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Serum Albumin and Short-Term Risk for Mortality and Cardiovascular
Disease among HIV-Infected Veterans

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A thesis submitted in partial satisfaction of the requirements for the
degree of Master of Science in Health and Medical Sciences in the
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Abstract

Serum Albumin and Short-Term Risk for Mortality and Cardiovascular Disease among HIV-Infected Veterans

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Objective: We examined the short-term and long-term associations of serum albumin with mortality and cardiovascular disease among HIV-infected veterans.

Design: Retrospective cohort analysis using a national database of U.S. veterans with HIV infection.

Methods: This analysis evaluated all HIV-infected veterans in the Department of Veterans Affairs HIV Clinical Case Registry (CCR), a national database comprised of demographic, clinical, laboratory, pharmaceutical, and viral status data. There were 25 522 patients enrolled between 1986 and 2007. We evaluated the associations of baseline and time-updated serum albumin levels with all-cause mortality, atherosclerotic cardiovascular disease, and heart failure by multivariate proportional hazards models.

Results: Over 21 years, there were 10 869 deaths; the cumulative mortality was 73.2 per 1000 person-years. After multivariate adjustment for covariates measured at baseline, the lowest category of serum albumin (<2.5g/L) was associated with a higher mortality risk compared with the highest category (>4g/L) (Hazard Ratio 3.00; 2.67– 3.37). However, when analyzed as a time-dependent model, the association strengthened substantially (15.1; 14.0–16.4). Findings were similar for atherosclerotic cardiovascular disease and heart failure. We stratified the baseline mortality model by year of follow up and found that albumin was more strongly associated with deaths that occurred within one year of baseline (9.29; 7.85–11.0) than in the second (1.66; 1.18– 2.33) or third (1.22; 0.77–1.96) year after measurement.

Conclusions: Among ambulatory HIV-infected patients, lower serum albumin levels are strongly predictive of mortality risk, particularly within one year.

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Part 1: Serum Albumin, Inflammation, and Adverse Outcomes in HIV-Infected Individuals

“What happened to these patients such that something as seemingly routine as scrofula made them ill enough to be admitted to hospital? In a word, inflammation. Once the John Wayne of the human immune response—the beneficent tough guy who came in and cleaned up the mess, whatever it was, with no consequences to the neighbours—inflammation is now better known for the problems it can create.” (1)

The advances over the last 20 years in the treatment of HIV infection have led to an increasing lifespan for those living with the virus, shifting the prognosis of HIV infection from a near certain death sentence to that of a chronic and manageable disease. Anomalous and surprising case studies, such as the “Berlin Patient” and “Mississippi Baby”, have even given rise to the hope of a cure (2) (3). However, while awaiting a definitive and replicable cure, a new model of medical management must be elucidated for those living with the health effects of chronic HIV infection. The most up-to-date therapies provide control of viral replication levels, thus preventing the depletion of immune cells and the concomitant progression to AIDS. Yet these benefits have unmasked a myriad of new challenges, a slew of non-AIDS or HIV-related morbidities and diseases. In turn, clinicians and researchers must address how these complications of chronic infection should be prevented, diagnosed, and managed. Research from other chronic infections and populations may provide insight in this emerging field of inquiry. Serum albumin measurements have proved valuable as a prognostic tool across numerous populations and disease states. This review aims to cover three overlapping concepts: the complications associated with chronic HIV-infection; chronic infections and populations with direct relevance to the HIV-infected population; and the markers of disease status and progression in HIV-infected individuals, with particular attention to serum albumin as a prognostic indicator. In so doing, this review will demonstrate the gaps in the literature assessing the short-term predictive value of serum albumin in discriminating risk for HIV-infected individuals. It seems possible that serum albumin may be an important marker of health status in this population.

The advent of combination therapies resulted in dramatic reductions in mortality and AIDS-associated opportunistic infections (4). Death rates had been climbing for years, and thus the effectiveness of the therapies released in 1996 marked the beginning of a new era (5); the rate of hospitalizations and opportunistic infections continued to decline in the years following (6). Advances in the treatment of HIV have led to direct improvement in the lifespan of HIV-infected individuals. Approximately 18% of new diagnoses of AIDS occurred in individuals older than 50 years of age; at the same time, mortality remains much higher in this population than in its non-infected counterpart (7).

The emerging causes of mortality have little association with HIV-related opportunistic infections or morbidities. The first reports of non-AIDS-related coronary artery disease occurred not long after the advent of combination antiviral therapies (8). While cardiovascular disease has been the most studied complication of chronic HIV infection, a myriad of other disorders has also appeared in this population: cancer, including lymphoma and liver cancer caused by hepatitis C; frailty, as defined by sarcopenia, osteoporosis and muscle weakness; liver kidney, cardiovascular and bone disease; neurological complications, especially dementia; and aging of the immune system, otherwise called immunosenescence (9). Taken together, the constellation of age-related disorders appearing earlier than expected in HIV-infected individuals has been called “the accelerated aging of HIV.”

The mechanisms of these processes are poorly understood. With cardiovascular disease, it is recognized that HIV-infected persons have higher rates of behavioral risk factors (10); abacavir and other protease inhibitors have also been implicated in the pathogenesis of cardiovascular disease (11), while other antivirals have been associated with protective changes in the

endothelium (12). The episodic treatment of HIV with antivirals aimed at lowering the cardiovascular complications showed no benefit over continuous treatment (13). To complicate the scenario, emerging evidence suggests that traditional risk factors and the toxicity of antivirals do not alone account for the increased rates of age-related illnesses (9). The strongest alternative mechanism for these processes is inflammation (9). In fact, the association between inflammation and chronic HIV infection has been recognized since the introduction of combination HIV treatments (1). Numerous studies have documented increased levels of inflammation in HIV-infected individuals, evidenced by elevated levels of C Reactive Protein (CRP) and Interleukin 6 (IL-6) (14) (15) (16) (17).

