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Serum Albumin Concentration and Waiting List Mortality in Idiopathic Interstitial Pneumonia

David A. Zisman, M.D., M.S., F.C.C.P.¹, Steven M. Kawut, M.D., M.S., F.C.C.P.^{3,4}, David J. Lederer, M.D., M.S.³, John A. Belperio, M.D.¹, Joseph P. Lynch III, M.D., F.C.C.P.¹, Marvin I. Schwarz, M.D., F.C.C.P.⁵, John A. Tayek, M.D.², David B. Reuben, M.D.¹, and Arun S. Karlamangla, Ph.D., M.D.¹

¹Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, dzisman@mednet.ucla.edu; jbelperio@mednet.ucla.edu; jplynch@mednet.ucla.edu; dreuben@mednet.ucla.edu; akarlamangla@mednet.ucla.edu ²Department of Internal Medicine, Harbor-UCLA Medical Center, Los Angeles, CA, jtayek@ladhs.org ³Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY sk2097@columbia.edu; dl427@columbia.edu and ⁴Department of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University, New York, NY, sk2097@columbia.edu; dl427@columbia.edu ⁵Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, marvin.schwarz@uchsc.edu

Abstract

Background: Hypoalbuminemia is a reliable predictor of mortality in patients with various illnesses as well as a predictor of disability and mortality in healthy older adults. The association between hypoalbuminemia and mortality in patients with idiopathic interstitial pneumonia remains unknown. The objective of this study was to examine the relationship between serum albumin concentration and mortality in a large cohort of patients with idiopathic interstitial pneumonia listed for lung transplantation.

Methods: In patients classified as having idiopathic pulmonary fibrosis, who were listed for lung transplantation with the United Network for Organ Sharing between January 1, 2004, and December 31, 2006 (N=1,269), we studied the relationship between serum albumin concentration at the time of listing and mortality while awaiting transplantation.

Results: Lower serum albumin was associated with increased mortality rate. Patients in lower categories of serum albumin had increased mortality rates before and after multivariable adjustment (p value for linear trend < 0.0001). Analysis with serum albumin as a continuous predictor indicated that the mortality rate increased by 54% with each 0.5 g/dL decrease in serum albumin concentration (95% confidence interval: 32% to 79%).

Conclusions: Lower serum albumin is strongly and independently associated with higher transplant-waiting list mortality in patients with idiopathic interstitial pneumonia.

Reprints and corresponding author: David A. Zisman, M.D., M.S., Interstitial Lung Disease Center, David Geffen School of Medicine at UCLA, 37-131 Center for Health Sciences, Los Angeles, CA 90095; phone 310-825-8689, FAX 310-206-8622, email: dzisman@mednet.ucla.edu.

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Keywords

Pulmonary fibrosis; interstitial lung disease; inflammation; albumin; prognosis

Introduction

Hypoalbuminemia is a reliable predictor of mortality in patients with various illnesses (1-6) as well as a predictor of disability and mortality in healthy older adults.(7-9) The prognostic value of low serum albumin may reflect ongoing inflammation, malnutrition or loss of albumin's protective effects (vasodilatation, inhibition of endothelial cell apoptosis, antioxidant effects and reduced platelet aggregation).(10-15)

While the role of inflammation in idiopathic pulmonary fibrosis (IPF) remains controversial, there is evidence that inflammation may be critical in this condition.(16,17) Serum albumin is a negative acute phase protein and therefore a readily available marker of inflammation.(18) The acute phase response leads to the release of acute phase cytokines including interleukin-6 (IL-6), which acts via specific hepatic receptors to inhibit the synthesis of albumin.(18) In addition, IL-6, via a positive autocrine feedback loop, promotes the proliferation of lung fibroblasts.(19,20) Other conditions, such as malnutrition and liver/kidney disease may also affect albumin levels. However, the association between hypoalbuminemia and mortality in patients with idiopathic interstitial pneumonia (IIP) remains unknown.

In this study, we evaluated the relationship between serum albumin concentration and mortality in a large cohort of patients with IIP listed for lung transplantation. We hypothesized that lower serum albumin concentration at the time of listing would be associated with higher mortality while awaiting lung transplantation.

Methods

Study Design

We analyzed data from the Organ Procurement Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database which was queried for individuals with idiopathic pulmonary fibrosis (IPF) listed for lung transplantation between January 1, 2004, and December 31, 2006. The diagnosis of IPF was not standardized and therefore, this category likely included patients with other IIP. The UCLA Institutional Review Board approved the study.

