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CLINICAL INVESTIGATIONS

Serum albumin concentration as an independent prognostic indicator in patients with pulmonary arterial hypertension

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Background: Serum albumin is a strong prognostic indicator for many disease processes, yet limited data exist regarding its prognostic relationship in pulmonary arterial hypertension (PAH). Our study aims to assess the relationship of hypoalbuminemia with disease severity and mortality in this population.

Hypothesis: Serum albumin concentrations are a predictor of outcomes in PAH.

Methods: A retrospective review of all patients with World Health Organization group 1 PAH evaluated between March 2001 and August 2008 was performed. Patients were stratified into groups based on serum albumin concentration ≤3.3 g/dL (hypoalbuminemia) vs >3.3 g/dL. Clinical, hemodynamic, and survival comparisons were compared between groups using Student *t* test and χ^2 test, followed by univariate analysis and multivariate logistic regression.

Results: A total of 163/273 (59.7%) patients had a documented serum albumin concentration. Hypoalbuminemia was present in 41 (25.2%) patients and serum albumin ≤3.3 g/dL represented the lowest quartile of serum albumin. Patients with hypoalbuminemia had higher rates of renal dysfunction (26.8% vs 9.8%, P =0.0069) and hepatic dysfunction (29.3% vs 6.6%, P <0.001), and lower hemoglobin levels (11.6 vs 13.4 g/dL, P < 0.001). Hemodynamic and functional capacity assessments were comparable between groups. Independent predictors of mortality included low albumin levels (hazard ratio [HR]: 0.485, P = 0.008), high right atrial systolic area (HR: 1.062, P = 0.003), low Fick-derived cardiac index (HR: 1.465, P = 0.016), and high New York Heart Association functional class (HR: 1.767, P = 0.042). Patients with hypoalbuminemia demonstrated a significantly lower survival rate at latest follow-up (P = 0.01).

Conclusions: Lower serum albumin concentrations in patients with PAH are associated with higher mortality and can serve as a marker of disease severity in this patient population.

KEYWORDS

Albumin, Mortality, Outcome, Prognostic, Pulmonary Hypertension

1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease process associated with pulmonary vascular remodeling and right heart failure that carries a high morbidity and mortality.[1,2] Although pulmonary artery pressures, functional capacity assessments, and patient symptoms are used to guide therapies, prognostication can still be challenging.[1,3–5] Studies have identified age, blood pressure, renal function, and biomarker abnormalities as predictors of adverse prognosis, and these clinical variables can be helpful in discussing prognosis with patients and guiding therapy.[6] Although serum albumin concentration has been found to be an important prognostic indicator in numerous other disease processes, limited data are available in the PAH population.[1,4–20] In patients with chronic heart failure, lower serum albumin levels have been associated with poor prognosis.[10–13,21] Similarly, in patients with congenital heart disease, lower albumin levels were more commonly seen with greater disease complexity.[14] Despite several studies examining the relationship between hypoalbuminemia and outcomes in heart failure patients, no study has systematically assessed the prognostic significance of albumin in a contemporary chronic PAH population. We therefore sought to investigate whether hypoalbuminemia is associated with worse long-term outcomes in PAH patients.

2 | METHODS

This historical cohort study was approved by the institutional review board of the University of Pittsburgh as minimal risk to subjects. A retrospective review of all adult patients with a confirmed diagnosis of World Heart Organization (WHO) group I PAH evaluated at the University of Pittsburgh Medical Center between March 2001 and August 2008 was performed. Patients were included if the diagnosis was confirmed following a hemodynamic right heart catheterization demonstrating precapillary PAH with clinical evaluation excluding other etiologies, including left heart failure and pulmonary disease. Patients younger than 18 years old were excluded, as were patients with WHO group II–V PAH and patients with incomplete outcome data, including missing clinical status at latest follow-up. Clinical, laboratory, and hemodynamic data were collected by manual review of the electronic medical record.