Claudio Franceschi and colleagues coined the term “inflamm-aging” to describe the state of chronic inflammation that accompanies old age (18). This disease state is the proposed mechanism by which elders’ organ function slowly deteriorates over time. Antigens continually test the body’s immune response, leading to a hyperactive and dysfunctional immune response resulting in tissue damage. Numerous disorders have been linked to inflammation associated with increased age, including Alzheimer’s disease, Parkinson’s disease, atherosclerosis, type 2 diabetes, sarcopenia, osteoporosis, cognitive decline, and frailty (19) (20) (21).

In elderly populations various markers of inflammation have been important in discriminating risk for adverse events. High CRP and fibrinogen levels have been associated with near-term death in a cohort of 5,828 elderly men (22); similarly, Harris et al demonstrated a 2.6-fold risk for death in elders with elevated levels of CRP and IL-6 (23); IL-6 alone aided in the stratification of risk for cardiovascular disease and death in a cohort of 620 older women (24). Genetic predisposition for elevated levels of IL-6 may negatively influence longevity, especially in men (25). The importance of inflammatory biomarkers, including CRP and IL-6, has been documented in the detection and risk stratification of heart failure for over 60 years (26).

IL-6 and CRP are rarely used laboratory tests in the clinical setting. However, IL-6, among other inflammatory cytokines, induces what is called the acute-phase response in the setting of inflammation. The acute phase response is a heterogeneous confluence of physiologic processes in which the body responds to several stimuli including infectious agents and tissue damage. Numerous measureable biomarkers are involved in this process, thus providing useful tools for the diagnosis and management of individuals with either chronic or acute inflammation. CRP is one protein induced during the acute phase response. Other protein factors whose blood levels increase during the acute-phase response include: complement, coagulation and fibrinolytic factors, antiproteases, transport proteins (e.g. ceruloplasmin, haptoglobin, hemopexin), granulocyte colony-stimulating factor, ferritin, angiotensinogen, among many others. Other proteins decrease during the acute-phase; these include: albumin, transferrin, factor XII, among others (27). Perhaps the most widely used clinical assays for the acute-phase response are CRP and erythrocyte sedimentation rate. Less commonly associated with the acute-phase response is serum albumin, which has traditionally been more associated with nutrition status, liver or renal disease. Nonetheless, decreased levels of serum albumin are a strong marker of an inflammatory state. In the setting of inflammation, levels will decrease by approximately 25% (27).

In 1989 Phillips and colleagues conducted the first study documenting the powerful ability of serum albumin to predict adverse outcomes. They used data from a prospective cohort of 7,735

middle-aged British men. “When serum albumin concentration was less than 40g/L, the mortality rate was 23/1000 per year compared with 4/1000 per year for a concentration equal to or above 48g/L. A similar pattern was observed for cardiovascular, cancer, and other deaths” (28). In the ensuing years additional studies documented the same associations across various populations and for multiple outcomes. The association between decreased levels of serum albumin and cardiovascular disease, for instance, was documented across several studies (29), with lower levels of serum albumin at least doubling the risk of adverse events (30). The predictive value of serum albumin may increase with older populations (31). Serum albumin levels have also been associated with heart failure (32). These observations led researchers to investigate whether or not serum albumin had a protective quality in preventing these outcomes; however, when studied, the administration of serum albumin to patients with hypoalbuminemia appeared to have no effect, suggesting that the decreased levels represented a serious disease state rather than a causal pathway (33). The study of serum albumin and adverse outcomes spans numerous other disease states and populations and is beyond the scope of this review. One population, however, where albumin has had limited investigation is in HIV-infected individuals.

The standard biomarkers of HIV disease severity and progression are viral load and CD4 count. The incidence of non-AIDS related morbidity and mortality is strongly associated with both of these measures (34); these trends appear to be graded and consistent across multiple levels of decreased concentrations (i.e., a “concentration-response”), aiding in the prediction of neoplasms, kidney disease, and mortality. However, CD4 count alone does not appear to capture and stratify risk entirely. For instance, CD4 count and viral load appear to be less useful in the prediction of cardiovascular disease outcomes. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group was a prospective observational study with 23,468 participants from 11 individual cohorts, with data collected between December 1999 and February 2002. The main purpose of this study was to investigate the associations between HIV medications and adverse outcomes, especially cardiovascular disease. At the same time, the researchers assessed the associations between other traditional risk factors and biomarkers and adverse outcomes. Age, gender, total cholesterol, hypertension, diabetes, lipodystrophy, and smoking were all associated with increased risk of myocardial infarction in a multivariable model. However, lower CD4 count showed only minimal association with adverse events (RR=1.27, 1.12-1.43); the risk for adverse events with elevated levels of HIV-1 RNA was nearly identical (RR=1.27, 1.12-1.43). Interestingly, in the univariate model both of these associations disappeared (35). In the ANRS C03 Aquitaine Cohort, Bonnet et al studied the associations of several factors with severe morbidity in an infected population, following over 3,863 individuals between 2000 and 2004 (36). AIDS-related events only accounted for 20% of adverse events. Cardiovascular disease accounted for 9%. In this cohort, CD4 count had an odds ratio (OR) of 0.87 (0.83-0.91) and HIV viral load had an OR of 1.16 (1.09-1.22) in the multivariate model. Ferry et al demonstrated similar findings in the APROCO/COPILOTE (ANRS C08) Cohort Study (37). Increased viral load has been associated with increased risk of heart failure in an HIV-infected population of veterans, even after adjusting for known risk factors (HR: 2.28, 1.57-3.32) (38). In conclusion, the traditional risk factors of CD4 count and viral load capture much but not all of the risk associated with chronic HIV infection. The predictive gap is especially apparent with cardiovascular disease, one of the most important non-AIDS related events in the HIV-infected population. If serious non-AIDS related morbidities occur at even high CD4 counts and low viral load, as pointed out by Philips et al in reviewing the HIV’s relationship with non-AIDS related

diseases (34), then other biomarkers must be evaluated for their predictive value in this population.

