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Hypoalbuminemia and Early Mortality After Lung Transplantation: A Cohort Study

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Abstract

Hypoalbuminemia predicts disability and mortality in patients with various illnesses and in the elderly. The association between serum albumin concentration at the time of listing for lung transplantation and the rate of death after lung transplantation is unknown. We examined 6808 adults who underwent lung transplantation in the United States between 2000 and 2008. We used Cox proportional hazard models and generalized additive models to examine multivariable-adjusted associations between serum albumin and the rate of death after transplantation. The median follow-up time was 2.7 years. Those with severe (0.5–2.9 g/dL) and mild hypoalbuminemia (3.0–3.6 g/dL) had posttransplant adjusted mortality rate ratios of 1.35 (95% CI: 1.12–1.62) and 1.15 (95% CI: 1.04–1.27), respectively. For each 0.5 g/dL decrease in serum albumin concentration the 1-year and overall mortality rate ratios were 1.48 (95% CI: 1.21–1.81) and 1.26 (95% CI: 1.11–1.43), respectively. The association between hypoalbuminemia and posttransplant mortality was strongest in recipients with cystic fibrosis and interstitial lung disease. Hypoalbuminemia is an independent risk factor for death after lung transplantation.

Keywords

Cystic fibrosis; hypoalbuminemia; interstitial lung disease; lung transplantation; prognosis

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Introduction

Lung transplantation is an effective therapy for advanced lung diseases, such as cystic fibrosis (CF), the interstitial lung diseases (ILD) and chronic obstructive pulmonary disease (COPD) (1,2). However, a scarce donor supply restricts lung transplantation to only a fraction of potentially eligible patients. Therefore, each transplant center attempts to "achieve the best use of donated organs" (3) by carefully selecting candidates with acceptably low predicted postoperative risks of death. While the Lung Allocation Score (LAS) system has improved organ allocation in the United States (4,5), recent data suggest that lung transplant recipients are sicker at the time of transplant than in prior years (6), and that the posttransplant survival measure of the LAS is in fact a poor predictor of post-transplant survival (7). Novel predictors of posttransplant survival time may improve allocation strategies and foster investigations of risk-reducing interventions.

Hypoalbuminemia (serum albumin < 3.5 mg/dL) (8,9) is a marker of poor overall health with influences from protein energy malnutrition (10), systemic inflammation (11,12) and hepatic and renal disease (13,14). Studies have shown that hypoalbuminemia has strong predictive validity for mortality across a number of pulmonary (15-17) and non-pulmonary diseases (18-20) and in healthy older adults (21-24). However, the association between pretransplant hypoalbuminemia and the rate of death after lung transplantation has not been examined to our knowledge.

We therefore examined the association of the serum albumin level at the time of listing for lung transplantation with the rate of death in a nationwide sample of lung transplant recipients in the United States. We hypothesized that a lower serum albumin level would be associated with an increased rate of death early after transplantation after accounting for potential confounders.

Methods

Data sources and participants

The Institutional Review Board on Human Research at the Columbia University Medical Center approved this study (approved protocol number: AAAB5142). All data were supplied by the United Network for Organ Sharing (UNOS) as a standard transplant analysis and research file supplemented with a coded center identifier based on Organ Procurement and Transplantation Network (OPTN) data as of March 1, 2010, as previously described (25).

There were 11 074 lung transplants performed in the United States between January 1, 2000, and December 31, 2008. We excluded pediatric recipients (age < 18; n = 441) and anyone who had a living donor transplantation (n = 59), lobar transplantation (n = 2) or previous lung transplantation (n = 382). We further restricted the cohort to patients with ILD, COPD or CF (which account for more than 80% of lung transplant procedures in the United States) to minimize confounding by diagnosis. We sought to exclude patients with albumin < 0.5 g/dL (there were none) or albumin levels ≥ 6.0 g/dL (n = 11) because the standard assay for serum albumin, the bromcresol green (BCG) method (26), is inaccurate outside this range (9). Recipients with missing serum albumin were also excluded (n = 1607). We excluded 190 recipients receiving mechanical ventilation at the time of transplantation in the primary analysis because we believed it would be a key confounder of the association between serum albumin and the risk of death after lung transplantation, but we included and adjusted for mechanical ventilation in *post hoc* analyses. After all exclusions, 6808 recipients were included in the primary analysis, of whom, 6435 had 1-year follow-up (Figure 1).

Variables and statistical analyses

We categorized serum albumin concentration into five groups. We chose an albumin concentration of 4.0–5.0 g/dL as the reference range because this is the reported normal range for multiple commercial BCG assays (standard assay to measure albumin concentration), it includes the 3.5–5.0 g/dL normal range previously reported in the literature (9), and because prior studies have indicated substantial mortality risk in older persons falling below thresholds of 3.8 and 4.3 g/dL (23,24).

Severe hypoalbuminemia was defined as less than the 5th percentile of serum albumin in the cohort (0.5–2.9 g/dL). Mild hypoalbuminemia was defined as the 5th to 25th percentile (3.0–3.6 g/dL), and low-normal albumin was defined as the 25th to the 50th percentile (3.7–3.9 g/dL). Elevated albumin was defined as an albumin greater than 5.0 g/dL.

A generalized additive model (GAM) with loess smoothing functions for continuous variables was used to examine the linearity of the association between serum albumin and the odds of death after lung transplantation at 1 year after transplantation (27). The GAM allows for the flexible specification of the relationship between serum albumin and the risk of death and helps minimize misspecification of potential confounding variables (27).

We estimated hazard ratios for albumin as a continuous and categorical predictor of 1-year and overall mortality after transplantation (ignoring retransplantation) using multivariable Cox proportional hazard models. Follow-up was administratively right censored on March 1, 2010. We selected covariates available in the OPTN dataset for inclusion into the multivariable models that were either mechanically plausible confounders of the relationship between serum albumin and the rate of death (i.e. possibly linked to serum albumin and the risk of death) or solely associated with the risk of death (i.e. precision variables). Variables were retained regardless of their statistical significance in multivariable models. Implausible recipient and donor BMI values (<10 kg/m^2 or >45 kg/m^2) were replaced with missing values. The proportionality assumptions of the Cox model were verified by examining log(-log(survival time)) plots and by regressing the Schoenfeld residuals against time to test for independence between residuals and time.