Clinical characteristics and outcomes of patients with and without documented serum albumin concentrations were initially compared to assess for bias. In patients with documented serum albumin levels, clinical data were compared between groups stratified based on the presence or absence of hypoalbuminemia (defined as a serum albumin concentration ≤3.3 g/dL based on prior studies). Clinical diagnoses, functional capacity assessments, and New York Heart Association (NYHA) classification were extracted from the electronic medical record. Time difference between initial diagnosis (including diagnosis date at another institution) and assessment at the study institution was included in the analysis. Hemodynamic data were derived from both transthoracic echocardiogram and invasive right heart hemodynamic catheterization. Cardiac output was calculated using the Fick formula per institutional protocol. Size and function quantification of the heart chambers was assessed by transthoracic echocardiogram. Severity of right ventricular dysfunction and dilation as well as presence and size of pericardial effusion were extracted per qualitative comments by the interpreting cardiologist. All right heart catheterizations were performed by board-certified interventional cardiologists with experience in invasive hemodynamic assessments, and echocardiograms were read by board-certified cardiologists.

Statistical analyses were performed using JMP 10.0.0 statistical software (SAS Institute, Cary, NC). Student *t* test and analysis of variance were used to compare continuous variables between groups, and χ^2 tests were used to compare categorical variables. Multivariate logistic regression analysis was performed using univariate predictors of mortality, including serum albumin concentration, age, gender, NYHA class, mean right atrial pressure, Fick-derived cardiac output, presence of connective tissue disease, presence of right ventricular dilation, right ventricular function, right atrial systolic area, presence of pericardial effusion, and creatinine. Cox regression analyses assessed multivariate predictors of mortality and results reported them as hazard ratio (HR) with 95% confidence interval (CI). An additional analysis adjusting for chronic kidney disease (CKD) and cirrhosis is included as Supporting Information, Supporting Table 1, in the online version of this article. Kaplan–Meier survival curves assessed survival outcomes. *P* values <0.05 were considered statistically significant.

3 | RESULTS

A total of 273 PAH patients were evaluated between March 2001 and August 2008; 163 (59.7%) patients had serum albumin values available and comprised the final study population. Follow-up data were available on all patients included in the study. There was no significant difference in survival between patients with and without a documented albumin level (overall mortality 57.1% vs 50.9%, respectively; $P = 0.317$). Mean follow-up was similar in patients with and without documented serum albumin levels (4.34 ±2.64 vs 4.59 ±2.67 years, respectively; $P = 0.436$). No significant differences in baseline clinical characteristics were noted between patients with and without documented serum albumin (data not shown), particularly considering other concurrent comorbidities such as cirrhosis and CKD are strongly associated with hypoalbuminemia.

Demographics of the final study population of 163 patients with a documented serum albumin level are shown in Table 1. Most patients were female (74%), with a mean age of 52.3 ±14.6 years. Most patients reported NYHA functional class II to III symptoms. Noninvasive and invasive hemodynamic measurements are noted in Table 2; the average mean PA pressure was severely elevated at 48 ±16 mm Hg. Echocardiographic right ventricular dilatation (50%) and systolic dysfunction (44%) were common, with 20% of patients demonstrating a significant pericardial effusion on echocardiography.

Mean serum albumin was 3.8 ±0.8 g/dL. The 41 (25.2%) patients with serum albumin in the bottom quartile (≤3.3 g/dL) were considered to have hypoalbuminemia (group 1) and were compared to the remaining patients (group 2). Table 1 illustrates clinical differences between patients with and without hypoalbuminemia. Patients with hypoalbuminemia had a shorter duration since PAH diagnosis than the remaining patients (1.7 years vs 2.7 years, $P = 0.009$) and more frequently had a prior diagnosis of cirrhosis (29% vs 7%, $P < 0.001$) and CKD (27% vs 10%, $P = 0.007$). Serum creatinine (1.4 vs 1.1 mg/dL, $P = 0.012$) and blood urea nitrogen (26 vs 20 mg/dL, $P = 0.044$) levels were higher in patients with hypoalbuminemia, whereas hemoglobin was lower (11.6 vs 13.4 g/dL, $P < 0.001$). Echocardiographic and invasive right heart catheterization–derived hemodynamic assessments were similar between groups. Patients with hypoalbuminemia were more likely to have a significant pericardial effusion (34% vs 15%, $P = 0.005$) (Table 2).