Six major studies have examined the relationship between serum albumin and HIV-infection, either as a direct measure of HIV disease progression or mortality in an HIV-infected population. After an extensive literature review, there is no evidence of a published study examining the relationship between serum albumin levels and non-AIDS related diseases, such as cardiovascular disease. **Table 1** summarizes the six studies (39) (40) (41) (42) (43) (44).

TABLE 1

Name	Year Author	Design	Participants	Predictor	Outcome
Serum Albumin as a Predictor of Survival in HIV-Infected Women in the Women's Interagency HIV Study.	2000 Feldman et al	Prospective cohort study	2,056 women from the Women's Interagency HIV Study (WIHS)	Baseline serum albumin	All-cause mortality
Serum Albumin Is a Powerful Predictor of Survival Among HIV-1-Infected Women	2003 Feldman et al	Prospective cohort study	1,941 women from the Women's Interagency HIV Study (WIHS)	Time-updated serum albumin	All-cause mortality
Hyponatremia, Hypochloremia, and Hypoalbuminemia Predict an Increased Risk of Mortality During the First Year of Antiretroviral Therapy Among HIV-Infected Zambian and Kenyan Women	2011 Dao et al	Prospective cohort study	661 women from the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Response Study in Zambia and Kenya	Baseline serum sodium, chlorine, and albumin	All-cause mortality
Serum Albumin as a Prognostic Indicator for HIV Disease Progression	2006 Mehta et al	Retrospective cohort study	453 injection drug users – men and women enrolled in the AIDS Link to the IntraVenous Experience (ALIVE)	Albumin levels before and after seroconversion	Progression to AIDS after HIV infection and seroconversion
Haemoglobin and Albumin as Markers of HIV Disease Progression in the Highly Active Antiretroviral Therapy Era: Relationships with Gender	2007 Shah et al	Retrospective cohort study	495 men and women enrolled in the Royal Free Cohort located at the Royal Free Centre for HIV Medicine in London	Albumin and hemoglobin levels taken as averages over 3 month periods	Progression to AIDS and all-cause mortality
Markers of HIV-1 Disease Progression in Individuals with Haemophilia Coinfected with Hepatitis C: a Longitudinal Study	2002 Sabin et al	Retrospective cohort study	111 males with haemophilia coinfected with hepatitis C registered at the Royal Free Hospital Haemophilia Centre in London	Serum albumin levels at baseline and time-updated	Progression to AIDS and all-cause mortality

The two largest and most relevant of these studies were led by Joseph Feldman at the State University of New York, Brooklyn. Both assessed the associations between serum albumin levels and mortality. However, the methodology and results differed in important ways. The first

(39), published in *AIDS* in 2000, analyzed baseline measurements of serum albumin as a predictor of mortality, using retrospective analysis from the prospective cohort, the Women's Interagency HIV Study (WIHS). In this cohort HIV-infected women were interviewed and examined every six months, at which time blood samples were also collected and analyzed. The final analysis included all women who were entered into the cohort and had at least one follow up visit, with viable laboratory measurements of both the predictor variable and other covariates, totaling 2,056 women. The predictor was examined both as a continuous and categorical variable. The measured outcome was all-cause mortality. The statistical analyses were conducted using both the Kaplan-Meier method and Cox's proportional hazard model, as the latter method helps to account for the variable time for each participant before being lost to follow up. Serum albumin concentration was divided into four categories: <3.5g/dL, 3.5-4.0 g/dL, 4.0-4.2 g/dL, and >4.2 g/dL. The hazard ratio for the lowest category of serum albumin compared to the highest was 3.1 (2.1 – 4.7). The association was graded with increasing levels of serum albumin. However, even levels between 4.0 and 4.2 were associated with an increased risk of mortality when compared with the highest category (HR=1.5, 1.0-2.1). These measures were adjusted for body mass index, CD4 cell count, and HIV-1 RNA levels. This study was the first to examine the potential power of albumin as a predictor of adverse outcomes in an HIV-infected population. Other studies would follow this one to fill in where this study left off.

Feldman conducted a second study three years later (40), using the same cohort, WIHS. This study included 1,941 women who had at least one follow-up visit after enrollment and the appropriate laboratory measurements. Feldman asked three additional questions: 1) how does albumin change over time in an HIV-infected population; 2) does analysis of serial levels of albumin over time improve the predictive value of the model; 3) do albumin measurements prior to the initiation of HAART predict outcomes after the initiation of HAART? The primary statistical method was the Cox proportional hazard model. It is worth explaining the method of the time-dependent analysis, as it is used in several subsequent papers and is essential to understanding the results of the Feldman paper. In baseline models, one measurement of serum albumin (sometimes an average of the first two) is used as a predictor for all outcomes until the participant is lost to follow up. In time-updated analyses, researchers update albumin and other covariates each time they are measured, and then carry the last measurement forward until the participant is censored.

