospective cohort	1527 pts with T2D / 2313 pts with CVD	Mean albumin level was 0.04-0.12 g/L lower in pts with **diabetes** and 0.02-0.06 g/L lower in those with **CVD**, compared with pts without these conditions	● Lower serum albumin level correlated with traditional risk factors and hemostatic variables ● On correction for these, there was no association between serum albumin and prevalent CVD
Horwich et al. / 2008 [40]	Prospective cohort	1726 **HFrEF** pts (age 52±13 years; LVEF 23±7%)	● One-year **survival**: 66% in pts with vs 83% in those without hypoalbuminemia (p<0.0001) ● Risk-adjusted HRs: 2.2 for 1-year and 2.2 for 5-year mortality	● Hypoalbuminemia was associated with higher NYHA class, higher BUN, creatinine level, CRP, and BNP but lower levels of sodium, hemoglobin, and cholesterol ● In pts with BMI <25kg/m^2, 27% had albumin ≤3.4 g/dL, *vs* 22% of those with BMI ≥25 kg/ m^2 (p<0.01)
Grimm et al. / 2009 [19]	Prospective cohort	285,930 hospital-based pts	● HRs for **all-cause-mortality** increased linearly with decreasing albumin levels from 1.05 in the 9th to 2.98 in the 1st decile ● In critically ill pts, HRs for all-cause-mortality ranged from 4.5 in the 9th decile to 9.5 in the lowest albumin category	Compared with women, men had an ~50% increased risk of death in almost every decile
Oda et al / 2014 [49]	Retrospective observational cohort	1385 normotensive men / 855 normotensive women without CVD at baseline	● Over a mean of 3.1 years, 242 men (17.5%) and 89 women (10.4%) developed hypertension ● Incidence of hypertension significantly decreased via the quartiles of albumin (p for trend=0.012) ● HR of hypertension: 0.78 for each one SD increase in albumin level (p<0.001)	Compared with the lowest quartile of serum albumin, the HRs of hypertension for the second, third and fourth quartiles were 0.765, 0.628 and 0.520, respectively (all p<0.001)
Kempny et al / 2015 [57]	Retrospective cross-sectional study	2886 pts with ACHD	● Hypoalbuminemia (<35 g/L) was present in 13.9% of pts ● Prevalence of **hypoalbuminemia** was significantly higher in pts with great complexity ACHD (18.2%) vs pts with moderate (11.3%) or simple ACHD lesions (12.1%, p<0.001) ● On univariable Cox regression analysis, hypoalbuminemia was a strong predictor of **outcome** (HR 3.37, p<0.0001)	● Mortality was 11.3% over a median of 5.7 yrs ● On multivariable Cox regression, after adjusting for several variables, hypoalbuminemia remained a significant predictor of **death**
Umeki et al. / 2016 [69]	Epidemiologic survey	1,905 healthy persons (783 males, 1,122 females; older than 40 y)	A low serum albumin level was an independent predictor of ● **all-cause death** (HR 0.39), ● cancer death (HR 0.43), ● death from infection (HR 0.21) & ● **cerebro-cardiovascular death** (HR 0.19)	After correcting for confounders, in the highest quartile vs lowest quartile of albumin: ● HR 0.59 for all-cause MR ● HR 0.15 for cerebro-CV MR
Alshawabkeh et al / 2016 [58]	Retrospective cohort	1,290 ACHD and 38,557 non-ACHD pts	Albumin level <3.2 g/dl was an independent predictor of 1-year **death or delisting** due to worsening	These were pts listed for heart transplantation
Akirov et al. / 2017 [10]	Prospective cohort	30,732 hospitalized pts	Compared with 2% **in-hospital mortality** with normal albumin on admission (3.5-4.5 mg/dL), mortality was higher at: ● 12% (HR 2.7) with mild (2.5-3.5 mg/dL) hypoalbuminemia and ● 34% (HR 6.1) with marked (<2.5 mg/dL) hypoalbuminemia ● Mortality was lower (0.5%, HR 0.3) with hyperalbuminemia (>4.5 mg/dL)	● Hyperalbuminemia on admission was evident in 6% of the pts (n=1838) ● **Mortality** at the end of follow-up was 29% with normal albumin levels, 67% with mild (HR 3.4) and 83% with marked hypoalbuminemia (HR 7.1), and 9% for hyperalbuminemia (HR 0.5)
Wada et al. / 2017 [31]	Retrospective cohort	2860 pts with CAD undergoing first **PCI**	After adjusting for known CV risk factors, serum albumin levels were significantly associated with incidence of: ● **MACE** (HR 1.74 per 1 g/dl decrease, p<0.0001) and ● **all-cause mortality** (HR 1.74, p= 0.0002)	Over a median of 7.4 years, survival curves continued diverging in rates of MACE among albumin tertiles (albumin <3.8 g/dl: 44.3% *vs* 3.8-4.1 g/dl: 38.0% *vs* >4.1 g/dl: 22.9%; log-rank p<0.0001)
Peacock et al. / 2017 [64]	Prospective cohort	5110 pts with **PAD**	By multivariable analyses low albumin was independently associated with increased: ● **mortality** (OR 1.8, p=0.001), ● **repeat surgery** (OR: 1.4, p<0.001), and ● length of stay (means ratio: 1.2, p<0.001)	When compared with pts with normal albumin, pts with more severe hypoalbuminemia (<2.8 g/dL), showed further increased risk of mortality (OR: 2.5),