Serum albumin was a significant univariate predictor of mortality ($P = 0.01$); the optimal serum albumin cutoff for predicting mortality based on receiver operating characteristic curve analysis was 3.3 g/dL. Table 3 presents independent predictors of mortality on multivariate analysis. On multivariate analysis, serum albumin concentration showed a significant inverse relationship with mortality (HR: 0.49, 95% CI: 0.28–0.83, $P = 0.008$), whereas higher NYHA class (HR: 1.8, 95% CI: 1.0–3.1, $P = 0.042$), decreased Fick-derived cardiac index (HR: 1.5, 95% CI: 1.1–2.0, $P = 0.016$), and right atrial systolic area (HR: 1.1, 95% CI: 1.0–1.1, $P = 0.003$) had strong direct relationships with mortality. Other univariate predictors of mortality were no longer significant after multivariate adjustment (Table 2). An additional analysis adjusting for CKD and cirrhosis found no difference among the variables, except that NYHA class only demonstrating a trend toward

TABLE 1 Characteristics of all patients with comparisons among subsets with serum albumin above or below 25th percentile (3.3 g/dL)

Characteristic	All Patients, n = 163	Albumin >3.3 g/dL, n = 122	Albumin ≤3.3 g/dL, n = 41	*P* Value
Age, y	52.3 ±14.6	51.8 ±14.9	53.8 ±13.9	0.45
Time between diagnosis and evaluation, y	2.6 ±3.7	2.7 ±2.9	1.7 ±2.7	0.0089
Female gender	120 (73.8%)	91 (74.6%)	29 (70.7%)	0.63
Caucasian race	146 (89.6%)	111 (91%)	35 (85.4%)	0.34
Connective tissue disease	54 (33.1%)	37 (30.3%)	17 (41.5%)	0.21
Cirrhosis	20 (12.3%)	8 (6.6%)	12 (29.3%)	0.0004
Chronic kidney disease	23 (14.1%)	12 (9.8%)	11 (26.8%)	0.0069
Body mass index, kg/m^2	28.3 ±10	28.9 ±8.2	27.3 ±9.1	0.34
NYHA class	2.47 ±0.69	2.48 ±0.66	2.44 ±0.79	0.76
6MWD, m	321 ±111	327 ±123	271 ±74	0.27
Prostanoid use	51 (31.3%)	38 (31.7%)	13 (31.4%)	0.6
β-blocker use	59 (36.2%)	52 (42.6%)	7 (17.1%)	0.003
PDE5 inhibitor use	13 (8%)	11 (9%)	2 (4.9%)	0.32
Calcium channel blocker use	38 (23.3%)	30 (24.5%)	8 (19.5%)	0.51
Serum sodium, mEq/L	139 ± 4	140 ± 3	136 ± 6	0.99
Serum creatinine, mg/dL	1.2 ± 0.7	1.1 ± 1	1.4 ±0.5	0.012
BUN, mmol/L	21 ±15	20 ±16	26 ±17	0.044
Hemoglobin, g/dL	13.1 ± 2.8	13.4 ±2.3	11.6 ±2.3	<0.001
Serum albumin, g/dL	3.8 ±0.8	4.2 ±0.5	2.6 ±0.6	<0.001

Abbreviations: 6MWD, 6-minute walk distance; BUN, blood urea nitrogen; NYHA, New York Heart Association; PDE5, phosphodiesterase 5. Data presented as mean ± standard deviation or n (%).

mortality. The Figure illustrates a Kaplan–Meier curve demonstrating a significantly lower survival among patients with lower serum albumin levels during long-term follow-up (log-rank $P = 0.01$). Mortality at latest follow-up was higher for patients with hypoalbuminemia (70.5% vs 51.2%, $P = 0.04$). Additional correlation analysis were performed between mean RA pressure and albumin ($r = -0.0082$, $P = 0.929$) and mean PA pressures with albumin ($r = 0.116$, $P = 0.202$) showing small interactions.