Data Collection

Patient characteristics at the time of listing and transplant data were obtained from a Standard Transplant Analysis and Research (STAR) file based on Organ Procurement and Transplantation Network (OPTN) data as of August 6, 2007.(21) Clinical staff at 78 transplant centers in the United States collected demographic and clinical data at the time of listing. Dates of listing, transplantation, and/or removal from the list were obtained from the STAR file. Deaths up to August 1, 2007 were determined using the Social Security Death Master File and the STAR dataset.(22)

Statistical Analysis

The primary endpoint was mortality after listing for lung transplantation. We used Cox proportional hazards regression analysis to examine the relationship between serum albumin at the time of listing and transplant waiting-list mortality rate, while adjusting for important covariates. Survival time was computed starting from the date of listing for transplantation. In

our primary analysis, those who did not experience an endpoint (transplantation, removal/de-listing or death before transplantation) were censored on August 1, 2007. Those who were transplanted were censored at the date of transplantation, and those who were removed from the list were censored at the date of de-listing. To examine the nature of the relationship between serum albumin concentration and mortality (whether there was a graded or threshold relationship), we categorized serum albumin concentration by quintiles, and regrouped the three middle quintiles into equi-spaced categories. The resulting five categories were: ≤ 3.3 ; 3.4-3.7; 3.8-4.1; 4.2-4.5; and ≥ 4.6 g/dL. Because a monotonic mortality trend was found across these five categories of serum albumin, we conducted Cox analyses with serum albumin as a continuous predictor. Models were adjusted for variables that influence survival in patients with IPF (age, gender, race, forced vital capacity (FVC) % predicted, flow rate of supplemental oxygen required at rest [O₂ Req], six-minute walk distance [6MWD], mean pulmonary artery pressure [MPAP] as determined by right-heart catheterization [RHC], and lung allocation score [LAS])(23) and variables that affect serum albumin (serum creatinine [SCr], body mass index [BMI], ever-smoker status, corticosteroid use, and diabetes mellitus).(10) Covariates were added to the model in three steps: 1) demographic variables; 2) measures of pulmonary status; and 3) conditions (or markers of conditions) that can affect serum albumin levels: BMI (as marker of malnutrition), SCr (as marker of renal dysfunction/proteinuria), corticosteroid use, diabetes mellitus, and ever-smoker status. Covariates with missing data were imputed using the mean or the mode of the distribution, and for each such covariate, we included a 0/1 indicator variable that flagged those with imputed values. In sensitivity analyses, we re-ran the final model after excluding those with imputed values (6MWD: 196; Ever-smoker status: 194; MPAP: 183; O₂ Req: 98; FVC % predicted: 26; corticosteroid use: 10, diabetes mellitus: 4). We added LAS to the final model to test if albumin has prognostic value independent of the LAS score. Since a major reason for removal from the transplant waiting list is worsening health, we conducted a sensitivity analysis in which everyone who was removed from the list was treated as if he/she had died on the date of removal. To address the possible bias from censoring due to transplantation, we also performed sensitivity analysis in which we assumed that everyone who was transplanted died on the day of the transplantation. Further, we also performed sensitivity analyses including post-transplant survival, including a time-varying covariate for the performance of lung transplantation. In supplementary analyses, we examined selected interaction terms (age*albumin and gender*albumin). The proportional hazards assumption was assessed using log-log plots. All tests were two-tailed, and p values of < 0.05 were required for statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC) and MedCalc for Windows, version 9.2.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

Of the 1,323 patients who were listed between January 2004 and December 2006, 54 were excluded because serum albumin concentrations were unavailable, reducing the sample size to 1,269 subjects. As shown in Table 1, there were no systematic differences between the study sample and those excluded. Table 2 compares major characteristics by categories of serum albumin concentration. Patients in categories 1 or 2 had significantly worse pulmonary status (lower values of forced vital capacity [FVC] % predicted and six-minute walk distance [6MWD], and higher corticosteroid use, flow rate of supplemental oxygen required at rest [O₂ Req] and lung allocation score [LAS]) compared to those in categories 4 or 5. Those in the highest category of albumin were more likely to have been smokers.