(*continued on next page*)

Table 2 (*continued*)

First Author/ Year	Type of Study	No of Participants	Results	Comments
				repeat surgery (OR: 1.6), and prolonged stay (means ratio 1.2)
Xia et al. / 2018 [28]	Prospective cohort	2305 pts with first-onset **MI** (median follow-up was 3y)	● Adjusted HRs for **all-cause death** were 1.21 (p=0.338) for intermediate and 1.74 (p=0.003) for low tertile (p-for-trend=0.001) ● Equivalent values for **CV death** were 1.13 (p=0.588) and 1.64 (p=0.022), respectively (p-for-trend=0.009) ● Adjusted HRs per 1-g/dl decrease in albumin levels: 1.66 (p=0.001) for all-cause death, 1.47 (p=0.024) for CV death, and 1.61 (P=0.012) for cardiac death	● 3 groups by albumin tertiles (≤3.62, 3.63-4.08, >4.08 g/dl) / Highest tertile group was used as reference
Wu et al. / 2018 [21]	Prospective cohort	77,531 community-dwelling persons (≥65 y)	Compared to albumin levels ≥4.4 g/dL: ● mildly low albumin levels (4.2-4.3 g/dL) were associated with an increased **all-cause mortality** risk (HR 1.16) (p<0.001), and ● albumin levels <4.2 g/dL were associated with significantly higher rates of all-cause, cancer, **CV**, and respiratory mortalities	● The curve of mortality risk was relatively flat at an albumin level ≥4.4 g/dL, and the mortality risk gradually increased as the albumin level declined ● Albumin levels ≥4.4 g/dL were associated with better survival
Wada et al. / 2018 [32]	Retrospective cohort	1316 pts undergoing first **PCI**	- Reduced serum albumin levels: higher event rate for **MACE** (log-rank, p< 0.0001) -Using the highest tertiles (>4.3 g/dL) as reference, adjusted HRs were: ● 1.97 for albumin levels of <3.9, ● 1.77 for albumin of 3.9-4.0, and ● 1.19 for albumin 4.1-4.3 g/dL	Decreased serum albumin concentration was associated with MACE even after adjusting for other independent variables (HR, 2.21 per 1 g/dL decrease; p=0.001)
Gotsman et al / 2019 [45]	Database cohort study	5779 **HF** pts	● Decreasing quartiles of albumin was significantly associated with **mortality** (HR 5.74 for lowest quartile compared to highest; P<0.001) ● Low albumin conferred higher mortality (P<0.001) ● Decreasing quartiles of albumin were a significant predictor of increased cardiac-related hospitalizations	● 12% of pts had low albumin (<3.5 g/dL) ● A decrease in albumin on follow-up was an independent predictor of increased mortality (HR 2.58, P<0.001)
Ronit et al. / 2020 [30]	Prospective cohort	100,520 persons free of prior CVD	● HR for **CVD** was 1.22 for albumin <35 g/L vs albumin 40-44.9 g/L and 1.23 for each 10 g/L lower plasma albumin -In analyses according to subtypes of CVD events, the HRs for each 10 g/L lower plasma albumin were: ● 1.17 for CAD, ● 1.25 for MI, ● 1.37 for any stroke, and ● 1.46 for ischemic stroke	● Association of plasma albumin with CVD outcome was almost linear ● Adjustments for potential confounders had little influence on the effect estimates ● Additional analysis assessing the association of extreme values with risk of CVD showed an almost linear increase in CVD rate with lower plasma albumin, especially <39 g/L
Shiyovich et al. /2020 [34]	Observational	5449 **PCI** pts	By multivariate analysis, Δalbumin was an independent predictor of long-term **MACE** following PCI (P< 0.001 for all): ● HR 1.4 for Δalbumin of 0-0.5 g/dL ● HR 2.2 for Δalbumin of 0.5-1 g/dL ● HR = 3.8 for Δalbumin of ≥1 g/dL [Δalbumin: changes in albumin]	● Pts with greater Δalbumin were older with higher prevalence of most CV risk factors and comorbidity ● Cumulative MACE rate: 49.5% over a median of 7 y ● MACE rates and rates of all MACE components increased gradually with the increase in Δalbumin
Berkovitch et al. / 2020 [53]	Prospective cohort	2608 **TAVI** pts	Among pts at advanced cardiac damage stage, incorporation of baseline albumin level identified the highest risk group, such that each 1 decrement in albumin levels was associated with a 3-fold increase in **mortality** (HR 2.77, p=0.001)	Evaluation of cardiac damage was based on pre-procedural echocardiographic characteristics
Kiani et al. / 2020 [54]	Registry cohort	36,242 **TAVI** pts	● Indices of frailty (anemia, albumin level, 5-min walk speed) were independently associated with mortality at 1 month and 1 year and provided incremental value in risk stratification for mortality ● Low albumin was the strongest predictor of **all-cause mortality** (HR 1.52)	Those with low albumin and slower walking speed had longer lengths of stay and higher rates of bleeding and readmission (p<0.001)
Kato et al / 2020 [44]	Registry cohort	3160 pts with acute **HF**	Increased albumin levels (n=1083, 34%) conferred a lower 1-year risk for a composite of **all-cause death and hospitalization** vs no increase in albumin levels (n=2077, 66%) (HR 0.78, P=0.0004)	When stratified by quartiles of baseline albumin levels, the favorable effect of increased albumin was stronger in the lower quartiles of albumin levels, but without a significant interaction effect (interaction P = 0.49)
Padkins et al / 2021 [22]	Retrospective cohort	2680 pts admitted to CCU	● Hospital mortality: 16% ● Pts with hypoalbuminemia (<3.5 g/dL) had higher **hospital mortality** (21% vs. 9%,	● Diagnoses included ACS, HF, cardiac arrest, and cardiogenic shock ● Post-discharge mortality was higher in

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Table 2 (*continued*)