TABLE 2 Hemodynamic characteristics of all patients with comparisons among subsets with serum albumin above or below 25th percentile (3.3 g/dL)

Variable	All Patients	Albumin >3.3 g/dL	Albumin <3.3 g/dL	*P* Value
EF, %[a]	55 ±8	55 ±8	57 ±5	0.98
RA pressure, mm Hg[a]	11.5 ±3.5	11.7 ±3.6	11.4 ±3.5	0.7
RA systolic area, cm^2[a]	20.5 ±8.8	20.6 ±9.1	20 ±8.2	0.73
TR velocity, m/s[a]	3.9 ±0.8	3.9 ±0.9	4 ±0.8	0.15
RVSP, mm Hg[a]	76 ±26	74 ±28	77 ±26	0.26
TAPSE, mm[a]	16 ±5.6	16 ±5.6	17 ±6	0.19
Significant RV dysfunction[a]	71 (43.6%)	51 (41.8%)	20 (48.8%)	0.3
Significant RV dilation[a]	81 (49.7%)	59 (48.4%)	22 (53.7%)	0.89
Significant pericardial effusion[a]	32 (19.6%)	18 (14.8%)	14 (34.1%)	0.005
Mean RA pressure, mm Hg[b]	9.9 ±8.7	9.8 ±9.4	10.2 ±6.3	0.8
RV systolic pressure, mm Hg[b]	74 ±25	76 ±26	69 ±24	0.2
RV end diastolic pressure, mm Hg[b]	13 ±14	13 ±6	15 ±8	0.34
PA systolic pressure, mm Hg[b]	76 ±25	77 ±26	73 ±22	0.44
PA diastolic pressure, mm Hg[b]	30 ±13	31 ±15	29 ±11	0.36
PA mean pressure, mm Hg[b]	48 ±16	49 ±16	46 ±15	0.37
PCWP, mm Hg[b]	12.7 ±8	12.7 ±8	12.7 ±10	0.51
Fick cardiac index, L/min/m^2[b]	2.80 ±1	2.7 ±0.92	3 ±1.18	0.11

Abbreviations: EF, ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RV, right ventricular; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitant. Data are presented as mean ±standard deviation or n (%).

[a] Noninvasive transthoracic echocardiographic measurement.

[b] Invasive right heart hemodynamic catheterization measurement.

TABLE 3 Multivariable predictors of mortality by Cox regression

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Serum albumin	0.485	0.284–0.829	0.008
Age	1.023	0.994–1.053	0.119
Female gender	0.809	0.355–1.842	0.613
NYHA class	1.767	1.019–3.060	0.042
Mean RA pressure	0.990	0.934–1.048	0.733
Decreased Fick cardiac index	1.465	1.075–1.998	0.016
Connective tissue disease	2.083	0.970–4.477	0.060
Significant RV dilation	0.868	0.667–1.130	0.292
Significant RV dysfunction	1.126	0.845–1.500	0.418
RA systolic area	1.062	1.020–1.106	0.003
Serum creatinine	0.992	0.641–1.534	0.970
Absence of pericardial effusion	0.584	0.226–1.508	0.266

Abbreviations: NYHA, New York Heart Association; RA, right atrial; RV, right ventricular.

4 | DISCUSSION

This is the largest reported study evaluating the prognostic value of serum albumin concentrations among patients with PAH. This is the first study to systematically describe the relevance of serum albumin levels for long-term prognosis in a contemporary PAH population. Our results demonstrate that lower albumin levels portend worse survival outcomes, and are associated with the presence of other systemic comorbidities that may reflect a more rapid disease progression. Serum albumin concentration level was among the strongest predictors of mortality of the studied clinical, hemodynamic, echocardiographic, and laboratory parameters on multivariate analysis. This finding is consistent with studies in other patient populations.[1,2,6–15,18]

