Association of Serum Albumin and Mortality Risk

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ABSTRACT. Reduced levels of serum albumin concentration, a routine blood test, within the "normal" range have been reported to be associated with mortality risk. The literature is reviewed, with a focus on cohort studies meeting specified criteria, and findings are summarized. In studies of many populations, comprising healthy subjects and patients with acute or chronic illness, serum albumin concentration is inversely related to mortality risk in a graded manner over its entire range; the estimated increase in the odds of death ranges from 24% to 56% for each 2.5 g/l decrement in serum albumin concentration. The association predicts overall and cause-specific mortality including cardiovascular mortality. It is likely that albumin concentration is a highly sensitive indicator of preclinical disease and disease severity. A direct protective effect of the albumin molecule is suggested by the persistence of the association after adjustment for other known risk factors and preexisting illness, and after exclusion of early mortality. Although biologically plausible, there is no direct evidence for this hypothesis. Serum albumin concentration is an independent predictor of mortality risk and could be useful in the quantification of risk in a broad range of clinical and research settings. J Clin Epidemiol 50;6:693-703, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. Serum albumin, mortality, prognosis

INTRODUCTION

Establishing prognosis is an integral part of medicine. Recent changes in the practice environment have provided impetus to quantify prognosis. One such change is the rationing of health care implicit in diagnosis-related groups and managed care. Another is the realization that the benefit of a therapy is most likely to exceed its cost in money and side effects only in patients at sufficiently high baseline risk [1]. It would be fortunate indeed if a widely applicable prognostic indicator were identified that was inexpensive, easily obtained, and offered graded information over its entire range. The subject of this review is the growing body of evidence that serum albumin concentration may be such an indicator.

METHODS

A computer search of the English-language literature for the years 1980-1996 was obtained to locate studies that quantitatively estimated the relative risk of mortality by serum albumin level. The MeSH headings—predictive value of tests, evaluation studies, risk factors, prognosis, and outcome—were combined with the OR Boolean operator. In addition, the terms survival and mortality were used as MeSH heading fragments to maximize retrieval. The above were combined with the exploded MeSH heading serum albumin and used to search MEDLARS. This search was supplemented by following up on bibliographies of the located studies. The identified studies were systematically evaluated and classified into primary studies [2-11], follow-up reports of primary studies [12-15], and other studies [16-28]. The primary studies are described in Table 1. The criteria for selecting a primary study considered design, sample size, patient population, adjustment for confounders, and appropriateness of modeling assumptions. To assess the impact of serum albumin level on mortality, only cohort studies were used, with the exception of two nested case-control studies. In both nested case-control studies, the exposure variable was gathered prior to the onset of disease [10,11]. Primary studies were at least 500 subjects in size, ranging from a minimum of 609 to a maximum of 17,440, and were based on well-defined groups, which could be easily generalized to target populations. All primary studies cited focused on variation of serum albumin concentration in the normal range, used multivariate models, such as logistic regression or Cox's proportional hazards model to adjust for potential confounders, and considered whether the modeling assumptions were appropriate. The findings of original and follow-up reports were summarized individually. Summarization of data by meta-analysis was unnecessary given the large sum-
TABLE 1. Primary studies of serum albumin and mortality risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (study*)</th>
<th>n</th>
<th>Mean age</th>
<th>Design</th>
<th>Maximum follow-up</th>
<th>Model</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2]</td>
<td>Hemodialysis, prevalent cases</td>
<td>12,099</td>
<td>58</td>
<td>Cohort</td>
<td>1 year</td>
<td>LR</td>
<td>D, C, B</td>
</tr>
<tr>
<td>[5]</td>
<td>Critical care admissions (APACHE III)</td>
<td>17,440</td>
<td>59</td>
<td>Cohort</td>
<td>Hospital discharge</td>
<td>LR</td>
<td>D, C, BP, B, F</td>
</tr>
<tr>
<td>[6]</td>
<td>Middle-aged men (British Regional Heart Study)</td>
<td>7,735</td>
<td>40-59</td>
<td>Cohort</td>
<td>10 years</td>
<td>LR</td>
<td>D, C, B, BP, S</td>
</tr>
<tr>
<td>[7]</td>
<td>National sample, aged 45-74 at entry into NHANES I</td>
<td>5,765</td>
<td>45-74</td>
<td>Cohort</td>
<td>16 years</td>
<td>Cox</td>
<td>D, C, B, BP, S</td>
</tr>
<tr>
<td>[8]</td>
<td>Community (Rancho Bernardo)</td>
<td>2,342</td>
<td>50-89</td>
<td>Cohort</td>
<td>3 years</td>
<td>LR</td>
<td>D, C, A, S, F</td>
</tr>
<tr>
<td>[9]</td>
<td>Community elderly (EPESE)</td>
<td>4,116</td>
<td>79</td>
<td>Cohort</td>
<td>5 years</td>
<td>Cox</td>
<td>Age, C, S, F, W</td>
</tr>
<tr>
<td>[10]</td>
<td>Professional and business-man (BUPA)</td>
<td>1,754</td>
<td>54</td>
<td>Nested case-control</td>
<td>10 years</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>[11]</td>
<td>Middle-aged men with increased cardiac risk (MRFIT)</td>
<td>609</td>
<td>47</td>
<td>Nested case-control</td>
<td>10½ years</td>
<td>LR</td>
<td>Age, BP, B, S</td>
</tr>
</tbody>
</table>