The abridged results of his study are as follows:

	Baseline		Time-updated	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Serum Albumin <3.5 g/dL vs >4.2 g/dL	5.6	3.3-9.7	13.0	7.3-23.1
CD4 Count <200 vs 500+	5.9	3.8-9.3	8.2	4.6-14.7
HIV RNA Level 100,000 + vs <4,000	4.6	2.3-9.1	4.0	2.3-7.0

The predictor in the first case is serum albumin, CD4 count in the second, and HIV RNA in the third; for all three predictors the outcome, or “hazard”, is death. The first analysis is adjusted for CD4 count, HIV-1 RNA, therapy status, and age; the second is adjusted for serum albumin, HIV-1 RNA, therapy status, and age; the third is adjusted for serum albumin, CD4 count, therapy status, and age. Above shows the results of only one category for each predictor; similar

relationships persisted through each of the other categories. While all three predictors are strong and relatively equivalent in value from baseline, time-updated serum albumin measurements surpass both CD4 count and HIV RNA levels in the short term. Moreover, in those women who died during the study period, albumin levels fell at a faster rate than for those who survived, 1.54 g/L/year vs 0.44 g/L/year, respectively. Finally, albumin levels taken prior to the initiation of HAART remained a strong predictor (HR=7.0, 3.6 – 13.5). This study was the first to highlight the power of serum albumin as a predictor of mortality, comparing both baseline values to time-updated values, which demonstrates the value of albumin measurements relative to traditional measures of HIV disease severity in predicting adverse outcomes, especially in the short term.

In 2011 Dao et al conducted a similar investigation with a population of women from Zambia and Kenya (41). However, instead of examining albumin levels prior to the initiation of therapy as a predictor of mortality once therapy was initiated, this study examined serum albumin, serum sodium, and serum chloride measurements at initiation of treatment as a predictor of mortality. The women enrolled in this study began therapy only because their CD4 counts had reached levels below 350 cells per microliter, a characteristic that distinguishes them from other studies. Moreover, women in this study were only followed for up to one year. The final analysis included 661 women. The statistical analyses were conducted using the Cox proportional hazard model. Serum albumin was entered as a dichotomous variable, either greater than 3.4 g/dL or less than that value. Hypoalbuminemia was associated with 3.7-fold risk of mortality (1.4-9.8). Both hyponatremia with hypochloremia and body mass index were stronger predictors in this study. The authors concluded that the decreased serum levels of chloride, sodium, and albumin likely reflect opportunistic infections or advanced HIV disease. Due to the large difference in the population sample for this study, both by geographic location and selection for those who were already very sick, it is difficult to compare these results to other studies conducted on serum albumin levels with mortality in HIV-infected individuals.

Mehta et al examined serum albumin as a predictor of HIV-infection progression to AIDS in a population of injection drug users (42). The AIDS Link to the IntraVenous Experience (ALIVE) cohort, which included 2,946 injection drug users recruited in the city of Baltimore. All were HIV free at study enrollment. This analysis included 453 individuals who were alive in 1995 and had contracted HIV. Three separate outcomes were analyzed: 1) diagnosis of AIDS-defining event; 2) mortality due to AIDS-related illness; 3) all-cause mortality. The predictor was serum albumin. Kaplan-Meier and Cox proportional hazard models were used in the statistical analyses. Serum albumin levels were dichotomized to be either above 3.5g/dL or below this value. Each measure was adjusted for gender, race, body mass index, alanine aminotransferase, aspartate aminotransferase, total bilirubin, platelet count, weight change, and duration of HCV infection. Low levels of albumin were associated with a 1.81-fold risk (1.16 – 2.84) of progression to AIDS, 2.21-fold risk (1.28 – 3.80) of AIDS-related mortality, and 2.36-fold risk (1.59 – 3.50) of all-cause mortality. These results further emphasize that albumin captures more than just AIDS-related illness, given that the hazard increases for all-cause mortality compared with AIDS-related mortality. However, it is also important to note the unique characteristics of this population compared to the general HIV-infected population. First, being injection drug users, these individuals likely have other co-infections and risk factors (beyond just HCV infection). Second, these individuals were recruited early in the HIV epidemic, and therefore may have

different outcomes than a population sampled today, especially with regard to AIDS-related mortality.

Shah et al examined both hemoglobin and albumin as prognostic biological markers for progression to AIDS (43). The participants were recruited at the Royal Free Centre for HIV Medicine in London. It included 291 patients in the final analysis. Like the Dao paper, all patients had already initiated therapy once analysis had begun. Both hemoglobin and serum albumin were dichotomized, with values less than 3.5 g/dL being defined as hypoalbuminemia (the cut point for serum hemoglobin differed by gender). Like the second Feldman study, this analysis included both baseline and time-dependent analyses, and demonstrated that the associations were stronger in the short term. The study adjusted for CD4 count, gender, ethnicity, viral load, time since diagnosis, calendar year of HAART, age at HAART initiation, and previous AIDS diagnosis. The analysis covered a two-year span after initiating therapy. In the time-dependent analysis, higher levels of hemoglobin had a 0.73-fold risk (0.55 – 0.82) compared with lower levels; higher levels of serum albumin had a 0.87-fold risk (0.83 – 0.91) compared with lower levels. The authors concluded, “Both albumin and haemoglobin were strong independent prognostic factors for risk of AIDS and death, regardless of gender.” The strength of hemoglobin compared to albumin is unique to this study, as no other investigation has examined hemoglobin and its associations with mortality in an HIV-infected population.

Sabin et al also investigated markers of disease progression from HIV to AIDS, with albumin being one of several predictors included in the analysis (44). This population was also distinct. It included 111 patients with hemophilia from the Royal Free Hospital Haemophilia Centre in London. The patients became infected with HIV between 1979 and 1985 through contaminated blood supply. The Cox proportional hazard model was used as the primary statistical analysis, using both baseline and serial measures of albumin over time. Unlike other analyses, they modeled albumin as a continuous variable with 1g/L increments. In their final analyses, albumin was the most significant predictor. From baseline, higher levels of serum albumin were associated with a 0.91-fold risk (0.84 – 1.00) for progression to AIDS and a 0.89-fold risk (0.82 – 0.96) of death. In the time-updated analyses, albumin was not significantly associated with progression to AIDS; however, it remained a strong predictor of mortality (all-cause?) (HR=0.88, 0.84 – 0.93). These data emphasize the importance of serum albumin as a predictor of mortality, especially in the short term for HIV-infected individuals, and also the value of albumin in predicting non-AIDS related mortality. The limitations of this study include the sample size and unique population composition, which was small and dated to a time from before modern treatments. Nonetheless, it points to the significance of albumin as a predictor in HIV-infected individuals.