Albumin is the most abundant serum protein, exclusively synthesized in the liver and subsequently secreted into the plasma, entering both the intra- and extravascular spaces.[20] Serum albumin levels are influenced by numerous factors that may influence patient outcomes, including nutritional status, inflammatory state, and liver function.[22] Liver dysfunction does not appear to be the most important determinant of decreased serum albumin levels in some disease processes, implicating other pathophysiologic mechanisms.[22,23] Breakdown of albumin occurs in intravascular compartments, likely with a large component derived from endothelial cells as well as capillary leakage. Heart failure patients may have an increased transcapillary escape rate of albumin, which is associated with higher right atrial pressures.[12] In animal studies, decreased albumin increases permeability in the lung vasculature, promoting pulmonary edema.[19] In patients with PAH, endothelial dysfunction and capillary leakage are common, which has been hypothesized to mediate loss of plasma proteins.[8,12,14,22,24]

Serum albumin integrates numerous pathophysiologic processes that are relevant for disease progression in patients with PAH, and therefore, hypoalbuminemia may represent a nonspecific risk marker of more advanced PAH. Hepatic dysfunction, malnutrition (cardiac cachexia), and systemic inflammation may be both the cause and consequence of progressive RV failure from PAH, leading to decreased synthesis of albumin by the liver.[20–23] Patients with hypoalbuminemia were found to have worse renal and hepatic function as well as overall lower hemoglobin levels. Although renal and hepatic dysfunction as well as inflammation and malnutrition can all predispose to lower albumin levels, the independent association of multiorgan dysfunction adds further evidence to the systemic effects of PAH and identifies an increased systemic disease burden. This relationship, as demonstrated in our population, is likely indicative of how phenotypic characteristics within the disease process affect outcomes. Similar to hypoalbuminemia resulting in higher mortality, the presence of hypoalbuminemia also reflects a higher degree of comorbid conditions and multisystem organ dysfunction in this patient population. An additional analysis found similar results when the presence of cirrhosis and CKD were excluded, highlighting the importance of hypoalbuminemia alone. The exact mechanism of hypoalbuminemia in patients with PAH remains uncertain and likely varies among patients; however, regardless of the mechanism, hypoalbuminemia remains a poor prognostic indicator.

A preclinical study by Hilliker et al. demonstrated an increased concentration of albumin in bronchoalveolar lavage specimens of rats with PAH, supporting the presence of vascular albumin leakage as a potential contributor to hypoalbuminemia.[2] Therefore, lower serum albumin levels may be a result of increased capillary permeability and subsequent loss of albumin in the intravascular space rather than solely a result of decreased hepatic production of the protein. Capillary dysfunction is an integral component of the underlying pathophysiology in PAH, so it is possible that the degree of capillary dysfunction may be associated with the degree of hypoalbuminemia. Additionally, albumin breakdown can occur within the intravascular compartment, likely precipitated by endothelial dysfunction and capillary leakage.[22]

Other studies have assessed the relationship between serum albumin levels and clinical outcomes in smaller PAH populations as a secondary endpoint. Kawut et al. demonstrated that higher albumin levels (HR: 0.37, 95% CI: 0.16–0.84, $P = 0.019$), as well as warfarin use, cardiac index, and acute vasoreactivity, were independently associated with improved transplant-free survival in 84 patients with PAH from 1994 to 2002.[1] Although this relatively small study demonstrates the association between albumin and outcomes in PAH patients, our data help to support the findings in a larger and more recent population. Echocardiographic and hemodynamic assessments in our study were performed during the same evaluation period,