First Author/ Year	Type of Study	No of Participants	Results	Comments
			adjusted OR 2.64, p<0.001) ● Albumin level was inversely associated with hospital mortality (adjusted OR 0.60 per 1 g/dL higher albumin level, p <0.001), with a stepwise increase in the hospital mortality at lower albumin levels	hospital survivors with hypoalbuminemia, and increased as a function of lower albumin levels
Shannon et al. / 2021 [24]	Prospective cohort	4947 community-dwelling persons	-1 g/dL lower baseline serum albumin level was associated with higher risk of: ● **Hospitalization** (incidence rate ratio - IRR 1.58; p<0.001) and ● **Death** (HR 1.67; p<0.001)	● Associations were weaker with older age but not different by frailty status or level of high-sensitivity CRP ● Associations between serum albumin, hospitalizations, and death were also similar in a real-world cohort of primary care pts
Zhou et al. / 2021 [70]	Prospective (registry) cohort	13,618 pts with ischemic **stroke** or TIA	● Over 3-months, compared with 40-44.9 g/L albumin group, pts in <35 g/L group had an increased risk of poor **functional outcome** (adjusted OR 1.37); and **mortality** adjusted HR 2.13) ● Also, low serum albumin levels were independently correlated with clinical outcomes at 1 year	● The relationship in per 10 g/L lower albumin with prognosis was consistently inversed (adjusted OR 1.17; adjusted HR 1.86)
Cinier et al. / 2021 [103]	Retrospective cohort	1011 **ICD** pts	● Pts in tertile 3 (T3) for CRP-to-albumin ratio (CAR) had higher risk of **mortality** (4.2 *vs* 11.0 *vs* 28.5%) compared with those in other tertiles ● Multivariable analysis: pts in T2 and in T3 had independently higher risk of all-cause mortality vs those in T1	Tertiles (T) according to mean CAR value: T1 0.20, T2 0.60 and T3 3.40 ● Mean follow-up: 38 months ● Finding was consistent in the unadjusted and adjusted multivariable models
Liu et al. / 2021 [104]	Retrospective cohort	1630 CAD pts after **PCI**	CRP-to-serum albumin ratio (CAR) was an independent predictor of **all-cause mortality** (HR, 2.678; p<0.001) and **cardiac mortality** (HR, 2.055; p=0.034)	● Pts were divided into 2 groups based on the CAR (CAR < 0.186; n = 1301 and CAR ≥ 0.186; n = 329) ● Mean follow-up: 37.6 months
Chahrour et al. / 2021 [63]	Retrospective cohort	35,383 **PAD** pts with lower extremity amputation	-**Mortality** rate: ● 11% in pts with very low albumin <2.5 g/dl ● 6.8% in pts with low albumin 2.5-3.39 g/dl ● 3.9% in pts with normal albumin ≥3.4 g/dl -Multivariable analysis: ● lower albumin levels was a risk-adjusted independent predictor of mortality	-After risk-adjustment, pts with higher mortality vs pts with normal albumin: ● very low albumin levels (adjusted OR 2.25, p<0.001) ● low albumin levels (adjusted OR 1.42, p<0.001) -Sensitivity analysis: a similar trend in pts undergoing above knee amputation but not in pts undergoing minor amputations