We used multiple imputation with a Markov Chain Monte Carlo method to account for missing covariate values in our multivariable analyses, as previously described (25,28,29). Predicted survival curves and plots of continuous associations of albumin and the risk of death were generated from models using the missing indicator method (30) since these analyses cannot be performed on multiply imputed datasets.

We created mixed-effects multivariable Cox models with transplant center modeled as a random effect. We employed a hierarchical modeling approach as follows: model 1 was adjusted for recipient factors (serum albumin concentration at the time of transplant listing, age, sex, diagnosis percent predicted forced expiratory volume in 1 s (FEV_1), diabetes mellitus, pretransplant steroid use, hospitalization at the time of transplant and BMI (categorized using the World Health Organization (WHO) classification as previously described (25)). Model 2 included model 1 covariates as well as donor factors (age, sex, height, BMI, presence of clinical or culture-confirmed bronchopulmonary infection noted on the OPTN Organ Procurement Form, smoking history of > 20 pack-years and cause of death. Model 3 included covariates from models 1 and 2 as well as transplantation procedure characteristics (single versus double lung transplant, allograft ischemic time and transplant era [dichotomized at May 4, 2005]).

The LAS was instituted on May 4, 2005 and hence missing LAS values depended on the date of transplantation and were not random. We therefore did not multiply impute LAS

score and instead evaluated the association between serum albumin and mortality after transplantation adjusting for the LAS only in those with an available LAS score. We performed *post hoc* analyses adjusting for donor–recipient cytomegalovirus (CMV) exposure mismatch, use of mechanical ventilation at the time of lung transplantation, oxygen use (liters per minute), mean pulmonary artery pressure (mm Hg) and distance (feet) walked during a 6-min walk test at listing.

The population attributable fraction (PAF) is the proportion of deaths related to an exposure of interest (and unmeasured and poorly measured confounders) and represents the greatest possible proportional reduction in the number of deaths if the exposure of interest were eliminated from the population (31). The PAF for all recipients at 1 year was estimated using the fully adjusted multivariable Cox proportional hazard model (model 3).

We examined interactions between serum albumin level and both diagnosis and BMI using likelihood ratio tests. Statistical significance was defined as two-tailed p values less than 0.05. Analyses were performed with Stata 11.0 (Stata Corp LP, College Station, TX, USA) and the GAM function in R 2.8.1 (R Foundation, Vienna, Austria) (32).

Results

Of the 11 074 lung transplant procedures performed in the United States between 2000 and 2008, 6808 patients met our inclusion criteria and were included in analyses (Figure 1). There were 3323 single-lung transplant recipients (1991 with COPD, 1328 with ILD and 4 with CF), and 3485 double-lung transplant recipients (1475 with COPD, 970 with ILD and 1040 with CF). The median age was 57 years (interquartile range, 49–62 years), and 57% were men. The median BMI (interquartile range) for CF, COPD and ILD patients was 19.0 (17.7–21.0), 24.0 (21.1–27.1) and 27.4 (24.4–30.0) kg/m^2, respectively. Among the 3408 who underwent lung transplantation under the LAS and had an LAS score, the median LAS score was 36.8 (interquartile range, 33.5–43.7). There was a median of 5 months (interquartile range, 1.5–13.5 months) between lung transplant listing and transplantation. Of the 6808 participants, 288 (4.2%) had severe hypoalbuminemia (0.5–2.9 g/dL), 1274 (19%) had mild hypoalbuminemia (3.0–3.6 g/d) and 1421 (21%) had a low-normal serum albumin concentration (3.7–3.9 g/dL) at the time of listing. Participants with hypoalbuminemia tended to be younger and were more likely to be female, have CF and diabetes, be hospitalized at the time of transplant, and undergo bilateral lung transplantation (Table 1).

For the entire cohort, the median survival time was 5.0 years (interquartile range, 1.8–8.8 years) with 84% (95% CI: 83– 85%) surviving at least 1 year. Figure 2 shows unadjusted and adjusted survival curves for categories of serum albumin ($p < 0.001$ for trend in both models). Compared to those with normal albumin levels, the overall multivariable-adjusted mortality rate ratios for severe and mild hypoalbuminemia were 1.35 (95% CI: 1.12–1.62) and 1.15 (95% CI: 1.04–1.27), respectively (model 3 in Table 2). A low-normal serum albumin concentration (3.7–3.9 g/dL) was associated with a multivariable-adjusted mortality rate ratio of 1.10 (95% CI: 1.00–1.21) compared to those with normal serum albumin. For each 0.5 g/dL decrease in serum albumin the multivariable-adjusted mortality rate ratio was 1.26 (95% CI: 1.11–1.43). Elevated serum albumin concentrations were detected in 73 (1.1%), and while the multivariable adjusted 1 year and overall mortality rate ratios were 1.50 (95% CI: 0.90–2.49) and 1.14 (95% CI: 0.81–1.61), respectively, neither association was statistically significant. When the percentage predicted forced vital capacity (FVC) at lung transplant listing was substituted for FEV_1 as a covariate, there was no meaningful change in the effect estimates for serum albumin specified as either a categorical or continuous variable.

Hypoalbuminemia was strongly associated with early (1-year) mortality. Compared to those with normal albumin levels, the multivariable-adjusted 1-year mortality rate ratios for severe and mild hypoalbuminemic recipients were 1.55 (95% CI: 1.17–2.05) and 1.33 (95% CI: 1.13–1.57), respectively (model 3 in Table 2). Those with a low-normal serum albumin concentration had a multivariable-adjusted 1-year mortality rate ratio of 1.19 (95% CI: 1.01–1.39) compared to those with normal serum albumin. For each 0.5 g/dL decrease in serum albumin concentration the multivariable-adjusted 1-year mortality rate ratio was 1.48 (95% CI: 1.21–1.81) (Table 2).