These six studies cover the relevant literature with regard to albumin as a biological marker for adverse outcomes in the HIV-infected population. Two primary clinical outcomes were included in these analyses: progression from HIV-infection to AIDS and mortality. All had specific niches within the HIV-infected population, whether by geographic location, gender, co-infection, or risk behaviors. None covered a broad, general population including both genders. There was also no consistent use of cut points across the studies. While some dichotomized serum albumin, others modeled it as a continuous variable, with varying increments and selected values. Some modeled albumin using only baseline values as a single predictor through the course of the study. In those

studies where albumin was measured serially over time, researchers were able to capture the value of serum albumin in the short term. Another difference between the studies that limits comparison is the difference in covariates. As previously mentioned, the causes for decreased serum albumin are multifactorial, including poor nutrition (decreased synthesis), liver disease (decreased production), renal disease (wasting of serum albumin in the urine); and chronic inflammation (decreased production or increased destruction). None of studies reviewed accounted for renal function in albumin levels, and surprisingly few accounted for liver function. The first reported non-AIDS related complications were cardiovascular disease and heart failure. Given the prevalence of these diseases in this population and the existing literature where albumin has been shown to be a powerful predictor of these outcomes in the general and elderly population, it is surprising that no study has examined these associations in an HIV-infected population. Cumulatively, these studies emphasize several important points. First, albumin is a strong predictor of mortality, especially in the long term. Second, albumin may predict progression from HIV to AIDS; however, this point is less relevant in an era when AIDS is relatively rare. Third, albumin likely captures some risk outside of the traditional prognostic markers, such as CD4 count and viral load. Fourth, it seems plausible that risk for cardiovascular disease may be among the risk factors captured by albumin, although this is not explicitly documented in any of the studies.

Thus, a final question remains, what role might serum albumin play in a prognostic index for the chronic management of HIV infection? Amy Justice and colleagues at the Department of Internal Medicine at Yale University have been investigating the possibility of such a prognostic index within a population of HIV-infected veterans (45) (46) (47). In the modern era of HIV treatment viral suppression is common and AIDS-related illnesses are uncommon. Thus, new prognostic devices must be used to stratify risk in this population. The Veterans Aging Cohort Study (VACS) Index includes age, CD4 count, HIV-1 RNA, hemoglobin, platelets, AST, ALT, creatinine, and HCV status. Liver function and kidney function are assessed with composite equations. Justice et al (46) (47) found that their index showed a significant, although not nearly ideal, level of discrimination for mortality with a C-Statistic of 0.77 ($P < 0.0001$). In a follow up to these studies, Justice examined whether or not markers of inflammation and coagulation improve the prognostic ability of the index, measuring IL-6, D-dimer, and sCD14 (a marker of monocyte activation). Her results demonstrated that D-dimer and sCD14 improved the VACS Index discrimination ability. However, it is important to note that both sCD14 and IL-6 are rarely used clinical tests, and not fully available across the United States.

Serum albumin is a common and easily obtained laboratory test that is ubiquitous in clinics and hospitals across the United States. As clinicians treating HIV-infected individuals transition to chronic management of disorders resulting from the accelerated aging of HIV, it will be important to stratify those persons at high and low risk for proper follow up and treatment. Past research in the field of elders sheds light on this population and these problems. Serum albumin has proven a remarkably powerful predictor of multiple adverse outcomes, especially those related to cardiovascular disease. This likely reflects serum albumin's role as a negative acute phase response protein, and thus as a marker of both chronic and acute inflammation. A number of studies have examined serum albumin's prognostic value in the HIV-infected population. These studies have demonstrated serum albumin as a strong predictor of mortality, especially in the short term. However, these studies have been limited by the nature of their study population,

methodological differences, and scope. None, surprisingly, has examined the associations of serum albumin with cardiovascular disease, despite the clear link in other populations. Moreover, researchers are currently working to develop a prognostic index for the management of chronic HIV infection. These indices have demonstrated promising, but limited risk stratification. Serum albumin may significantly improve the discriminatory ability of an index for HIV-infected individuals, especially as a possible short-term marker of inflammation, capturing a range of non-AIDS-related adverse outcomes, including cardiovascular disease.

Serum Albumin and Short-Term Risk for Mortality and Cardiovascular Disease among HIV-Infected Veterans

Joshua Lang^a, Rebecca Scherzer^{b,c}, Cristin C. Weekley^d, Phyllis C. Tien^{b,c}, Carl Grunfeld^b and Michael G. Shlipak^{b,c}

Objective: We examined the short-term and long-term associations of serum albumin with mortality and cardiovascular disease among HIV-infected veterans.

Design: Retrospective cohort analysis using a national database of U.S. veterans with HIV infection.

Methods: This analysis evaluated all HIV-infected veterans in the Department of Veterans Affairs HIV Clinical Case Registry (CCR), a national database comprised of demographic, clinical, laboratory, pharmaceutical, and viral status data. There were 25 522 patients enrolled between 1986 and 2007. We evaluated the associations of baseline and time-updated serum albumin levels with all-cause mortality, atherosclerotic cardiovascular disease, and heart failure by multivariate proportional hazards models.

Results: Over 21 years, there were 10 869 deaths; the cumulative mortality was 73.2 per 1000 person-years. After multivariate adjustment for covariates measured at baseline, the lowest category of serum albumin (<2.5 g/L) was associated with a higher mortality risk compared with the highest category (>4 g/L) (Hazard Ratio 3.00; 2.67–3.37). However, when analyzed as a time-dependent model, the association strengthened substantially (15.1; 14.0–16.4). Findings were similar for atherosclerotic cardiovascular disease and heart failure. We stratified the baseline mortality model by year of follow up and found that albumin was more strongly associated with deaths that occurred within one year of baseline (9.29; 7.85–11.0) than in the second (1.66; 1.18–2.33) or third (1.22; 0.77–1.96) year after measurement.