The median follow-up period was 88 days (range, 1 to 1305). A total of 254 (20%) patients died before transplantation, 70 (5%) were removed from the waiting list, and 841 (66%) underwent lung transplantation. There was no association between serum albumin concentration and the probability of lung transplantation (mean serum albumin: 3.93 g/dL in

transplanted group vs. 3.89 g/dL in not transplanted group; $p = 0.14$). Although serum albumin was weakly correlated with LAS, which is used to prioritize IIP patients for transplantation ($r = -0.17$, 95% CI: -0.11 to -0.23), there were no significant differences between the proportions of patients transplanted across categories of serum albumin ($p = 0.54$; Table 2).

Patients in lower categories of serum albumin had increased mortality rates before and after multivariable adjustment, and mortality rates increased monotonically across decreasing albumin categories (Table 3 and Figure 1). In analysis with albumin concentration as a continuous predictor, each 0.5 g/dL decrease in serum albumin concentration was associated with mortality hazard ratio (HR) of 1.79, and this association weakened only slightly after multivariable adjustment: adjusted HR = 1.54 (95% CI, 1.32 - 1.79; $p < 0.0001$). Results were similar after additionally adjusting for LAS: HR = 1.49 (95% CI, 1.25 - 1.79; $p < 0.0001$). In sensitivity analyses, after excluding everyone with imputed values, the association was similar: adjusted HR = 1.56 (95% CI, 1.22 - 1.96; $p < 0.0001$). After adjusting for transplantation as a time-dependent covariate (including post-transplant survival), the results remained significant: (per 0.5 g/dL decrease), HR = 1.39 (95% CI, 1.23 - 1.56; $p < 0.0001$). In additional sensitivity analyses in which anyone who was removed from the transplant waiting list before receiving a transplant was assumed to have died on the date of de-listing, the association persisted: adjusted HR = 1.41 (95% CI: 1.23 - 1.62). Furthermore, in sensitivity analysis aimed to address possible bias from censoring due to transplantation, we assumed that everyone who was transplanted died on the day of the transplantation; the albumin-mortality association remained strong and significant: (per 0.5 g/dL decrease), adjusted HR = 1.24 (95% CI, 1.15 - 1.34; $p < 0.0001$). Lastly, when incorporated in the Cox proportional hazards regression analysis, interaction terms were not significant (age*albumin: $p = 0.64$ and gender*albumin: $p = 0.49$).

Discussion

Low serum albumin was strongly and independently associated with high transplant-waiting list mortality in IIP. A surprising finding in the study was the graded relationship between albumin and mortality, characterized by marked increases in mortality rate with even small reductions in serum albumin concentration. There was a 54% increase in mortality rate with 0.5 g/dL decrease in serum albumin concentration, and a 3.65-fold increase with 1.5 g/dL decrease, such as from 4.5 g/dL to 3.0 g/dL.

Hypoalbuminemia is a powerful predictor of mortality in patients with various illnesses,(1-6) suggesting that either reduced availability of albumin or the underlying cause of hypoalbuminemia reduces survival. Albumin has a number of essential physiologic effects necessary for normal health such as vasodilatation, inhibition of endothelial cell apoptosis, antioxidant effects and reduced platelet aggregation.(10-15) However, simply administering albumin to patients with hypoalbuminemia has not been shown to improve survival or reduce morbidity,(24,25) suggesting that the underlying cause of hypoalbuminemia, rather than low albumin levels per se, is responsible for the increased mortality.

The leading causes of hypoalbuminemia are malnutrition, reduced synthesis by the liver, renal losses, and chronic inflammation. Hypoalbuminemia is frequently attributed to malnutrition; however, albumin levels remain virtually unchanged even in the presence of severe protein calorie malnutrition until near terminal starvation.(26) Albumin levels are also decreased as a direct result of protein loss from the body, such as in the nephrotic syndrome, or as a consequence of reduced synthesis as occurs with liver disease.(10,11,18) In this study, we included adjustment for serum creatinine level, and reduced renal functioning did not explain the observed albumin-mortality association in IIP.

The observation that serum albumin is a negative acute phase protein supports the contention that serum albumin is a marker of inflammation.(18) The acute phase response starts with a local reaction at the site of injury characterized by activation of granulocytes and mononuclear cells, which in turn release acute phase cytokines (interleukin-1 [IL-1], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF- α], and interferons). IL-6 acts via specific hepatic receptors as a potent inducer of acute phase protein synthesis (C-reactive protein, amyloid-A) and simultaneously inhibits the synthesis of albumin.(18) Activated endothelial cells, monocytes/macrophages and fibroblasts are the major sources of IL-6 during systemic inflammation(18) and IL-6, via a positive autocrine feedback loop, promotes the proliferation of lung fibroblasts. (19,20) Hypoalbuminemia may thus be a marker of ongoing inflammation and fibroblast activity in patients with IIP, and together may explain the reduced survival observed in hypoalbuminemic IIP patients.