The multivariable adjusted GAM-fitted model showed a linear inverse association between serum albumin and the risk of death at 1 year for albumin values between 2 g/dL and 5 g/dL, but a weaker relationships below 2 g/dL (Figure 3). The significance of this subtle nonlinear relationship is uncertain given that only 59 (0.9%) participants had albumin levels below 2, and linear p for trend tests across categories of albumin were significant (Table 2). The multivariable-adjusted GAMs showed that continuous variables for recipient and donor BMI ($p = 0.23$ and 0.73, respectively), FEV1 ($p = 0.48$), recipient oxygen use (L/min) at the time of listing ($p = 0.30$) and recipient mean pulmonary artery pressure (mm Hg) at the time of listing ($p = 0.59$) all had a linear relationship with the rate of death at 1 year, and age ($p = 0.01$) and graft ischemic time ($p = 0.04$) did not. Addition of quadratic terms for age and graft ischemic time corrected for nonlinearity in the GAMs (age ($p = 0.70$), age^2 ($p = 0.71$), ischemic time ($p = 0.25$), ischemic time^2 ($p = 0.17$). These quadratic terms were therefore used in the Cox proportional hazards models.

In the subgroup of 4247 participants transplanted on or after May 4, 2005 (the day the LAS system was implemented), an LAS score was available for 3408 (80%). The median LAS score was highest among participants with severe hypoalbuminemia and decreased across categories of higher serum albumin (Table 1). After adjusting for LAS and all other model 3 covariates in the subset with an available LAS score (n = 3408), the 1-year mortality rate ratios for severe and mild hypoalbuminemia were 1.37 (95% CI: 0.95–1.97) and 1.28 (95% CI: 1.01–1.62), respectively, compared to normal serum albumin (Table S1). For each 0.5 g/dL decrease in serum albumin, the 1-year mortality rate ratio was 1.36 (95% CI: 1.04–1.78).

We performed *post hoc* analyses to determine whether mechanical ventilation at the time of transplant, donor–recipient CMV mismatch, mean pulmonary artery pressure (mm Hg) at listing, oxygen use (L/min) at listing, or 6-min walk distance (feet) at listing would confounded the association between serum albumin and posttransplant mortality. Adjustment for these factors did not substantially change our findings that lower serum albumin was associated with a higher rate of death in the first year after transplantation (Table S2).

The association between serum albumin concentration and the rate of death did not appear to vary by BMI (p for interaction = 0.20), but the association did appear to vary by diagnosis (p for interaction = 0.02). Figure 4 shows multivariable-adjusted survival curves for categories of serum albumin concentration stratified by diagnosis. Both multivariable-adjusted 1-year and overall survival varied significantly across albumin categories in both CF ($p = 0.013$ and 0.015) and ILD ($p = 0.019$ and 0.008) patients, but not in COPD patients ($p = 0.144$ and 0.140). Hypoalbuminemia was strongly associated with early mortality in CF and ILD recipients: for every 0.5 g/dL decrease in serum albumin the adjusted 1-year mortality rate ratio was 2.28 (95% CI: 1.32–3.96) and 1.40 (95% CI: 1.03–1.90), respectively. In COPD recipients, there was no association found between serum albumin concentration and the overall mortality rate, but for each 0.5 g/dL decrease in serum albumin, the adjusted 1-year mortality rate ratio increased 1.38 (95% CI: 1.01–1.90) (Table 3).

The PAF of hypoalbuminemia was 10.7%, suggesting that hypoalbuminemia (and related unmeasured and poorly measured confounders) contributed to up to 10.7% of deaths in the first year after transplantation (Table 4). Among those with CF and ILD, below normal serum albumin concentrations contributed up to 32.2% and 12.2% of deaths in the first year after transplantation, respectively.

Discussion

We have shown that hypoalbuminemia at the time of listing for lung transplantation is independently associated with a higher rate of death after lung transplantation. The risk appeared to be highest early after transplantation and varied by disease, with the greatest risk for CF patients and the least risk for COPD patients. Our findings support the hypothesis that extrapulmonary measures of overall health are important determinants of outcomes after lung transplantation.

While it is possible that hypoalbuminemia might directly contribute to poor outcomes after lung transplantation by promoting oxidative injury or platelet aggregation (33,34), it is more likely that hypoalbuminemia and early posttransplant mortality share common antecedent causes. The concentration of albumin in serum is determined by the balance between its synthesis in the liver and its catabolism by the vascular endothelium (11,14). Hypoalbuminemia can therefore be a result of reduced synthesis due to liver disease and protein malnutrition, enhanced catabolism due to inflammation or to renal loss (11,14,19). Since liver and kidney disease are rare among waitlisted lung transplant candidates, malnutrition and systemic inflammation are likely responsible for hypoalbuminemia in this population, and might lead to a higher risk of death by predisposing to infection and lung inflammation, or perhaps by contributing to a state of reduced physiologic reserve (frailty). Systemic inflammation is a primary cause of age-related muscle loss (sarcopenia), which is associated with hypoalbuminemia (35,36). Sarcopenia and its related clinical phenotype of frailty have been shown to predict complications after general surgery and mortality after liver transplantation (37,38). Future investigations that focus on identifying other measures of sarcopenia and frailty in patients listed for lung transplantation have promise to improve lung allocation and outcomes after lung transplantation.

We found that hypoalbuminemia had the strongest association with early posttransplant mortality in recipients with CF. Serum albumin levels parallel the decline in nutritional status caused by recurrent respiratory infections in CF (39). Supplemental nocturnal gastrostomy tube feeding has been shown to augment height and weight gain, and decrease infection rates and lung function decline in children with CF (40,41). While hypoalbuminemia in CF patients might be preventable with aggressive nutritional interventions, such as nocturnal gastrostomy feeding or orally ingested nutritional supplements, our findings should not be interpreted as supporting this practice, since we did not examine the effect of nutritional intervention on lung transplant outcomes.