Abbreviations: LR = multiple logistic regression; Cox = Cox's proportional hazards model; B = serum biochemistry; C = clinical diagnoses; D = demographics (age, gender, race, education); BP = blood pressure; A = alcohol; S = smoking; F = functional state/activity; R = renal function; W = weight.

*Study acronyms are explained in the text.

ple sizes and similarity of individual study results, and, in any event, would have required several assumptions (i.e., homogeneity of study design, cohorts, definitions, measurements, and case finding) which are problematic for observational studies [29]. In addition to the primary studies, other published reports that examined serum albumin and risk in small specialized groups, or used only univariate methods or retrospective design, are cited for their concordance with the results of the primary studies.

SERUM ALBUMIN IN DISEASE

In populations with disease, the quantitative relationship of serum albumin with mortality and morbidity has been demonstrated in four primary studies [2–5] and numerous other studies of populations with disease [16–28]. In no other setting has the predictive value of serum albumin been so strongly embraced as in the care of patients with end-stage renal disease; indeed, the Health Care Financing Administration established serum albumin concentration as a quality assurance criterion for dialysis facilities [30]. Serum albumin concentration is used as a marker of visceral protein status [31]. Although accelerated coronary disease had traditionally been perceived as the greatest threat to survival in end-stage renal disease [32], recent studies consistently have found the strongest predictors of the survival of dialysis patients are measures of their visceral and somatic protein status, rather than of atherogenic risk [2,3,16]. Thus, survival on dialysis correlates directly and independently with the serum concentrations of albumin, creatinine, and, ironically, cholesterol. When many clinical and biochemical predictors of survival are examined as candidate predictors, in univariate or multivariate analyses, serum albumin concentration is generally found to be the most important prognostic factor. The relationship of serum albumin to survival is graded and extends to values in the normal range. This was first reported by Lowrie and Lew [2] in a pioneering study of 1-year survival in more than 12,000 established hemodialysis patients. The study used multiple logistic regression to adjust for age, race, gender, diabetes, cause and duration of end-stage renal disease, and the serum concentrations of urea, creatinine, cholesterol, potassium, and other routine blood measurements. The odds of death increased by 56% for each 2.5 g/l decrement in serum albumin. Figure 1 shows the odds ratios for albumin treated as a categorical variable adjusted for the same covariates. The albumin value used as a predictor in this study was an average of up to 18 monthly measurements starting 6 months before the study up to the end of the time at risk. By including values measured during the time at risk—including antemortem values—in the calculation of “baseline” serum albumin, this approach may have exaggerated the association, because serum albumin often declines significantly just before death. However, the authors confirmed the strength of the association in a later study of 6-month survival in 13,473 hemodialysis patients which used logistic regression to adjust for age, gender, race, diabetes, renal diagnosis, and dialysis dose [12]. Average monthly serum albumins (over
FIGURE 1. Risk of 1-year mortality by serum albumin in hemodialysis. Bars represent odds ratios determined by multiple logistic regression (covariates are specified in the text). Compared to the reference category (41–45 g/l), the risk of death is significantly greater ($p < 0.05$) for each group with a lower serum albumin value. (Adapted from [2]).

the 4 months prior to the time at risk) strongly predicted survival over the next 6 months. The odds of death increased by 43% for each 2.5 g/l decrement in baseline albumin. Other studies reported that even single determinations of albumin concentration predict survival in end-stage renal patients for up to several years [3,16]. The United States Renal Data System (USRDS) Case Mix Study found that initial serum albumin predicted survival in 3399 incident hemodialysis patients followed for up to 4½ years adjusting for comorbid conditions [13]. They used the Cox proportional hazards model to adjust for the presence of coronary disease, heart failure, neoplasm history, diabetes, and active smoking. Whether the relationship persists after adjustment for the severity of comorbid conditions has not been reported.