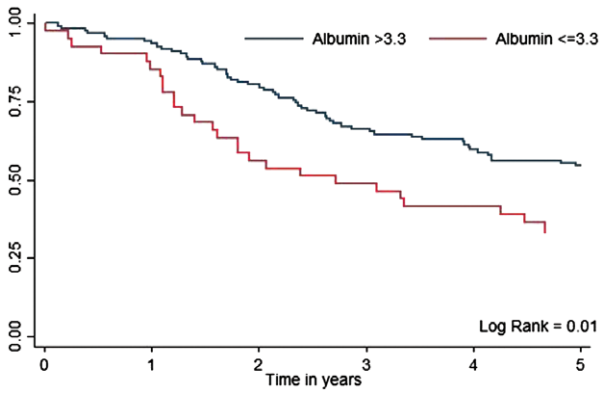

FIGURE 1 Kaplan-Meier curve assessing mortality among patients with serum albumin >3.3 mg/dL and ≤3.3 mg/dL

allowing for more accurate comparisons. Haddad et al. examined outcome predictors in 119 hospitalized patients with acutely decompensated PAH, demonstrating an association between low serum albumin and increased hospital mortality. The aim of this study was to identify factors associated with an increased likelihood of mortality or urgent transplantation within 90 days of admission, and also demonstrated higher respiratory rate, renal dysfunction, hyponatremia, and tricuspid regurgitation severity as other significant markers, adding further evidence to the systemic effects of PAH.[11] The study by Haddad et al. confirms the importance of hypoalbuminemia as a predictor of PAH outcomes in a more recent patient cohort, but differs significantly from our study in that it focused on hospitalized patients who reflect an especially high-risk cohort.

Interestingly, the time from initial PAH diagnosis was significantly lower in patients with hypoalbuminemia. This is counter-intuitive, as a more significant decrease in albumin level would be expected as the disease progresses over time (longer time from diagnosis), and may suggest that hypoalbuminemia reflects a more rapidly progressive disease course with a worse outcome. This may reflect the severity of endothelial dysfunction, along with many of the other factors as contributors, and helps to support the hypothesis that worsening endothelial dysfunction is associated with the underlying mechanism for hypoalbuminemia. Ha et al. mention that albumin has pleiotropic properties, including aiding in the conversion of prostaglandins.[20] Additionally, increased severity in endothelial dysfunction and damage creates the platform for hypoalbuminemia.[23] Therefore, a diminished amount of circulating albumin likely plays a role in the pathophysiology surrounding PAH, potentially as both a cause and consequence of disease progression.

We found no difference among hemodynamic and functional capacity metrics as a function of serum albumin levels, except for a larger predisposition to a significant pericardial effusion in patients with hypoalbuminemia. Pericardial effusion formation in PAH is a known adverse prognostic finding, and the lack of independent association between pericardial effusion and mortality when corrected for serum albumin may suggest that hypoalbuminemia might mediate this finding.[1] These findings help to reinforce the necessity for additional models and variables to predict progression and severity of PAH. Although traditional indices of functional capacity are reduced among both subsets, additional measures of disease severity with higher sensitivity are necessitated, as demonstrated in recent studies in other patient populations.[25]

Several inherent study limitations exist, as with other retrospective observational studies. Only 60% of patients evaluated at our institution during this time period had a serum albumin level documented, although an initial baseline analysis showed no difference in follow-up or outcomes between patients with and without documented serum albumin values. The study institution is a tertiary care academic medical center, and therefore, most patients were diagnosed prior to referral, which will influence time-dependent outcomes. The study population included patients from nearly a decade ago, in the setting of a rapid evolution in the therapeutic armamentarium for PAH, with relatively few patients on PAH-specific therapies at initial evaluation. Additional laboratory and clinical variables needed to distinguish among the many potential pathophysiologic processes driving hypoalbuminemia in these patients were not available, and it remains possible that certain specific etiologies for hypoalbuminemia might have different prognostic relevance. Further studies are needed to assess the incremental value of serum albumin concentrations in conjunction with various scoring systems. We were not able to consistently calculate validated PAH prognostic risk scores, such as the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) Registry risk score,[3] to determine the incremental prognostic value of serum albumin when added to these established risk models. Although these limitations exist, strengths of our study include a relatively large patient population, comparisons of extensive clinical variables including invasive hemodynamics, and a relatively long follow-up period.

5 | CONCLUSION

Our study found that lower serum albumin concentrations in patients with PAH are associated with more systemic comorbidities and decreased survival, potentially representing a more progressive clinical course. Although our data suggest that serum albumin concentrations can be used as a nonselective marker for disease severity, further prospective studies are needed to confirm these findings.