Among participants with COPD, we found that pretransplant hypoalbuminemia was only weakly associated with 1-year mortality and was not associated with overall mortality. While the hazard ratios for early mortality among those with severe hypoalbuminemia were notably lower for participants with COPD compared to those with ILD (1.27 and 1.48, respectively), the hazard ratios for albumin as a continuous variable were almost identical for these two groups (1.38 and 1.40, respectively) and were statistically significant. The reasons for this discrepancy is not clear, but may be a result of the smaller number of COPD participants with severe hypoalbuminemia (n = 71), the arbitrary thresholds separating albumin categories, and/or differences in the influences of systemic inflammation and nutritional status on albumin levels between participants with and without COPD.

Elevated serum albumin concentrations (5.1–5.9 g/dL) were detected in 73 (1.1%) recipients and multivariable adjusted mortality rate ratios ranged from 1.14 to 1.50, but neither association was statistically significant. It is likely that serum albumin was misclassified in some of these cases. For example, total protein may have been recorded instead of albumin. Accordingly, patients with low total protein concentrations between 5.1 g/dL and 5.9 g/dL will likely also be hypoalbuminemic and therefore have a higher posttransplant mortality. Elevated albumin is most often associated with severe dehydration, which is unlikely at the time of transplant listing because patients are already receiving care from many healthcare providers. Severe vitamin A deficiency is associated with elevated serum albumin (42), and CF patients are at risk for fat-soluble vitamin deficiencies due to fat malabsorption. However, only three CF recipients had elevated serum albumin at the time of transplant listing, and such severe vitamin A deficiency seems unlikely given these patients are receiving medical care.

Our study has several limitations. First, we retrospectively ascertained serum albumin concentrations as reported by transplant center personnel. Interlaboratory variation in the measurement of serum albumin concentration is unlikely, since a standard assay, the BCG method (9,26), is used for the measurement of serum albumin. Second, serum albumin was recorded at the time of listing for lung transplantation rather than at the time of transplantation. It is likely that the serum albumin at transplantation differed from that at the time of listing, since these events were a median of 5 months apart, thereby misclassifying albumin for many study participants. Since it is likely that this error is independent of the risk of death after transplantation, we would expect such misclassification to bias toward the null. If so, our results may underestimate the true association between serum albumin and the risk of death after transplantation. Prospective studies with attention to the timing of albumin measurement may provide additional information about the predictive validity of serum albumin in this setting. Third, inclusion of imprecisely measured confounders and failure to include unmeasured confounders in our models could have contributed to some or all of the associations we observed. Our findings, however, were independent of important potential confounders such as diagnosis, BMI, diabetes, corticosteroid use, donor characteristics and procedural characteristics. Nevertheless, residual confounding by other factors cannot be entirely excluded.

In summary, we found that hypoalbuminemia at lung transplant listing was independently associated with a higher risk of death in a nationwide cohort of lung transplant recipients, and accounted for up to 11% deaths in the first year after lung transplantation. Our findings should prompt investigations of extrapulmonary factors, such as systemic inflammation, sarcopenia and frailty that might contribute to early complications of lung transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure

The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

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Abbreviations

CF	cystic fibrosis
COPD	chronic obstructive pulmonary disease
CMV	cytomegalovirus
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GAM	generalized additive model
ILD	interstitial lung disease
LAS	lung allocation system
OPTN	Organ Procurement and Transplantation Network
PAF	population attributable fraction
UNOS	United Network for Organ Sharing
WHO	World Health Organization

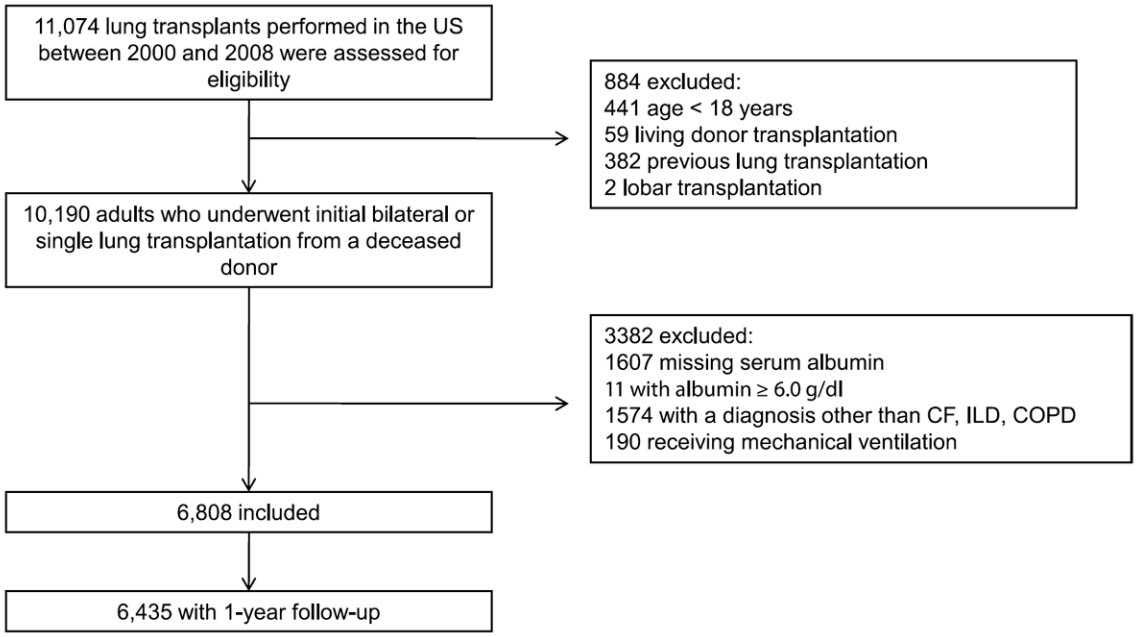
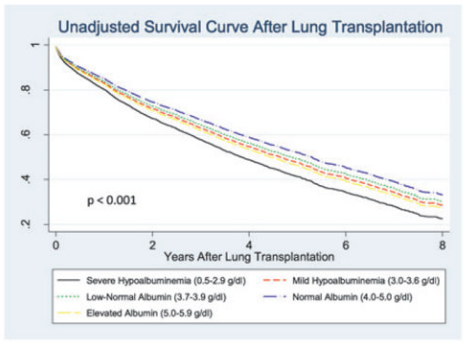