Variation in albumin concentration may reflect variation in nutritional state in dialysis patients, at nutritional risk from anorexia, dialytic losses of amino acids and proteins, acidosis, and resistance to anabolic hormones such as insulin and growth hormone [16,33]. Given this risk, it is logical but potentially expensive to try parenteral nutritional therapy in this population. The level of albumin may predict the response to nutritional therapy. One large retrospective study found that intradialytic parenteral nutrition was associated with improved survival only in patients with serum albumin below 30 g/l [34].

The relationship of albumin to survival in renal transplant patients was shown by Guijarro et al. [4]. Using the Cox proportional hazards model, they analyzed the survival of a cohort of 706 transplant recipients receiving grafts between 1976 and 1991 who survived at least 6 months and were followed for up to 19 years (mean follow-up 7 years). Serum albumin was measured at 3 months, 6 months, 1 year, and annually thereafter and was modeled as a time-averaged time-dependent covariate. For each 2.5 g/l decrement in serum albumin, mortality risk increased by 40%, adjusting for age, diabetic nephropathy, chronic diseases, high-density lipoprotein-cholesterol, renal function, and prednisone dose. In a Kaplan-Meier analysis, the association between albumin level and mortality persisted even when deaths occurring up to 10 years after the measurement were excluded.

Serum albumin level has been found to be an independent predictor of survival in critical care. The APACHE (Acute Physiology and Chronic Health Evaluation) prognostic schemes have been at the forefront in risk assessment in critically ill patients [5,35]. These multivariate logistic models quantify risk by assessing the presence and severity of a broad range of physiologic disturbances and comorbid conditions. The second version, APACHE II, did not include albumin concentration as an independent predictor. Some have found APACHE II poorly predictive in hypoalbuminemic patients [36]. Based on a prospective study of 17,440 admissions to intensive care units, serum albumin was included for the first time in the latest version (APACHE III) which was significantly more predictive [5].

The association of low serum albumin with a poor prognosis has been reported in a variety of generally small-scale studies in acute and chronic settings, including the postop.
erative period [17,18], geriatrics [17,19–21], hip fracture [22], and cancer [23–26]. In one of the largest such studies, Herrmann et al. [27] retrospectively analyzed the outcomes of 15,511 patients consecutively admitted to Beth Israel Hospital who were over the age of 40 and had serum albumin measured within the first 48 hours. This group comprised roughly one-half of all hospital admissions. (Excluded were another 15,478 patients admitted concurrently but without serum albumin determinations in the first 48 hours.) Age-adjusted mortality and length of stay were each strongly and inversely correlated with initial albumin level. The independent predictive value of serum albumin was demonstrated by using multiple logistic regression with stepwise variable selection to adjust for age, gender, hematocrit, and the concentrations of sodium, potassium, and calcium. Adjusting for these factors, the odds of death rose by 39% and odds of a hospital stay lasting over 10 days by 16% for each 2.5 g/l reduction in initial serum albumin. Although the models did not adjust for potential confounding by comorbidity or severity of illness (e.g., acute vs. elective admission), serum albumin remained predictive within acute diagnoses. For example, in patients with myocardial infarction, each 2.5 g/l decrement in albumin was associated with an 18% increase in the odds of death. Because serum albumin was not obtained randomly, the findings of this study cannot be generalized to all admissions. In fact, serum albumin was not determined during the initial 48 hours in half the patients, a group that was significantly younger and included a higher proportion of elective admissions than the study cohort. Obviously, the omission of these cases raises the possibility of biased selection. Since the excluded patients had a lower mortality rate (7% vs. 6%, $p < 10^{-11}$) and, probably, a higher mean serum albumin concentration, it is likely that the relationship between mortality and albumin level would have persisted even if these cases were included in the study. In a similar study from the Cooperative Cardiovascular Project, serum albumin below 30 g/l on hospital admission increased the odds of 30-day mortality after acute myocardial infarction by 62% (compared to higher or missing albumin values) in a cohort of 14,581 elderly patients [28]. By multiple logistic regression, the effect of albumin was independent of a broad range of other risk factors including age, heart failure, vital signs, renal function, electrocardiographic abnormalities, functional status, and cancer history. However, only 69% of the cohort had albumin measurements. Since the group with missing values was not chosen randomly, again, generalizability and selection bias are potential problems.