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REFERENCES

1. Kawut SM, Horn EM, Berekashvili KK, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. *Am J Cardiol*. 2005;95:199–203.
2. Hilliker KS, Bell TG, Lorimer D, et al. Effects of thrombocytopenia on monocrotaline pyrrole-induced pulmonary hypertension. *Am J Physiol*. 1984;246 (6 pt 2):H747–H753.
3. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest*. 2012;141:354–362.
4. Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest*. 2012;142:448–456.
5. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122:164–172.
6. Al-Naamani N, Palevsky HI, Lederer DJ, et al. Prognostic significance of biomarkers in pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2016;13:25–30.
7. Arques S, Roux E, Sbragia P, et al. Usefulness of serum albumin concentration for in-hospital risk stratification in frail, elderly patients with acute heart failure. Insights from a prospective, monocenter study. *Int J Cardiol*. 2008;125:265–267.
8. Ataga KI, Brittain JE, Moore D, et al. Urinary albumin excretion is associated with pulmonary hypertension in sickle cell disease: potential role of soluble fms-like tyrosine kinase-1. *Eur J Haematol*. 2010;85:257–263.
9. Diller GP, van Eijl S, Okonko DO, et al. Circulating endothelial progenitor cells in patients with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension. *Circulation*. 2008;117:3020–3030.
10. Grodin JL, Lala A, Stevens SR, et al. Clinical implications of serum albumin levels in acute heart failure: insights from DOSE-AHF and ROSE-AHF. *J Card Fail*. 2016;22:884–890.
11. Haddad F, Peterson T, Fuh E, et al. Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail*. 2011;4:692–699.

12. Hesse B, Parving HH, Lund-Jacobsen H, Noer I. Transcapillary escape rate of albumin and right atrial pressure in chronic congestive heart failure before and after treatment. *Circ Res*. 1976;39:358–362.
13. Horwich TB, Kalantar-Zadeh K, MacLellan RW, et al. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J*. 2008;155:883–889.
14. Kempny A, Diller GP, Alonso-Gonzalez R, et al. Hypoalbuminaemia predicts outcome in adult patients with congenital heart disease. *Heart*. 2015;101:699–705.
15. Kurtul A, Murat SN, Yarlioglues M, et al. Usefulness of serum albumin concentration to predict high coronary SYNTAX score and in-hospital mortality in patients with acute coronary syndrome. *Angiology*. 2016;67:34–40.
16. Plakht Y, Gilutz H, Shiyovich A. Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAM-II) project. *Int J Cardiol*. 2016;219:20–24.
17. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;35:1286–1293.
18. Yoo HH, Martin LC, Kochi AC, et al. Could albumin level explain the higher mortality in hemodialysis patients with pulmonary hypertension? *BMC Nephrol*. 2012;13:80.
19. Kraft SA, Fujishima S, McGuire GP, et al. Effect of blood and albumin on pulmonary hypertension and edema in perfused rabbit lungs. *J Appl Physiol (1985)*. 1995;78:499–504.
20. Ha CE, Bhagavan NV. Novel insights into the pleiotropic effects of human serum albumin in health and disease. *Biochim Biophys Acta*. 2013;1830:5486–5493.
21. Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. *J Card Fail*. 2011;17:451–458.
22. Ballmer PE. Causes and mechanics of hypoalbuminaemia. *Clin Nutr*. 2001;20:271–273.
23. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial*. 2004;17:432–437.
24. Zhou C, Townsley MI, Alexeyev M, et al. Endothelial hyperpermeability in severe pulmonary arterial hypertension: role of store-operated calcium entry. *Am J Physiol Lung Cell Mol Physiol*. 2016;311:L560–L569.
25. Snipelisky D, Kelly J, Levine JA, et al. Accelerometer measured daily activity in heart failure with preserved ejection fraction: clinical correlates and association with standard heart failure severity indices. *Circ Heart Fail*. 2017;10:e003878.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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