Figure 1. Study participants



Severe Hypoalbuminemia	288	139	49	19	7
Mild Hypoalbuminemia	1274	701	358	145	34
Low-Normal Albumin	1421	847	458	192	35
Normal Albumin	3752	2304	1165	455	91
Elevated albumin	73	41	17	7	2

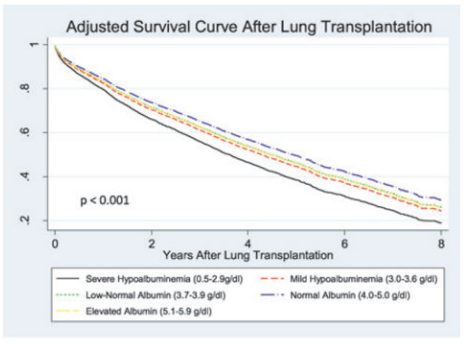


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Figure 2. Unadjusted and multivariable-adjusted survival curves for the entire cohort (n = 6808) for severe hypoalbuminemia (2.9–3.6 g/dL), mild hypoalbuminemia (3.0–3.6 g/dL), low-normal albumin (3.7–3.9 g/dL), normal albumin(4.0–5.0 g/dL) and elevated albumin (5.1–5.9 g/dL) serum concentrations at lung transplant listing

Adjusted survival estimates are adjusted for recipient covariates (age, sex, FEV_1, WHO BMI category, diagnosis, diabetes, use of steroids before transplant and hospitalization at transplant), donor covariates (age, sex, BMI, height, smoking >20 pack years, pulmonary infection and donor cause of death), and procedure covariates (single vs. double lung transplant, transplant year (dichotomized at May 4, 2005, the date the LAS score was implemented), and graft ischemic time). From Table 2, unadjusted and adjusted $p < 0.001$ for trend in both models. *Bottom*: numbers indicate the number of surviving lung transplant recipients at each time point.

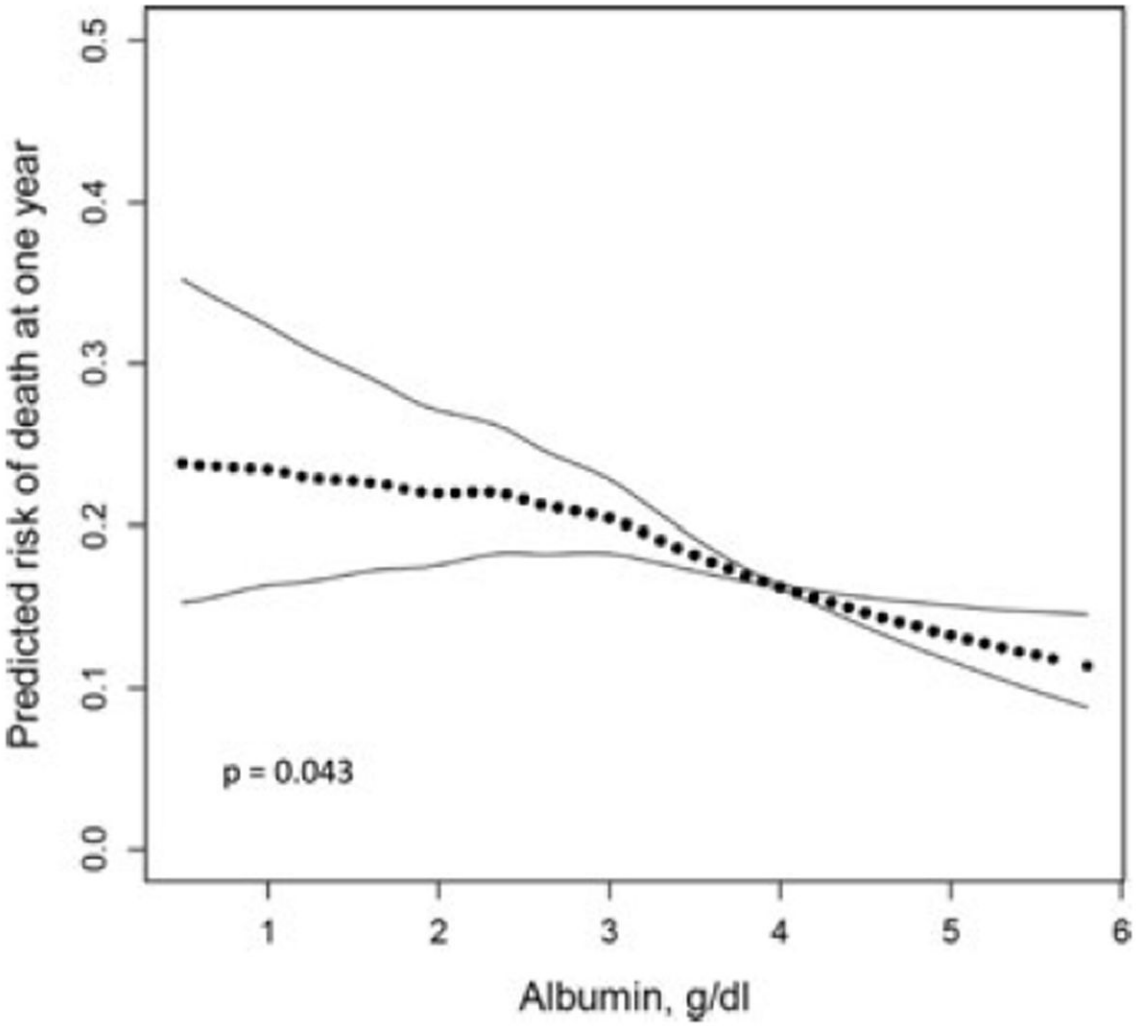

Figure 3. Multivariable-adjusted generalized additive model fitted continuous relationship of serum albumin concentration (g/dL) at lung transplant listing for the risk of death at 1 year for the entire cohort (n = 6808)

Estimates are adjusted for covariates listed in model 3 in the footnote to Figure 2. The significant p-value (0.043) for the smoothed curve for 1-year survival suggests a subtle nonlinear threshold of risk below serum albumin concentrations of 2 g/dL and above 5 g/dL. There is a linear inverse relationship between serum albumin concentrations of 2 and 5 g/dL with overall higher 1-year mortality for lower serum albumin. The significance of this subtle nonlinear relationship is uncertain given that only 59 (0.9%) participants had albumin levels below 2, and linear p for trend tests across categories of albumin were significant (Table 2).