The albumin-mortality association seen in IIP patients awaiting transplantation was independent of LAS, the score used to prioritize patients for lung transplantation. Future investigation will be required to determine whether serum albumin measurements at the time of listing may be combined with LAS to improve transplant prioritization.

Our study has several limitations that need to be acknowledged. First, in an effort to isolate the effects of inflammation-related hypoalbuminemia, we adjusted for various non-inflammatory causes of hypoalbuminemia but were limited to the covariates that were available in the OPTN/UNOS database. Some of these covariates may have been imperfect surrogates for those conditions. For instance, although we used BMI as a correlate of malnutrition, we were unable to directly assess nutritional intake. However, given the high BMI (27.2) of those with the lowest serum albumin levels, it is highly unlikely that they were clinically malnourished. Further, we used serum creatinine to adjust for urinary protein loss, since proteinuria was not measured.(27) Similarly, corticosteroid use and diabetes may have not accurately characterized factors influencing albumin synthesis such as endogenous cortisol and insulin levels.(10) Moreover, we could not adjust for hepatic dysfunction. While renal and liver dysfunction could have caused hypoalbuminemia in our study, this is less likely as patients with other solid organ diseases are usually excluded from listing for lung transplantation. We were also limited by our inability to directly assess inflammation via measurements of proinflammatory cytokine levels. Hence, in this study, the mechanism underlying the association between hypoalbuminemia and death is unclear. Future investigation will be required to determine the reasons for low serum albumin levels in patients with IIP. Another issue is that the diagnosis of IPF was not standardized. Although we suspect that our cohort was composed mainly of IPF patients, the patients in our cohort did not have rigorous documentation of IPF by the standards set forth by ATS/ERS,(28) and some likely had other IIP. Therefore, any comparisons between our results and other cohorts of well-defined IPF subjects should be made with caution. Nonetheless, diagnostic heterogeneity may actually increase the generalizability of our results to patients with IIP awaiting lung transplantation. Finally, a large group of patients underwent transplantation and were censored at the time of transplantation. This could limit the generalizability of our findings to all IIP mortality, and be applicable only to mortality while awaiting transplantation. However, the lack of an association between albumin and the probability of transplantation in this cohort indicates that our findings are not likely to have been biased by censoring at the time of transplantation, and that the albumin-mortality association documented here may be applicable to all IIP mortality. Consistent with this, after adjusting for transplantation as a time-dependent covariate and including post-transplant survival, low serum albumin remained strongly and independently associated with high mortality in IIP. Furthermore, in sensitivity analysis in which we assumed that everyone who was transplanted died on the day of the transplantation, low serum albumin also remained strongly and independently associated with high mortality in IIP. Some weakening was

expected, as these estimates are underestimates of the real relationship between albumin and mortality, as they represent an overcompensation for the transplant censoring concern.

In summary, low serum albumin is strongly and independently associated with poor survival in patients with IIP listed for lung transplantation. Further investigation will be required to clarify the mechanisms underlying this association. Such research may lead to interventions that may lower the risk of mortality among IIP patients.

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Abbreviations

BMI, body mass index
 CI, confidence interval
 FVC, forced vital capacity
 HR, hazard ratio
 IIP, idiopathic interstitial pneumonia
 IL-6, interleukin-6
 IPF, idiopathic pulmonary fibrosis
 LAS, lung allocation score
 MPAP, mean pulmonary pressure as determined by right-heart catheterization
 OPTN, Organ Procurement Transplantation Network
 O₂ Req, flow rate of supplemental oxygen required at rest
 RHC, right-heart catheterization
 SCr, serum creatinine
 STAR, Standard Transplant Analysis and Research
 UCLA, University of California, Los Angeles
 UNOS, United Network for Organ Sharing
 6MWD, six-minute walk distance

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Figure 1.