Yoshioka et al / 2021 [29]	Retrospective cohort	1424 pts with acute **MI**	● Over a median of 4.1 years, the primary endpoint (composite of **hospitalization for HF and CV death**) occurred in 19% of pts with low (<3.8 g/dL) albumin at 1 year after discharge and 3.3% of pts with normal albumin (adjusted HR 2.76; P=0.007)	● The **all-cause death** rate was 29.7% vs 4.3% (adjusted HR, 4.02; P<0.001) ● The prognostic impact of remote low serum albumin was consistent across albumin status in the acute phase of MI
Kalkan et al. / 2022 [97]	Prospective cohort	4599 **STEMI** pts with PCI	Multivariate analysis showed age (increase 50-67 years; HR 1.34) and uric acid/albumin ratio (UAR) (increase 1.15-1.73; HR: 1.33) were associated with **mortality**	● Median age of pts: 58 years; 78% male ● Mortality in the entire group was 11.9% ● Median follow-up: 42 months
Yoshioka et al / 2022 [39]	Registry cohort	1724 **MI** pts with PCI	● Higher cumulative 3-year incidence of moderate/severe **bleeding** in the low (<3.8 g/100 ml) serum albumin group (30.8% vs 11.9% & 7.7% in the other groups (p<0.001) ● After adjusting for confounders, the low serum albumin group showed excess risk of bleeding events relative to normal serum albumin (HR 1.56; p=0.026)	Other groups: middle serum albumin, 3.8 to 4.1 g/100 ml and; normal serum albumin, ≥4.2 g/100 ml
Meta-Analyses				
Vincent et al / 2003 [85]	90 cohort studies (41 prospective / 45 retrospective / 4 both)	291,433 hospitalized pts	Each 10-g/L decline in serum albumin level significantly raised the odds of: ● **mortality** by 137%, ● **morbidity** by 89%, ● prolonged ICU stay by 28%, ● prolonged hospital stay by 71%, and ● increased resource utilization by 66%	There was a suggestion that complication rates may be reduced at a serum albumin level of >30 g/L, achieved during albumin administration
Cabrerizo et al. / 2015 [86]	9 studies (7 prospective, 2 retrospective)	7280 hospitalized pts / 17857 community dwelling pts	-Elderly living in the community: clear association between albumin levels and **long-term mortality** (at 3-12 years) -Elderly living in care homes: albumin was associated to **short-term mortality** (1 year) but not to long-term mortality	Low levels of albumin were associated with higher mortality during hospital stay
Peng et al. / 2019 [47]	9 (7 retrospective, 2 prospective)	16,763 **HF** pts (7 studies with acute HF, 2 studies with chronic HF)	-*Acute HF* pts with hypoalbuminemia had: ● Increased **in-hospital mortality** (RR 4.90) and ● Increased long-term **all-cause mortality**	The median follow-up duration ranged from 1 to 5 years