**SERUM ALBUMIN IN THE GENERAL POPULATION**

Six primary studies of adequate design have recently tested the value of serum albumin as a predictor of survival in the general population [6–11]. Although the association had been noted in the past, the current interest in this area was kindled by a “serendipitous” finding in the British Regional Heart Study reported by Phillips et al. in 1989 [6,37]. In this prospective study of 7735 men followed for 8 to 10 years (after a baseline interview and multiphasic screen), decrements in albumin level within the normal range were correlated with increasing mortality. Using multiple logistic regression, the relationship was shown to be independent of age, social class, residence, smoking intensity, systolic blood pressure, serum levels of cholesterol and calcium, forced expiratory volume (FEV1), and preexisting disease (Fig. 2). For each 2.55 g/l decrement in serum albumin, the odds of death rose by 47%. Similar trends were found for cardiovascular, cancer, and other deaths examined separately. The trends for total and cause-specific mortality persisted even after excluding death during the first 5 years of follow-up. This diminishes the likelihood that the association is largely due to preclinical disease.

The above finding was confirmed in the National and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study which examined overall mortality in 5765 men and women 45 to 74 years of age followed for 9 to 16 years [7]. Overall mortality was inversely correlated to albumin concentration, stratified into tertiles, <42, 42–44, and >44 g/l. This study used the Cox proportional hazards model with adjustment for age, smoking, systolic pressure, diabetic status, serum cholesterol, and education. The relationship of albumin to risk persisted even after excluding deaths occurring in the first 5 years of follow-up.

The association was also confirmed in two older cohorts [8,9]. The Rancho Bernardo Heart and Chronic Disease study prospectively tested the predictive value of serum albumin in a community-based cohort of 2342 subjects aged 50–89 without overt malnutrition followed for 3 years [8]. Adjusting for age, gender, alcohol, tobacco, and exercise, there was a 24% increase in the odds of death for each 2.5 g/l decrement in albumin. The trends were similar when patients with and without prior disease were examined separately. The National Institute on Aging made similar findings in their prospective study of the relationship of serum albumin and 5-year survival in a community-based cohort of 4116 elderly subjects with mean age of 78 (The Established Population for the Epidemiologic Study of the Elderly [EPESE]) [9]. There was a graded increase in risk with decreasing albumin concentration within the normal range which was not affected by adjustment for age, race, education, smoking, body mass index, functional status, and comorbid conditions (cancer, diabetes, myocardial infarction, stroke, anemia, serum creatinine above 0.13 mM [1.5 mg/dl], and prior hip fracture). The relative risks stratified by gender are shown in Table 2. For the 2630 women, the effect of albumin persisted ($p < 0.05$) even if deaths in the first year were excluded, for 1486 men, the effect of albumin <35 g/l weakened after the first year, but the effect of the other levels persisted ($p < 0.05$) (Fig. 3).
Albumin and Mortality

Only one primary study did not find a significant relationship between albumin concentration and 10-year mortality, in a nested case-control analysis of 877 men who died and 877 age-matched controls derived from the British United Provident Association (BUPA) cohort of employed men aged 35–64 [10]. The authors suggested that the relationship is less likely to be observed in a healthy worker cohort, which is less subject to confounding by social class and chronic illness than a community-based cohort. The samples of cases and controls selected were clearly atypical, however, in that there was no association between smoking and mortality; in fact, nonsmokers had a 92% increase in their odds of death (p < 10⁻⁵).

**CARDIOVASCULAR MORTALITY**

The association of albumin level with lower cardiovascular mortality in the British Regional Heart cohort, reported by Phillips et al. [6], first raised the intriguing question of whether albumin concentration is a cardiovascular protective factor. In a nested case-control study, Kuller et al. [11] tested this relation in 609 men enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) using stored frozen sera collected at baseline. A significant linear trend was found between decrement in serum albumin and odds of fatal coronary events (p < 0.01) or combined fatal and nonfatal coronary events (p < 0.01; Fig. 4), 7 to 10 years after enrollment, in analyses that adjusted for age, diastolic blood pressure, smoking, and serum cholesterol. The period of 7 to 10 years was used because most stored sera of men with earlier deaths had already been used for other studies. Coincidentally, this circumstance reduces the likelihood that preclinical disease is responsible for this finding.