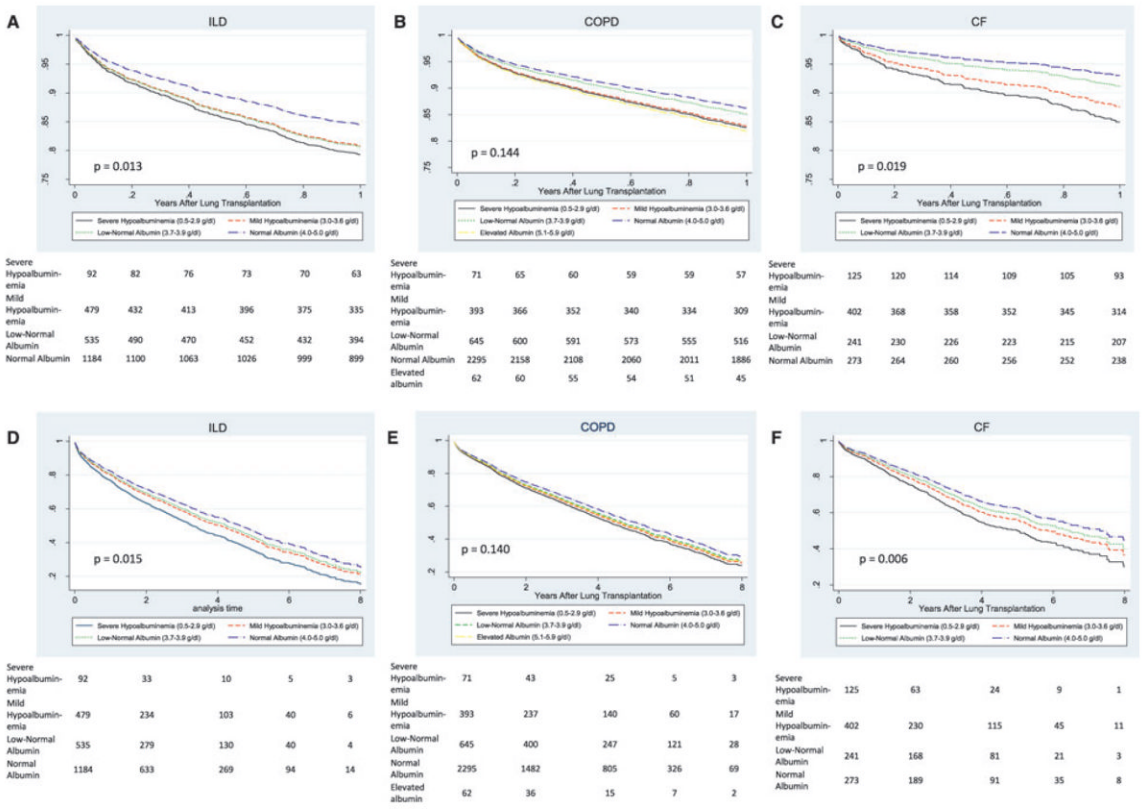

Figure 4. Multivariable-adjusted survival curves for categories of serum albumin concentration at lung transplant listing

Survival censored at 1-year (A) and overall survival (D) for patients who had ILD (n = 2290); survival censored at 1-year (B) and overall survival (E) for patients who had COPD (n = 3466); and survival censored at 1-year (C) and overall survival (F) for patients who had CF (n = 1041). Survival estimates are derived from the stratified Cox model described in Table 3. *p*-Values are for trend tests across albumin categories from Table 3. *Bottom*: numbers indicate the number of surviving lung transplant recipients at each time point.

Table 1

Recipient, donor and procedure characteristics at the time of transplantation

	Number of patients with data available	Severe hypoalbuminemia 0.5–2.9 (g/dL)	Mild hypoalbuminemia 3.0–3.6 (g/dL)	Low-normal albumin 3.7–3.9 (g/dL)	Normal albumin 4.0–5.0 (g/dL)	Elevated albumin 5.1–5.9 (g/dL)
Number transplanted	6808	288 (4.2%)	1274 (19%)	1421 (21%)	3752 (55%)	73 (1.1%)
Recipient characteristics						
Age, years	6808	48 (28–60)	55 (35–61)	57 (48–62)	58 (52–62)	59 (55–62)
Male	6583	160 (56%)	672 (53%)	793 (56%)	2241 (60%)	46 (63%)
Height, cm	6613	167 (162–175)	168 (161–175)	170 (163–178)	170 (163–178)	173 (165–178)
Weight, kg	6733	63.6 (52.6–77.0)	66.1 (53.7–80.3)	70.7 (58.1–82.9)	71.7 (60.3–83.4)	65.3 (55.5–80.2)
BMI, kg/m^2	6608	22.2 (18.8–26.6)	23.4 (19.6–27.7)	24.4 (20.8–28.0)	24.9 (21.5–28.1)	22.6 (20.7–26.1)
FEV1,% predicted	6403	27 (19–45)	28 (20–46)	28 (19–48)	25 (18–48)	21 (16–29)
FVC,% predicted	6410	44 (33–55)	43 (34–56)	47 (37–70)	49 (39–61)	50 (38–63)
LAS[1]	3408	41.2 (36.0–53.2)	39.4 (34.9–48)	37.9 (33.8–45.8)	35.5 (32.9–41.1)	33.6 (32.4–34.9)
Hospitalized	6808	61 (21%)	139 (11%)	102 (7.2%)	215 (5.7%)	3 (4.1%)
Corticosteroid use	6455	130 (48%)	662 (55%)	706 (50%)	1617 (45%)	32 (46%)
Diabetes	6750	78 (28%)	286 (23%)	192 (14%)	364 (9.7%)	6 (8.2%)
Pre-LAS	2561	71 (25%)	504 (40%)	587 (41%)	1373 (37%)	26 (36%)
Post-LAS	4247	217 (75%)	770 (60%)	834 (59%)	2379 (63%)	47 (64%)
Recipient diagnosis						
ILD	2298	92 (32%)	479 (38%)	535 (38%)	1184 (32%)	8 (11%)
COPD	3466	71 (25%)	393 (31%)	645 (45%)	2295 (62%)	62 (85%)
CF	1044	125 (43%)	402 (32%)	241 (17%)	273 (73%)	3 (4.1%)
Donor characteristics						
Age, years	6808	29 (29–44)	30 (20–44)	28 (20–43)	30 (20–45)	27 (19–38)
Male	6808	174 (60%)	731 (57%)	897 (63%)	2388 (64%)	54 (7%)
Height, cm	6793	173 (165–180)	170 (165–178)	173 (166–180)	173 (167–180)	175 (168–180)
Weight, kg	6808	72.9 (62.1–84)	72.6 (61.2–83)	73 (63.6–83.9)	73 (64–84.8)	73 (60–82.8)
BMI, kg/m^2	6779	24.4 (21.6–27.5)	24.4 (21.6–27.6)	24.2 (21.6–27.6)	24.3 (21.7–27.2)	24.2 (21.7–27.4)
Smoked (>20 pack-years)	6768	50 (17%)	271 (21%)	269(19%)	722 (19%)	13 (18%)
Bronchopulm. infection	6808	72 (25%)	313 (25%)	366 (26%)	947 (25%)	21 (29%)