Conclusions: Among ambulatory HIV-infected patients, lower serum albumin levels are strongly predictive of mortality risk, particularly within one year.

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Keywords: albumin, cardiovascular disease, ESRD, GFR, kidney

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Introduction

In HIV-infected individuals, researchers have identified a constellation of diseases appearing much earlier in life than expected, including atherosclerotic cardiovascular disease and heart failure [1,2]. Albumin is a negative acute phase response protein and marker of inflammation [3]. Lower levels of serum albumin have been associated with higher rates of atherosclerotic cardiovascular disease, heart failure, and mortality in elderly non-infected persons [4,5]. Because HIV is characterized by systemic inflammation, serum albumin might have prognostic value within the HIV-infected population. Although a few studies have evaluated associations of serum albumin with mortality in the HIV-infected population [6–9], none, to our knowledge, has examined atherosclerotic cardiovascular disease or heart failure. In this study we investigated the hypothesis that low levels of serum albumin would independently predict increased risk of mortality, atherosclerotic cardiovascular disease, and heart failure in a national registry of HIV-infected individuals. Moreover, we hypothesized that serum albumin would have greater value for predicting near-term adverse outcomes relative to long-term adverse outcomes.

Methods

Data Sources

In this retrospective cohort analysis, we studied HIV-infected veterans in the Department of Veterans Affairs HIV Clinical Case Registry (CCR), a national database comprised of demographic, clinical, laboratory, pharmaceutical, and vital status data compiled from the VA electronic medical record [10]. In order to supplement demographic and clinical data, we linked the CCR data to the VA National Patient Care Database, the VA Beneficiary Identification and Records Locator Subsystem (BIRLS) Death File, and Medicare claims data.

Study Participants

We included all HIV-infected patients in the Veterans Health Administration who had measurements of outpatient serum albumin, serum creatinine and a urine dipstick between 1986 and 2007. Participants were entered into the cohort at the time of their first outpatient serum albumin measure following initial documentation of HIV infection. 25 522 participants were included in our analysis.

Outcomes

The three primary outcomes were: time from study entry to death; to incident atherosclerotic cardiovascular disease; and to hospitalization for heart failure (Supplemental description in the appendix). Individuals were analyzed from the time of their first outpatient serum albumin measure until they were censored either by an

outcome event or by the end of follow-up – January 31st, 2007.

Primary Predictor

Our primary predictor was baseline serum albumin, defined as an average of the first and second measurements after the initial diagnosis of HIV. We categorized serum albumin as follows: ≥ 4.0 , 3.5–3.9, 3.0–3.4, 2.5–2.9, and < 2.5 g/dL. For the outcomes of atherosclerotic cardiovascular disease and heart failure, we combined the two lowest categories as < 3.0 g/dL, due to small numbers of events occurring in the < 2.5 g/dL category.

Covariates

The analysis accounted for demographic characteristics, including age, race, and gender. HIV-related prognostic indicators included CD4 Count and Viral Load. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) equation. Urine dipstick results were used to quantify proteinuria. Comorbidities included body mass index in kg/m^2 (BMI), hypertension, diabetes, dyslipidemia, hepatitis C (HCV), hepatitis B (HBV), liver disease, and smoking. Antiretroviral Therapy (ART) exposure, either any or none, was an additional covariate.

Statistical Analyses

For longitudinal analyses, we constructed three models. First, baseline models utilized the index value of albumin and all other covariates. We also conducted a sensitivity analysis, restricting the baseline analysis to exclude those with either kidney or liver dysfunction. Second, we conducted time-updated analyses, which updated albumin and other covariates each time they were measured, and carried the last measurement forward until the participant was censored. In these analyses, we adjusted for the recency and frequency of albumin measurements as separate indicator variables. Third, for the mortality outcome only, we repeated the baseline model with stratification on the follow-up interval: year 1, year 2, and year 3.

We used multivariable Cox proportional hazards models to estimate the association of serum albumin levels with time to event. Tests for the proportional hazards assumption were based on the Schoenfeld residuals. We also repeated these analyses separately for the periods before and after 1996, when HAART was widely implanted in VA care. In order to discriminate between incident atherosclerotic cardiovascular disease and heart failure, we conducted a sensitivity analysis using the competing-risks regression according to the method of Fine and Gray (1999). Inclusion of covariates in the multivariable adjusted Cox model was based on significant univariate associations ($P < 0.05$) between each candidate covariate and the outcome. We determined serum albumin's risk discrimination by the C-statistic, and compared its prognostic strength with other

clinical risk factors. Analyses were conducted using Stata software version 11.0.

Results

Individuals with lower baseline albumin levels were older on average and more likely to be black. Those with lower levels of albumin also had lower CD4 counts, higher viral load, lower eGFR, lower BMI, a lower prevalence of dyslipidemia, a higher prevalence of proteinuria, HCV, HBV and liver disease, and less exposure to ART. The overall median number of albumin measures was 8 (IQR 3–18), including 10 (4–22) measures among survivors, and 6 (3–14) among those that died during follow up. There were 10 689 deaths, 1083 atherosclerotic cardiovascular events, and 435 cases of heart failure. There were 347 cerebrovascular events, 652 myocardial infarctions, and 174 documented cases of peripheral vascular disease.

After multivariable adjustment for covariates measured at baseline (Table 1 Baseline), the lowest category of baseline albumin was associated with a 3-fold risk of mortality (<2.5 vs. >4 g/L), little association with composite CVD events (HR = 0.99), and a 1.5-fold risk of CHF. In contrast, in the time-dependent model (Table 1 TDC),

the lowest albumin category had approximately a 15-fold risk for mortality, a 3-fold risk for atherosclerotic cardiovascular events, and a 12-fold risk for heart failure. Similar results were seen for individuals enrolled in both the pre- and post-HAART eras (Supplemental Digital Content 1 & 2). In the competing-risks analysis, associations remained similar across albumin categories (Supplementary Digital Content 3).