The NHANES I Epidemiologic Follow-up Study, cited in the previous section, also examined cause-specific mortality [7]. Cardiovascular mortality and noncardiovascular mortality were each inversely correlated to albumin concentration, stratified into tertiles, <42, 42–44, and >44 g/l, adjusting for age, smoking, systolic pressure, diabetic status, serum cholesterol, and education. Coronary mortality, ex...
examined in age-gender-race subgroups, was inversely related to albumin concentration in white men aged 45–64, but not aged 65–74, while in white women a trend to reduced risk was observed in both age ranges but was not significant; (there were too few black subjects for subgroup analysis). In a subsequent analysis of the NHANES I cohort (that adjusted for all the previous covariates as well as hemoglobin, body mass index, and cardiac history), stroke incidence and stroke death were 30% to 50% lower in the highest albumin tertile compared to the lowest tertile [13].

In the EPESE cohort, cited above, the relationship between albumin concentration and overall risk (Table 2, Fig. 3) persisted for specific causes of mortality examined separately (circulatory, cancer, respiratory, and other) [9]. In a follow-up analysis, the relationship of serum albumin to coronary disease was examined in this elderly population, excluding deaths during the first year of follow-up, adjusting for blood pressure, lipids, alcohol, and the previously noted covariates [14]. Increasing albumin was associated with a graded decrease in risk of coronary death and of incident events in the women, but not in the men studied. The authors could not propose a pathophysiologic reason for this difference, and speculated that the high absolute mortality rate observed in the reference group among the men may...
Albumin and Mortality

FIGURE 4. Risk of late fatal and nonfatal coronary events in MRFIT study by serum albumin <44 g/l (n = 218), 44–45 g/l (n = 120), 46–47 g/l (n = 90), and >47 g/l (n = 131). Bars represent odds ratios determined by multiple logistic regression (covariates listed in the text); p < 0.01 for linear trend. (Adapted from [11].)

have contributed to a blunting of the calculated relative risk for albumin in men. The influence of gender on the albumin–coronary risk relationship was similar in the NHANES I cohort [7]. Although the apparent interaction of albumin level with gender is not readily explained biologically, that albumin is predictive at all is remarkable given the failure of an established coronary risk factor such as cholesterol to be predictive in the elderly [38].

In renal transplant patients, serum albumin predicted both cardiovascular death (37% risk increase per 2.5 g/l decrement) and noncardiovascular death (51% increase per 2.5 g/l decrement), in the study by Guijarro [4] cited above. In these patients, serum albumin was also an independent predictor of combined morbidity and mortality due to cerebrovascular disease and due to peripheral vascular disease, adjusting for diabetes, smoking, pretransplant vascular diseases, and other significant covariates [15]. Albumin also predicted combined morbidity and mortality from ischemic heart disease independently of diabetes and high-density lipoprotein-cholesterol, but not after adjustment for age [15].

EPIDEMIOLOGIC BASIS FOR THE ASSOCIATION

Is the graded association between serum albumin concentration and mortality due to the association of albumin with other confounding variables which are, in fact, increasing mortality (Fig. 5)? In considering this question, it is important to first review the factors known to result in variation in serum albumin. The serum concentration of albumin is principally related to the rates of albumin synthesis and catabolism (each approximately 12 to 15 grams/day [39–41]), but it is also influenced by lymphatic return, state of hydration, rates of transcapillary escape, and external losses (e.g., nephrotic syndrome, burns) [42]. In starvation, both synthesis and catabolism fall [39]. In nephrotic syndrome, synthesis rises and catabolism tends to fall [41,43]. Albumin synthesis is believed to be regulated by hepatic interstitial oncotic pressure [39,40,44]. Cytokines and acidosis can depress albumin synthesis, which may be of clinical relevance [45,46]. The usual half-life of albumin is 20 days [39]. Transcapillary escape of intravascular albumin, normally 4%/hour, reflects capillary hemodynamics and permeability; increased rates are associated with injury, disease, and chronic cigarette smoking [40,43,47,48].