	Number of patients with data available	Severe hypoalbuminemia 0.5–2.9 (g/dL)	Mild hypoalbuminemia 3.0–3.6 (g/dL)	Low-normal albumin 3.7–3.9 (g/dL)	Normal albumin 4.0–5.0 (g/dL)	Elevated albumin 5.1–5.9 (g/dL)
Recipient cause of death						
Head trauma	3644	157 (56%)	672 (54%)	782 (56%)	1980 (54%)	53 (74%)
Cerebrovascular	2387	97 (35%)	449 (36%)	473 (34%)	1354 (37%)	14 (19%)
Anoxic brain injury	569	22 (7.8%)	114 (9.2%)	117 (8.4%)	311 (8.5%)	5 (6.9%)
CNS tumor	61	5 (1.8%)	6 (0.5%)	18 (1.3%)	32 (0.9%)	0 (0%)
Missing	147	7 (2.4%)	33 (2.6%)	31 (2.2%)	75 (2.0%)	1 (1.4%)
Procedure characteristics						
Bilateral transplant	6808	202 (70%)	765 (60%)	710 (50%)	1773 (47%)	35 (48%)
Ischemic time, hours	6031	5.0 (4.0–6.1)	5.0 (3.8–6.1)	4.6 (3.6–5.8)	4.5 (3.5–5.6)	4.5 (3.3–5.3)

[1]Only recipients transplanted after May 4, 2005, have a Lung Allocation Score (LAS).

Percentages indicate the percentage of patients with a characteristic in a given category of serum albumin.

Table 2

Associations between serum albumin concentration at lung transplant listing and mortality after lung transplant

	Total	Severe hypoalbuminemia 0.5–2.9 (g/dL)	Mild hypoalbuminemia 3.0–3.6 (g/dL)	Low-normal albumin 3.7–3.9 (g/dL)	Normal albumin 4.0–5.0 (g/dL)	Elevated albumin 5.1–5.9 (g/dL)	p-for trend	Albumin HR for every 0.5 g/dL decrease	p-Value
Number transplanted (%)	6808	288	1274	1421	3752	73			
Median follow-up time years (IQR)	2.69 (1.06–4.51)	1.98 (0.99–3.56)	2.18 (1.00–4.18)	2.77 (1.07–4.76)	2.85 (1.14–4.70)	2.26 (0.93–3.96)			
Number with 1-year follow-up	6435	269	1188	1352	3558	68			
% Survived 1-year (95% CI)	84 (83–85)	79 (73–83)	81(79–83)	83 (81–85)	85 (84–87)	77 (66–85)			
Person years	20 495	688	3652	4369	11 580	206			
Overall mortality									
Mortality rate per year (95% CI)	0.15 (0.14–0.15)	0.19 (0.16–0.23)	0.16 (0.15–0.17)	0.15 (0.14–0.16)	0.14 (0.13–0.15)	0.17 (0.12–0.23)	<0.001	0.13 (0.11–0.14)	<0.001
Model 1: HR for death (95% CI)		1.35 (1.12–1.62)	1.15 (1.04–1.27)	1.10 (1.00–1.21)	1	1.14 (0.81–1.73)	<0.001	1.28 (1.11–1.46)	0.001
Model 2: HR for death (95% CI)		1.35 (1.12–1.62)	1.15 (1.03–1.27)	1.10 (1.00–1.21)	1	1.14 (0.81–1.61)	<0.001	1.26 (1.11–1.43)	0.001
Model 3: HR for death (95% CI)		1.35 (1.12–1.62)	1.15 (1.04–1.27)	1.10 (1.00–1.21)	1	1.14 (0.81–1.61)	<0.001	1.26 (1.11–1.43)	0.001
1-year mortality									
Mortality rate per year (95% CI)	0.18 (0.17–0.19)	0.24 (0.19–0.31)	0.21 (0.19–0.24)	0.19 (0.16–0.21)	0.16 (0.14–0.17)	0.26 (0.16–0.42)	<0.001	0.15 (0.12–0.18)	<0.001
Model 1: HR for death at 1-year (95% CI)		1.52 (1.15–2.01)	1.35 (1.14–1.60)	1.19 (1.01–1.39)	1	1.49 (0.90–2.47)	<0.001	1.48 (1.21–1.81)	<0.001
Model 2: HR for death at 1-year (95% CI)		1.52 (1.15–2.01)	1.34 (1.14–1.58)	1.20 (1.02–1.40)	1	1.50 (0.90–2.48)	<0.001	1.47 (1.21–1.80)	<0.001
Model 3: HR for death at 1-year (95% CI)		1.55 (1.17–2.05)	1.33 (1.13–1.57)	1.19 (1.01–1.39)	1	1.50 (0.90–2.49)	<0.001	1.48 (1.21–1.81)	<0.001

All Cox models include the random effect of transplant center as a shared frailty component.