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Table 2 (*continued*)

First Author/ Year	Type of Study	No of Participants	Results	Comments
			(RR 1.75) -*Chronic HF* pts with hypoalbuminemia had a: ● 3.5-fold higher risk for long-term all-cause mortality	
Hsieh et al. / 2019 [55]	11 (5 prospective cohort, 6 retrospective cohort)	6456 **TAVI** pts	A low serum albumin level was associated with increased risk of: ● early (≤30 d) **death** following TAVI (HR = 1.16, p=0.005) ● late **mortality** (>30d) following TAVI (HR = 1.10, p=0.002) ● No significant heterogeneity (I^2=0%)	After excluding low-quality studies, low serum albumin was still associated with increased mortality risk (HR = 1.09; p=0.003)
Seidu et al. / 2020 [87]	48 (observational cohort studies)	1,492,237 healthy persons or general populations with both healthy and prevalent cases of CVD at baseline	Multivariable adjusted RRs comparing the top *vs* bottom third of serum albumin levels were: ● 1.03 for T2D; ● 0.60 for **CVD**; ● 0.74 for **CAD**; ● 0.57 for **CAD death**; ● 0.76 for **MI**; ● 0.66 for **all-cause mortality**; ● 0.71 for VTE; ● 0.65 for cancer mortality; and ● 0.62 for fracture	Heterogeneity between contributing studies of T2D was partly explained by sample sizes of studies (p for meta-regression = 0.035)
Liu et al. / 2020 [56]	10 (9 retrospective, 1 prospective)	8,236 **TAVI** pts	Low albumin was significantly associated with a: ● ~two-fold increase in 30-day all-cause mortality (HR, 2.09) and ● 61% increase risk for one-year mortality (HR, 1.61)	● Sensitivity analyses showed the results to be robust ● The association of low albumin level with an increase in one-year mortality risk was not modified by study design, albumin cut-off value, STS-PROM, and study quality
Zhu et al. / 2020 [88]	8 (3 consecutive design, 5 retrospective)	21667 **ACS** pts	ACS pts with low serum albumin level had an increased risk of **all-cause mortality** (RR 2.15) after adjusting for important covariates	Subgroup analysis: impact of low serum albumin level was stronger in hospital mortality (RR 3.09) than long-term all-cause mortality (RR 1.75)
Ronit et al. / 2020 [30]	14 (12 prospective, 2 nested case control)	150,652 individuals free of prior CVD	RR for a **CVD event** per 10 g/L lower plasma albumin: 1.96	Analyses using **CVD mortality** as an outcome gave similar results
Pignatelli et al. / 2020 [89]	15 (11 prospective, 4 retrospective)	65,077 healthy persons and CVD pts	● Persons with serum albumin <3.8 g/dL had a combined HR of 2.16 for **CV events** ● An increased risk for CV events was also evident using serum albumin as a continuous variable (HR=1.89) ● Men and women had a similar risk for CV events (HR 1.46, and HR 2.46, respectively)	Similar risk of CV events between primary and secondary prevention studies (HR 1.79, and HR 2.47, respectively)
Hirata et al. / 2020 [71]	3 (prospective cohort)	1,427 oldest persons (36 >110 y, 572 at 105-109 y, 288 at 100-104 y, and 531 at 85-99 y)	Among other markers (NT-proBNP, IL-6, cystatin C and cholinesterase) associated with all-cause mortality independent of traditional CV risk factors, only low **albumin** was associated with **high mortality** across age groups	During follow-up, 1,000 persons (70%) died
El Iskandarani et al. / 2021 [48]	48 studies (9 prospective, 25 retrospective, 14 secondary analyses of RCTs)	44,048 pts with **HF**	● In 10 studies of acute HF, in-hospital **mortality** was ~4-fold higher in hypoalbuminemia (OR 3.77) ● Hypoalbuminemia was also associated with a significant increase in long-term mortality (OR 1.5), especially at 1-year post-discharge (OR 2.44; I^2 = 11%)	Hypoalbuminemia was found in 32% of HF pts with marked heterogeneity (I^2 = 98%) Pooled AUC (0.73) was comparable to serum BNP in predicting mortality in HF pts