Kaplan-Meier survival estimates for patients with idiopathic interstitial pneumonia listed for lung transplantation by categories of serum albumin concentration. Group 1: serum albumin = 1.7 - 3.3 g/dL; Group 2: serum albumin = 3.4 - 3.7 g/dL; Group 3: serum albumin = 3.8 - 4.1 g/dL; Group 4: serum albumin = 4.2 - 4.5 g/dL; Group 5: serum albumin = 4.6 - 5.3 g/dL. Log-rank test between groups: $p < 0.0001$; Wilcoxon test between groups: $p < 0.0001$. Proportional hazards adjusted HR (95% CI) for Group 1 = 5.8 (2.5-13.7); Group 2 = 2.3 (1.1-5.3); Group 3 = 1.9 (0.9-4.2); Group 4 = 1.8 (0.8-4.1); Group 5 = 1.0 (reference group); p value for linear trend: <0.0001

Table 1

Descriptive Statistics for Major Characteristics

Characteristic	Mean (SD) or %	Mean (SD) or % [*]	P-value [#]
	Study Sample (n=1269)	Missing Albumin (n=54)	
Age (years)	56.3 (8.7)	56.9 (9.9)	0.64
Males (%)	65.2	63.0	0.74
Race (%)			0.35
Non-Hispanic white	78.3	81.5	
Hispanic white	8.3	1.9	
Non-Hispanic Black	8.8	13.0	
Asian	2.1	1.9	
Other [*]	2.5	1.7	
Ever-smoker (%)	58.9	52.1	0.35
BMI	27.6 (4.4)	25.7 (5.2)	0.28
FVC % predicted	49.2 (16.8)	47.9 (16.4)	0.60
O ₂ Req (L/min)	3.5 (3.5)	3.5 (5.3)	0.10
6MWD (ft)	753.9 (520.8)	521.2 (577.7)	0.21
MPAP (mm Hg)	24.9 (9.4)	20.8 (9.4)	0.43
Serum creatinine (mg/ml)	0.91 (0.4)	0.94 (0.4)	0.58
Corticosteroid use (%) [§]	52.7	56.5	0.31
Diabetes mellitus (%)	17.0	10.2	0.21
LAS	45.3 (14.1)	43.5 (11.3)	0.41
Transplanted (%)	66.3	61.1	0.43

^{*} Includes: American Indian/Alaska native, Native Hawaiian/Pacific Islander

[§] Receiving ≥ 5 mg of prednisone daily at the time of listing for lung transplantation BMI = body mass index; FVC = forced vital capacity; LAS = lung allocation score; MPAP = mean pulmonary artery pressure as determined by right-heart catheterization; O₂ Req = flow rate of supplemental oxygen required at rest; 6MWD = six-minute walk distance.

[#] We compared the variables of interest, using standard tests for comparing means (Student t test), and proportions (Chi-Square test or the Fisher's exact test, if cell sizes were small).

Table 2
Patient Characteristics by Categories of Serum Albumin Concentration

Characteristic	n	Category 1	Category 2	Category 3	Category 4	Category 5
Serum albumin (g/dL)		1.7 - 3.3	3.4 - 3.7	3.8 - 4.1	4.2 - 4.5	4.6 - 5.3
Number	1269	137	259	456	330	87
Age (years)	1269	55.2 ± 9.8	56.1 ± 8.7	56.3 ± 8.2	56.7 ± 8.8	57.1 ± 8.7
Males (%)	1269	61.3	62.2	65.1	66.7	74.7
Race (%)	1269					
Non-Hispanic white		73.0	72.6	78.9	83.9	78.2
Hispanic white		8.0	12.0	6.8	7.0	10.3
Non-Hispanic Black		13.1	10.8	8.6	6.1	8.1
Asian		4.4	1.9	2.0	1.5	2.3
Other*		1.5	2.7	3.7	1.5	1.1
Ever-smoker (%)	1075	60.3	51.6	59.9	57.0	79.7
BMI	1269	27.2 ± 4.3	27.4 ± 4.8	28.1 ± 4.2	27.7 ± 4.4	28.6 ± 3.4
FVC % predicted [¶]	1243	47.7 ± 16.8	46.9 ± 14.6	48.6 ± 16.7	51.3 ± 17.9	53.4 ± 18.1
O ₂ Req (L/min) ^{**}	1171	6.4 ± 5.3	3.8 ± 3.6	3.5 ± 2.8	3.1 ± 3.0	2.7 ± 2.0
6MWD ^{***} (ft)	1073	440.0 ± 479.0	735.3 ± 503.8	828.0 ± 485.5	861.5 ± 551.5	982.7 ± 438.1
MPAP (mm Hg)	1086	25.9 ± 10.8	25.9 ± 9.6	25.5 ± 9.4	25.0 ± 9.0	24.7 ± 7.7
Serum creatinine (mg/ml)	1269	0.96 ± 0.83	0.88 ± 0.22	0.90 ± 0.21	0.90 ± 0.21	0.95 ± 0.49
Corticosteroid use (%) [§]	1259	63.6	59.3	56.2	42.6	36.1
Diabetes mellitus (%)	1265	24.3	14.3	17.1	16.4	14.9
LAS [#]	1018	50.7 ± 18.6	46.4 ± 15.0	44.5 ± 13.0	43.4 ± 11.9	43.0 ± 13.0
Transplanted (%)	841	62.8	64.1	65.8	69.1	70.1
Removed from list (%)	70	3.7	4.6	6.6	5.4	5.7