Model 1: Adjusted for recipient characteristics (age, age^2, sex, diagnosis, FEV_1, diabetes, steroid use, hospitalized at the time of transplant, and BMI categorized using the World Health Organization Classification [WHO] scheme as previously described [24]).

Model 2: Model 1 + donor characteristics (age, sex, height, BMI, pulmonary infection, smoking > 20 pack years, donor cause of death).

Model 3: Model 2 + procedure characteristics (single vs. double lung transplant, graft ischemic time, graft ischemic time^2 and year of transplant (dichotomized at May 4, 2005, the date the LAS score was implemented).

Table 3

Associations between serum albumin concentration at lung transplant listing and the mortality after lung transplantation, stratified by diagnosis

	Total	Severe hypoalbuminemia 0.5–2.9 (g/dL)	Mild hypoalbuminemia 3.0–3.6 (g/dL)	Low-normal albumin 3.7–3.9 (g/dL)	Normal albumin 4.0–5.0 (g/dL)	Elevated albumin 5.1–5.9 (g/dL)	p-Value for trend	Albumin HR for every 0.5 g/dL decrease	p-Value
ILD									
Number transplanted (%)	2298	92	479	535	1184	8			
Cox proportional hazard model									
Mortality rate per year (95% CI)	0.17 (0.16–0.18)	0.25 (0.19–0.34)	0.19 (0.16–0.21)	0.18 (0.15–0.20)	0.16 (0.15–0.20)		0.006		
Model 3: HR for death (95% CI)		1.37 (1.01–1.85)	1.15 (0.97–1.35)	1.10 (0.94–1.29)	1		0.015	1.32 (1.07–1.62)	0.009
Censored at 1-year									
Mortality rate per year (95% CI)	0.22 (0.20–0.24)	0.33 (0.25–0.49)	0.25 (0.21–0.31)	0.24 (0.20–0.30)	0.20 (0.16–0.22)		0.001		
Model 3: HR for death at 1-year (95% CI)		1.48 (0.96–2.27)	1.27 (0.99–1.63)	1.25 (0.99–1.59)	1		0.013	1.40 (1.03–1.90)	0.031
COPD									
Number transplanted (%)	3466	71	393	645	2295	62			
Cox proportional hazard models									
Mortality rate per year (95% CI)	0.14 (0.13–0.15)	0.17 (0.12–0.24)	0.13 (0.15–0.18)	0.14 (0.13–0.16)	0.13 (0.13–0.14)	0.16 (0.11–0.23)	0.113		
Model 3: HR for death (95% CI)		1.18 (0.82–1.69)	1.13 (0.96–1.33)	1.08 (0.95–1.24)	1	1.15 (0.79–1.67)	0.140	1.14 (0.94–1.39)	0.180
Censored at 1-year									
Mortality rate per year (95% CI)	0.16 (0.15–0.17)	0.20 (0.11–0.36)	0.20 (0.16–0.25)	0.16 (0.13–0.20)	0.15 (0.13–0.17)	0.22 (0.12–0.40)	0.103		
Model 3: HR for death at 1-year (95%)		1.27 (0.70–2.30)	1.30 (0.99–1.71)	1.11 (0.88–1.41)	1	1.34 (0.75–2.41)	0.144	1.38 (1.01–1.90)	0.043
CF									
Number transplanted (%)	1044	125	402	241	273	3			
Cox proportional hazard model									
Mortality rate per year (95% CI)	0.13 (0.12–0.14)	0.17 (0.13–0.22)	0.15 (0.12–0.16)	0.13 (0.10–0.15)	0.10 (0.09–0.13)		0.003		
Model 3 HR for death		1.51 (1.05–2.19)	1.29 (0.98–1.70)	1.20 (0.89–1.60)	1		0.019	1.55 (1.09–2.20)	0.016

	Total	Severe hypoalbuminemia 0.5–2.9 (g/dL)	Mild hypoalbuminemia 3.0–3.6 (g/dL)	Low-normal albumin 3.7–3.9 (g/dL)	Normal albumin 4.0–5.0 (g/dL)	Elevated albumin 5.1–5.9 (g/dL)	p-Value for trend	Albumin HR for every 0.5 g/dL decrease	p-Value
Censored at 1-year									
Mortality rate per year (95% CI)	0.14 (0.12–0.17)	0.21 (0.14–0.31)	0.17 (0.13–0.22)	0.13 (0.90–0.19)	0.97 (0.66–0.14)		0.005		
Model 3 HR for death at 1-year		2.17 (1.19–3.96)	1.73 (1.06–2.84)	1.32 (0.76–2.29)	1		0.006	2.28 (1.32–3.96)	0.003

[1]Too few observations to calculate meaningful effect estimates and were excluded from the associated models.

Estimates are adjusted for covariates listed in model 3 in the footnote to Figure 2.

Table 4

Multivariable-adjusted population attributable fractions stratified by diagnosis

	Number transplanted	PAF at 1 year (%)
All recipients	6808	10.7
Interstitial lung disease	2233	12.2
Chronic obstructive Pulmonary disease	3360	5.5
Cystic fibrosis	990	32.2

PAF= population attributable fraction.

The PAF for all recipients at 1 year was estimated using the multi-variable Cox proportional hazard model 3 from Table 2. The PAF for specific diagnoses was estimated using the multivariable Cox proportional hazard model 3 from Table 3. The PAF is the proportional reduction in the number of deaths if the exposure of interestwere eliminated from the population. For example, if all lung transplant recipients had a normal albumin, up to 10.7% of deaths might be prevented in the first year after transplantation.