When sensitivity analyses were conducted for the baseline model, excluding individuals with either liver or kidney dysfunction, the hazard ratio remained similar for comparisons of <2.5 vs. >4 g/L (HR 2.6, 2.0–3.5). Furthermore, in the time-dependent model of mortality, the hazard ratio for the <2.5 g/L category was 15.5 (13.8–17.5).

We stratified the baseline mortality model by year of follow up (Fig. 1). The baseline albumin appeared strongly associated with deaths that occurred within one year (HR = 9.29 for <2.5 vs. >4 g/L), but showed substantially weaker associations subsequently. For risk discrimination of 1-year mortality, serum albumin alone had a C-statistic of 0.74. The clinical model without albumin had a C-statistic of 0.83 ($P < 0.0001$) which improved to 0.86 with the addition of albumin to the model.

Table 1. Association of Serum Albumin with Mortality, Atherosclerotic Cardiovascular Disease and Heart Failure, 1986–2007.

Level of Albumin, g/dL	Hazard Ratio (95% Confidence Interval)				
	≥4.0	3.5–3.9	3.0–3.4	2.5–2.9	<2.5
Mortality (n = 10 689)					
Baseline Albumin					
Demographic-Adjusted	1.0 (Reference)	1.45 (1.38–1.52)	2.03 (1.92–2.15)	3.04 (2.87–3.22)	4.49 (4.02–5.02)
Multivariable-Adjusted	1.0 (Reference)	1.34 (1.27–1.40)	1.68 (1.58–1.78)	2.27 (2.14–2.42)	3.00 (2.67–3.37)
Time-updated Albumin					
Demographic-Adjusted	1.0 (Reference)	1.93 (1.80–2.06)	4.84 (4.52–5.17)	12.8 (12.0–13.6)	33.5 (31.2–36.1)
Multivariable Adjusted	1.0 (Reference)	1.65 (1.54–1.77)	3.37 (3.15–3.61)	7.02 (6.58–7.50)	15.1 (14.0–16.4)
Composite Atherosclerotic Cardiovascular Event (n = 1083)					
Baseline Albumin					
Demographic-Adjusted	1.0 (Reference)	1.05 (0.91, 1.21)	1.13 (0.94, 1.36)	1.26 (1.01, 1.56)	–
Multivariable-Adjusted	1.0 (Reference)	1.01 (0.88, 1.17)	0.97 (0.80, 1.18)	0.99 (0.79, 1.25)	–
Time-updated Albumin					
Demographic-Adjusted	1.0 (Reference)	1.34 (1.15, 1.56)	2.46 (2.07, 2.91)	3.47 (2.89, 4.18)	–
Multivariable-Adjusted	1.0 (Reference)	1.35 (1.16, 1.58)	2.36 (1.98, 2.82)	3.15 (2.58, 3.86)	–
Heart Failure (n = 435)					
Baseline Albumin					
Demographic-Adjusted	1.0 (Reference)	1.22 (0.96, 1.55)	1.92 (1.46, 2.51)	2.40 (1.79, 3.22)	–
Multivariable-Adjusted	1.0 (Reference)	1.13 (0.89, 1.43)	1.45 (1.09, 1.93)	1.53 (1.10, 2.11)	–
Time-updated Albumin					
Demographic-Adjusted	1.0 (Reference)	3.01 (2.16, 4.20)	7.91 (5.66, 11.1)	19.3 (13.9, 26.6)	–
Multivariable-Adjusted	1.0 (Reference)	2.75 (1.97, 3.84)	6.07 (4.31, 8.55)	11.7 (8.3, 16.5)	–

Note: Demographic adjusted models are adjusted for age, sex and race; Multivariable adjusted Cox models are adjusted for factors with a P value <0.05 in univariate analysis. All covariates are baseline measures. For mortality, multivariate adjusted model includes these covariates: serum albumin, age, race, sex, eGFR, urine dip, CD4 count, viral load, anti-retroviral therapy, body mass index, hypertension, diabetes, hepatitis C, hepatitis B, liver disease, and smoking (only dyslipidemia was not entered). For atherosclerotic cardiovascular events, multivariate adjusted model includes these covariates: serum albumin, age, race, sex, eGFR, urine dip, viral load, BMI, hypertension, diabetes, dyslipidemia, and smoking (antiretroviral therapy, hepatitis C, hepatitis B, liver disease, and CD4 count are excluded). For CHF event, multivariate adjusted model includes these covariates: serum albumin, age, race, sex, eGFR, urine dip, CD4 count, body mass index, hypertension, diabetes, dyslipidemia, and smoking (antiretroviral therapy, hepatitis C, hepatitis B, liver disease, and viral load are excluded).