The measurement of serum albumin is sensitive to methodology [49]. Bromcresol green, the usual method, tends to overestimate ALB because interference by acute phase reactants, serum globulins that are elevated in patients with inflammation [49–51]. The bromcresol purple method, by contrast, is in good agreement with immunological methods such as immunonephelometry [49,52–54]. The positive interference with bromcresol green is dependent on reaction time and temperature, parameters which vary by laboratory [50,55]. The absolute overestimate is generally reported to be greater for albumin concentrations in the low range (<25 g/l [56], <30 g/l [57], <35 g/l [58]), since such patients often have elevated globulins. Although this bias may not be important to the study of healthy populations, it may result in the "misclassification" of high-risk patients with low serum albumin and inflammatory disease as having higher serum albumin, resulting in an exaggeration of slope of the albumin-risk curve. In dialysis patients, the dye assays have significantly different performance. Although there are some discordant reports, in general, bromcresol green is in closer agreement with immunological methods [30,52], whereas bromcresol purple underestimates serum albumin in dialysis patients [53,55,59]. The explanation, at least in the case of bromcresol purple, is probably that uremic li-
gands interfere with the binding of albumin to the dye molecule [59]. If lesser degrees of renal failure also depress the apparent concentration of serum albumin by the dye methods [60], then variations in renal function in a population or individual would result in spurious variation in albumin level.

In fact, only a small part of the variation of albumin concentration can be explained. In a multivariate model of serum albumin in the EPESE cohort, higher albumin was independently associated with younger age, living alone, no activity of daily living limitations, not smoking or smoking less than one pack per day, living in the community, no history of prior hospitalization in the past year or of prior hip fracture or cancer, and absence of anemia [61]. However, the model explained only 16% of the variance in albumin concentration. The effect of age was slight. Adjusting for covariates, serum albumin decreased by 0.8 g/l for each decade increment in age in this elderly group. The age-related decline in serum albumin, found in numerous studies, may be intrinsic to aging or the indirect result of the decline in dietary intake and rise in comorbidity that often accompany aging [62]. In a study of community-dwelling elderly free of wasting illnesses, Sahyoun et al. [21] confirmed the independent correlation of albumin with age, functional state, and hematocrit, and, in addition, found it was independently associated with serum cholesterol, serum prealbumin, and less than two alcoholic drinks per week. A correlation between albumin and hematocrit has also been reported in young adults [63]. Phillips et al. [6] reported that, in middle-aged men, serum albumin decreased with age, cigarette smoking, and prior disease and was directly correlated with serum cholesterol, forced expiratory volume (FEV1), and social class. In dialysis patients, serum albumin, a marker of visceral protein status, correlates directly with serum cholesterol and prealbumin (both visceral protein markers), serum urea (reflecting recent protein intake), and hematocrit, and inversely with age [64–66]. It has generally not been found to correlate with either hemodialysis dose or dietary protein intake [12,16], although, in two recent smaller studies [66,67] a direct correlation with dialysis dose was found.

In addition to indicating a reduced visceral protein state, decrements in serum albumin appear to be accompanied by musculoskeletal frailty and susceptibility to injury. In hemodialysis patients, serum albumin correlates with serum creatinine, a somatic protein (muscle) marker [64,65]. In a study of ambulatory elderly subjects free of obvious inflammatory disease, serum albumin correlated directly with muscle mass (by dual-energy X-ray absorptiometry), adjusting for age, dietary protein, and comorbidity [68]. In a prospective study of white women 45 years and older participating in the NHANES I study, serum albumin level correlated inversely with the risk of hip fracture, compatible with the clinical observation that poor nutritional status is prevalent in patients presenting with hip fracture [69].