ACHD = adults with congenital heart disease; ACS = acute coronary syndrome; AUC = area under the curve; BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CAD = coronary artery disease; CCU = cardiac care unit; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; ICD = implantable cardioverter defibrillator; IL = interleukin; MACE = major adverse cardiovascular events; MI = myocardial infarction; MR = mortality rate; NYHA = New York Heart Association; OR = odds ratio; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; pts = patients; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; STEMI = ST-elevation myocardial infarction; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality; T2D = type 2 diabetes; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack.

In the same context, a retrospective cohort study of 1630 CAD patients showed that CAR can also independently predict CAD severity and long-term adverse outcomes in CAD patients after PCI [104]. Patients in this study were divided into two groups based on the CAR value (CAR <0.186; n=1301 and CAR ≥0.186; n=329). There were significant differences between the two groups in the incidences of all-cause mortality (P<0.001) and CV mortality (P=0.003). Multivariate regression analyses demonstrated that CAR was an independent predictor of all-cause mortality (HR, 2.678; P<0.001) and CV mortality (HR, 2.055; P=0.034).

9. Albumin supplementation

Hypoalbuminemia may compromise the formation of the endothelial glycocalyx and albumin infusion therapy to replenish albumin may promote maintenance of the glycocalyx layer, mitigate inflammation, and ameliorate alveolar-capillary membrane permeability, as shown in preclinical studies [105]. However, this approach has not lived up to clinical expectations. Although albumin supplementation may be an intuitive and plausible approach, its efficacy has not been established and in patients with hypoalbuminemia, priority is focused on diagnosing

and managing the underlying condition [13,106]. Albumin supplementation remains a costly therapy and should be limited to clinical conditions where its efficacy has been proven, such as treatment or prevention of severe clinical complications in patients with liver cirrhosis with refractory ascites (e.g., hepatorenal syndrome or renal failure after paracentesis of ascites), and fluid resuscitation in critically ill patients (e.g. in the setting of sepsis and septic shock), when crystalloids and other colloids are not effective or contra-indicated [107–110]. Human albumin is also used in spontaneous bacterial peritonitis, and in patients with nephrotic syndrome with serum albumin <2 g/dL, with marked hypovolemia and/or acute pulmonary edema and/or acute renal failure [110]. A recent patient chart review study indicated that albumin was used appropriately in 68%, mostly for sepsis and septic shock, hypovolemia and hypotension; however, there was also a 32% inappropriate use of albumin [109].

As detailed in this review, albumin has pleiotropic physiological activities including antioxidant, anti-inflammatory, and antithrombotic effects and positive effects on vessel wall integrity (Fig. 1) [111,112]. Its administration can promote a negative fluid balance in hypoalbuminemia and in conditions associated with edema. Albumin versus artificial colloid infusion has the potential to preserve renal function in critically ill patients. However, these potential benefits need to be confirmed in clinical studies.