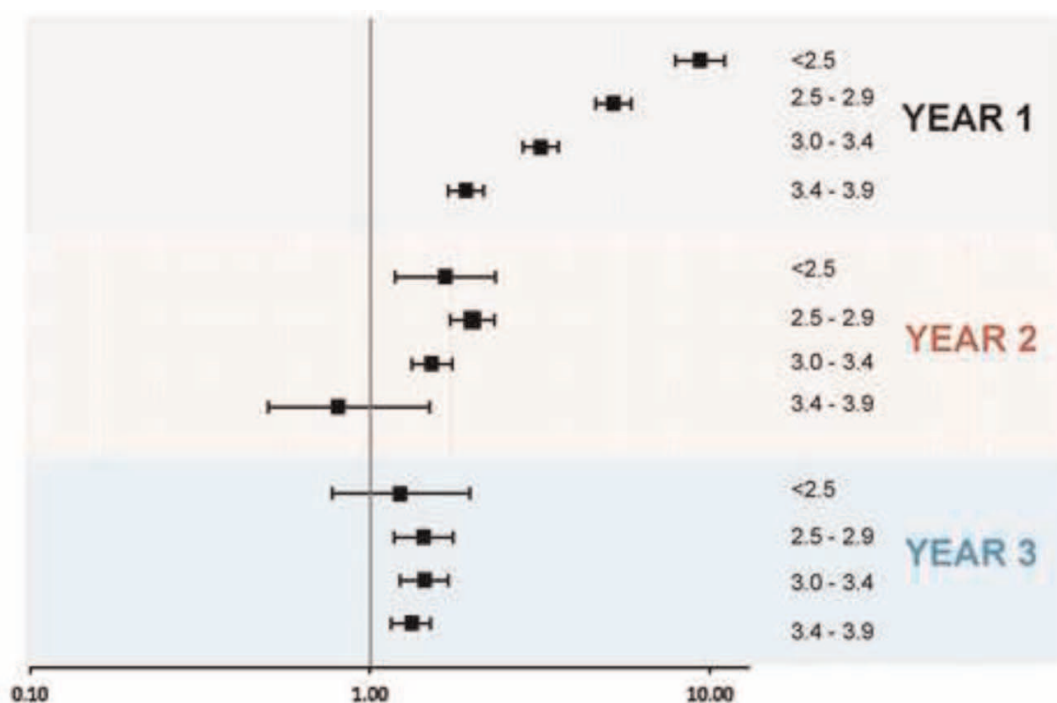


Fig. 1. Baseline serum albumin associations with mortality stratified by year of follow up. Association of baseline serum albumin categories (<2.5, 2.5–2.9, 3.0–3.4, and 3.5–3.9 g/dL) with mortality risk, stratified by year of follow up, in multivariate-adjusted proportional hazards models.

Discussion

We found albumin to be a remarkably strong, independent predictor of one-year mortality, atherosclerotic cardiovascular disease, and heart failure. The associations of serum albumin with mortality weakened substantially after the first year of measurement. Time-dependent models of albumin demonstrated that the lowest levels of serum albumin were associated with a 15-fold risk for mortality, a 3-fold risk for atherosclerotic cardiovascular events and a 12-fold risk for heart failure. These findings were consistent in both the pre- and post-HAART eras. For 1-year mortality, serum albumin was the single strongest predictor, having an individual C-statistic of 0.72, and significantly increasing the overall multivariate model from 0.83 to 0.86.

Previous smaller studies of serum albumin in HIV-infected populations have reported similar findings [9,11–13]. Feldman and colleagues from the Women's Interagency HIV Study (WIHS) reported a relative hazard of 3.1 for baseline measurements of less than 3.5 g/dL compared to concentrations greater than 4.2 g/dL, and a relative hazard of 13 for the same categories in a time-updated model [6,7]. However, none of these reports spanned the pre- and post-HAART eras; and

none, to our knowledge, have examined serum albumin's association with atherosclerotic cardiovascular events and heart failure.

The underlying mechanisms remain unclear. To our knowledge, there is no direct physiologic link between serum albumin and the adverse outcomes explored herein. Causes of decreased serum albumin levels are multifactorial, and include poor nutrition (decreased synthesis), liver disease (decreased production), renal disease (wasting of serum albumin in the urine) and chronic inflammation (decreased production or increased destruction). Albumin remained a strong predictor of mortality after adjusting for multiple factors. Moreover, we found in a sensitivity analysis that, when individuals with liver and kidney dysfunction were excluded, the association remained nearly identical for baseline and time-updated models. This suggests that a more transient process such as inflammation is responsible for the lower levels of albumin. HIV infection is associated with higher levels of IL-6 and high sensitivity C-reactive protein (hsCRP), which also predict mortality [14,15], but neither was available in this clinical registry. It seems likely that serum albumin captures a dynamic process of inflammation in HIV infection that has clinical importance in the short-term.

Researchers have identified a number of “non-HIV” markers for inclusion in a prognostic survival index in HIV infection [16]. These indices have been shown to improve discrimination of mortality within the HIV-infected population. Serum albumin could potentially add to such an index, particularly as a possible “early warning” for short-term morbidity and mortality.

Our study had the following strengths. We had a large sample for our analyses, spanning a 20-year period. There were multiple measures of serum albumin for each participant, allowing time-dependent analyses and extensive covariate evaluation. We are also the first study, to our knowledge, to use serum albumin as a prognostic marker for atherosclerotic cardiovascular disease and heart failure in HIV-infected individuals, both from baseline and in a time-updated model.

Our study also had several important limitations. First, we cannot fully account for the potential confounding effects of serum albumin measurement on our findings, as this testing may be informative about prognosis independent of the albumin concentration itself. We attempted to account for this by adjusting for the frequency and recency of albumin measures; in fact, we found that the median number of albumin measures was greater among survivors than non-survivors. Second, we cannot determine the mechanisms for the association between albumin and adverse outcomes; although we hypothesize that inflammation is a likely pathway, inflammation markers are not part of routine clinical care. Third, we found a lower prevalence of smoking than has been reported in other HIV-infected populations; this raises the possibility that rates of smoking were underreported in our cohort. Fourth, given the dependency on diagnostic codes, we cannot be certain that we capture all cardiovascular events; however, we do not have reason to suspect that the albumin associations would be biased by the event capture. Fifth, our results may not be generalizable to populations poorly represented in our analysis.

In summary, we found that lower levels of serum albumin predict mortality, atherosclerotic cardiovascular events, and heart failure, particularly within one year. These findings suggest the possibility that serum albumin reflects a state of inflammation in HIV-infected individuals similar to the elderly population. Serum albumin measurements could potentially improve the prediction of short-term adverse outcomes in HIV-infected individuals.

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Conflicts of interest

None declared.

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