BMI = body mass index; FVC = forced vital capacity; MPAP = mean pulmonary artery pressure as determined by right-heart catheterization; O₂ Req = flow rate of supplemental oxygen required at rest; 6MWD = six-minute walk distance; LAS = lung allocation score

* Includes: American Indian/Alaska native, Native Hawaiian/Pacific Islander

¶ Comparisons were significant at the p<0.01 level by Chi-Square test.

§ Receiving ≥ 5mg of prednisone daily at the time of listing for lung transplantation. Comparisons were significant at the p<0.01 level by Chi-Square test.

- ¶ Comparisons were significant at the $p < 0.05$ level by ANOVA: category 2 vs categories 4 and 5
- ** Comparisons were significant at the $p < 0.05$ level by ANOVA: category 1 vs all other categories
- *** Comparisons were significant at the $p < 0.05$ level by ANOVA: category 1 vs all other categories; category 2 vs categories 4 and 5
- # Comparisons were significant at the $p < 0.05$ level by ANOVA: category 1 vs categories 3, 4 and 5

Table 3
Hazard Ratios by Categories of Serum Albumin Concentration

	Category 1	Category 2	Category 3	Category 4	Category 5	p Value for Trend
Serum albumin (g/dL)	1.7 - 3.3	3.4 - 3.7	3.8 - 4.1	4.2 - 4.5	4.6-5.3	
Unadjusted HR (95% CI)	8.5 (3.8-19.0)	3.2 (1.5-7.0)	2.2 (1.0-4.8)	1.9 (0.9-4.2)	1.0	<0.0001
Model 1 HR (95% CI)	9.6 (4.2-21.5)	3.5 (1.6-7.6)	2.5 (1.12-5.3)	1.8 (0.8-4.1)	1.0	<0.0001
Model 2 HR (95% CI)	6.0 (2.6-13.8)	2.5 (1.1-5.5)	2.0 (0.9-4.3)	1.8 (0.8-4.0)	1.0	<0.0001
Model 3 HR (95% CI)	5.8 (2.5-13.7)	2.3 (1.1-5.3)	1.9 (0.9-4.2)	1.8 (0.8-4.1)	1.0	<0.0001

HR = hazard ratio

Model 1: Adjusted for demographics (age, gender, and race).

Model 2: Adjusted for demographics and pulmonary function (FVC % predicted, flow rate of supplemental oxygen required at rest, six-minute walk distance, and mean pulmonary artery pressure as determined by right-heart catheterization).

Model 3: Adjusted for demographics, pulmonary function and other potential confounders (body mass index, corticosteroid use, diabetes mellitus, serum creatinine, and ever-smoker status).

Table 4
Hazard Ratios by Continuous Serum Albumin Concentration

	Hazard ratio (95% CI) [§]	P-value
Unadjusted	1.79 (1.56 – 2.00)	<0.0001
Model 1	1.82 (1.59 – 2.10)	<0.0001
Model 2	1.54 (1.33 - 1.79)	<0.0001
Model 3	1.54 (1.32 - 1.79)	<0.0001

Model 1: Adjusted for demographics (age, gender, and race).

Model 2: Adjusted for demographics and pulmonary function (FVC % predicted, flow rate of supplemental oxygen required at rest, six-minute walk distance, and mean pulmonary artery pressure as determined by right-heart catheterization).

Model 3: Adjusted for demographics, pulmonary function and other potential confounders (body mass index, corticosteroid use, diabetes mellitus, serum creatinine, and ever-smoker status).

[§] Hazard ratio per 0.5 g/dL decrease in serum albumin concentration