The association between albumin level and mortality may be noncausal and entirely explained by confounding of factors that influence both serum albumin and mortality risk (arrows b and c in Fig. 5). Even after adjusting for potential confounders such as disease, there can still be residual confounding. Disease, by inducing anorexia and malnutrition, can result in reduction in serum albumin [31]. This reduction may vary with disease progression—from preclinical to end stage. If a known disease is categorized as a binary variable in a predictive model, without regard to severity, then risk which is actually associated with disease severity (arrow c in Fig. 5) may mistakenly be attributed to albumin. Elevation of cytokines represents another potential mechanism through which disease severity, including preclinical disease, could confound the relationship between serum albumin and mortality. Cytokines, such as tumor necrosis factor and interleukin-1, are involved in the pathogenesis of many disease states [70,71], and can depress serum albumin concentrations (by modulating albumin gene expression, catabolism, and transcapillary escape [40,46,72,73]). Although cytokines are known primarily as mediators of inflammation, their levels are elevated in disease processes without obvious inflammation, such as congestive heart failure and atherogenesis [74,75]. The cytokines tumor necrosis factor and interleukin-1 may have an active role in atherogenesis, for example, by influencing endothelial activation and vascular smooth muscle proliferation [75]. Another potential source of residual confounding is grouping of smoking and alcohol intake into binary variables or any broad categories that do not take into account the intensity of smoking and/or alcohol intake, since intensity may accelerate the reduction of albumin.

**POTENTIAL BIOLOGICAL MECHANISMS**

A direct protective effect of serum albumin (arrow a in Fig. 5) is possible based on a variety of biological mechanisms. Albumin is the quantitatively most important source of thiol in plasma [76,77]. This thiol group can bind covalently to nitric oxide and protect it from degradation. Infusion of nitrosylated albumin has a vasodilatory effect comparable in magnitude to infused nitric oxide, but with a longer duration of effect. Thus, albumin is a potential nitrosodilator and, hence, could modulate coronary disease and other vascular processes. A recent in vitro observation supports a direct protective effect of albumin on vascular endothelial cells, a cell type having specific albumin receptors [78]. Increasing the concentration of albumin in the medium of cultured human endothelial cells was associated with increased protection from apoptotic cell death, with peak protection at physiologic concentrations [78]. Another potentially important protective effect of serum albumin is enhancement of removal of reactive oxygen species, which are implicated in the pathogenesis of many diseases such as atherosclerosis, cancer, and ischemia/reperfusion injury.
There is now evidence that albumin is, in fact, a significant antioxidant in blood and extracellular fluids. Albumin may also be directly beneficial by increasing the capacity of the serum to bind potential toxins and improved wound healing and bowel function. The association of albumin level and mortality meets the causal criteria of temporal sequence, reproducibility, strength of association, dose-response relation, and biological plausibility. However, a critical gap in establishing a causal relation is the absence of evidence from clinical trials. Raising albumin concentration by the administration of exogenous albumin did not improve the outcome in a series of small randomized trials in critically ill hypoalbuminemic patients. This does not, however, exclude the possibility that the association between decrements in serum albumin and poor outcome is causal. In an acute and complex pathophysiologic setting, interruption of a single disease pathway may not be sufficient to improve outcome. Moreover, it may be irrelevant in the acute setting to reverse a factor that operates on a chronic time frame, just as acute cholesterol reduction will not benefit an acute myocardial infarction. Nonetheless, much work remains in establishing a cause and effect relationship between serum albumin and mortality.

CONCLUSIONS

In 10 studies of large size and adequate design, mortality was predicted by serum albumin concentration across a broad range of serum values in populations with and without disease. In the studies that treated albumin as a continuous variable, the estimated increase in risk for each 2.5 g/l decrement in albumin ranged from 24% to 56%. The association between decrements in albumin concentration and mortality may be due to confounding by comorbidity. However, since the association persisted in populations without prior illness and after exclusion of early mortality, it is unlikely that more complete adjustment for the severity of comorbid conditions would eliminate the association. Albumin concentration may be a highly sensitive measure of disease severity or presence (e.g., as an indicator of cytokine levels) not reflected by the usual, more specific clinical tests. Although biologically plausible, there is no evidence that the albumin molecule itself mediates the association.

Serum albumin level could be utilized in observational studies and clinical trials to better quantify baseline risk. In patients with systemic diseases associated with visceral protein depletion, nutritional therapy and anabolic strategies status should be studied together with disease-specific therapy. As a corollary, the resistance of low serum albumin to attempts to raise it may indicate even worse prognosis. The clinician needs to be mindful that variations of albumin concentration within the “normal” range are relevant to prognosis and may reflect a preclinical condition or worsening of a known disorder, as well as primary or secondary malnutrition. The paucity of randomized trials to assess the efficacy of specific nutritional interventions limits the options available to the clinician. Future studies will determine whether serum albumin proves to be simply a marker of overall health status or a target for therapy similar to blood pressure, cholesterol, and obesity.

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References