A small study of 12 septic patients with severe hypoalbuminemia showed that albumin supplementation sufficient to nearly double serum concentrations had no clinically significant effect in reducing microvascular permeability [113]. Similarly, albumin replacement to correct hypoalbuminemia in 18 critically ill patients showed no clinical benefit compared to 22 controls [106]. In the same context, a large multicenter, open-label trial, which randomized 1818 patients with severe sepsis to receive either 20% albumin and crystalloid solution or crystalloid solution alone, showed that albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 1 and 3 months [114]. However, a sub-analysis of this trial according to disease severity showed that patients with septic shock randomized to albumin supplementation had a lower risk of death (RR with septic shock 0.87; 95% CI 0.77–0.99; RR without septic shock, 1.13; 95% CI, 0.92 to 1.39) vs those receiving crystalloids alone. Interestingly, albumin was not administered as a resuscitation fluid in this trial, but as an agent to remedy hypoalbuminemia.

A small randomized controlled trial (RCT) examined whether supplementation with oral branched-chain amino acids (BCAAs) improved serum albumin and clinical outcomes in 18 HF patients with hypoalbuminemia (<3.5 g/dL), of whom 9 received oral BCAA granules added to standard therapy for 28 days during their hospital stay or until discharge (BCAA group) and were compared with 9 controls [115]. Sixteen patients completed the study. The mean period of BCAA supplementation was 18.4±8.4 days. Serum albumin significantly increased in the BCAA group (mean difference vs baseline, 0.44 g/dL; P=0.014), while it did not change in controls (0.18 g/dL). The cardiothoracic ratio significantly decreased in the BCAA group only (- 2.3%; P=0.014).

10. Conclusion

Albumin is the most abundant circulating protein in blood, accounting for ~50% of the plasma protein, deemed an essential transport protein which binds and transports various pharmaceutical agents and substances. Most importantly, it maintains the oncotic (colloid-osmotic) pressure of blood and influences the physiological function of the circulatory system, in addition to its antioxidant, anti-inflammatory and antithrombotic properties (Figs. 1 and 2). Evidence has also accumulated and is herein reviewed, that attests to albumin's very important role as a robust predictor of CV risk in several groups of patients, including patients in the general population, patients with CAD, ACS and MI, particularly those undergoing PCI, patients with acute or chronic HF, patients with hypertension, AF, patients with aortic stenosis undergoing TAVI, patients with CHD or endocarditis, and patients with PAD and/or ischemic stroke (Fig. 3). Serum albumin is routinely determined in all hospitalized patients and rightfully so for its robust prognostication value; in those with subnormal albumin levels on admission, repeat measurement is advisable before discharge and later during follow-up; seeking and managing possible underlying etiologic condition(s) is of utmost importance (Table 1). Hypoalbuminemia, ascribed to a variety of causes, is a strong prognosticator of increased all-cause and CV mortality according to several cohort studies and meta-analyses in hospitalized and non-hospitalized patients with or without comorbidities (Table 2). Hypoalbuminemia may also affect the binding and consequently the efficacy and safety of several CV drugs. Normalization of albumin levels before discharge confers lower mortality risk, compared with hypoalbuminemia before discharge. Interestingly, modified forms of albumin, such as the IMA, also bears prognostic value in patients with coronary or peripheral artery disease. When albumin is combined with other risk factors, such as uric acid and CRP, the prognostic value is enhanced when considered jointly as the UAR and CAR.

As hypoalbuminemia may confer several adverse CV effects via various mechanisms, one would expect that albumin infusion therapy might replenish albumin and restore the damage, e.g., by promoting maintenance of the glycocalyx layer, mitigating inflammation, and improving alveolar-capillary membrane permeability, as shown in preclinical studies. However, these expectations have not been realized in clinical studies, except for the treatment or prevention of severe clinical complications in patients with liver cirrhosis with refractory ascites, or critically ill patients in the setting of sepsis and septic shock, when crystalloids and other colloids are not effective or contra-indicated. Human albumin has also benefited patients with spontaneous bacterial peritonitis, and patients with nephrotic syndrome with serum albumin < 2 g/dL, marked hypovolemia and/or acute pulmonary edema and/or acute renal failure. Thus, in the majority of cases with hypoalbuminemia, priority is focused on diagnosing and managing the underlying condition. The CV effects of hypoalbuminemia and relevant issues have been herein reviewed, large cohort studies and meta-analyses are tabulated and the physiologic effects of albumin and the deleterious effects of low albumin are pictorially illustrated.

Declaration of Competing Interest

AAM, TAM, HM and **ASM** have no conflict of interest to declare; **DPM** has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk.

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