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Pulmonary Hypertension In Patients with Pulmonary Fibrosis Awaiting Lung Transplant

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Abstract

Pulmonary hypertension (PH) may complicate idiopathic pulmonary fibrosis (IPF) but the prevalence of PH in IPF remains undefined. We sought to describe the prevalence of PH in IPF.

We analyzed the lung transplant (LT) registry for the US (January 1995 to June 2004) and identified IPF patients who had undergone right heart catheterization (RHC). We defined PH as a mPAP of $\geq$ 25 mm Hg and severe PH as an mPAP of > 40 mm Hg. Independent factors associated with PH were determined.

Of 3,457 persons listed, 2,525 (73.0%) had undergone RHC. PH affected 46.1% of subjects. Approximately 9% had severe PH. Variables independently associated with mild to moderate PH were: need for oxygen, PCWP, and FEV1. Independent factors related to severe PH included: pCO2, age, FEV1, PCWP, need for oxygen, and race. A sensitivity analysis in subjects with PCWPs of < 15 mm Hg did not appreciably alter our findings.

PH is common in IPF awaiting LT, but the elevations in mPAP are moderate. Lung volumes alone do not explain the PH. Given the prevalence of PH and its relationship with surrogate markers for quality of life (e.g. ADLs), future trials of therapies for this may be warranted.

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology associated with progressive parenchymal fibrosis.[1] Patients with IPF face substantial morbidity and mortality and report substantially impaired quality of life.[2] Lung transplant (LT) represents the lone intervention that potentially improves survival in IPF.[3]

Pulmonary hypertension (PH) is evolving as an important factor which can adversely affect outcomes in chronic lung disease. In advanced chronic obstructive pulmonary disease (COPD), some recommend therapy directed at controlling the pulmonary artery pressure.[4] In fibrotic lung diseases more akin to IPF, such as sarcoidosis, secondary PH is common and is a marker for early death.[5,6]

Less is known about PH in IPF. Epidemiologically, several retrospective analyses indicate that PH in IPF may be frequent.[7-9] Illustrating the emerging interest in PH and IPF, Ghofrani and colleagues examined the impact of sildenafil on pulmonary hemodynamics in lung fibrosis and concluded that it caused pulmonary vasodilation and improved gas exchange.[10] Others have explored inhaled agents in IPF related to PH as well.[11]

With the advent of newer options for treating PH coupled with the lack of effective therapies for IPF, targeting PH appears attractive. However, before studying interventions it is important to define the prevalence and extent of this process. With improved information regarding the prevalence of and clinical factors associated with PH in IPF, clinicians can better determine whom to evaluate for PH, and researchers can design more appropriate clinical trials. Thus, to explore the frequency of PH in IPF, we retrospectively analyzed the United States LT registry. Our specific objectives were to

describe the prevalence of PH in IPF, to assess the severity of PH in this population, and to identify clinical variables that correlated with PH.

Methods

Subjects

We identified patients with PH and IPF through reviewing the LT registry maintained by the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplant Network (OPTN). We included all adult subjects listed for LT for IPF between January 1995 and June 2004. The diagnoses of IPF were based on the reports of the referring transplant center. Surgical lung biopsy was not required for the diagnosis of IPF and given the time period covered many patients were listed before the development of the recent consensus statement regarding the clinical diagnosis of IPF. The type of proposed LT did not affect eligibility for enrollment in our cohort. Since our focus was PH we required patients to have undergone right-heart catheterization (RHC) as part of their transplant evaluation. Subjects who did not have a RHC were excluded. There were no additional exclusion criteria.

Endpoints

The presence of PH represented the primary endpoint while severe PH served as a secondary endpoint. We defined PH as a mean pulmonary artery pressure (mPAP) of $\geq$ 25 mm Hg and severe PH as a mPAP of > 40 mm Hg.

Study Co-variates

We recorded information concerning demographics and pulmonary function testing. The forced expiratory volume in 1 second (FEV1) and the forced vital capacity (FVC) comprised the pulmonary function measures of interest. UNOS does not maintain data regarding the diffusion of carbon monoxide (DLCO) and did not begin collecting the FEV1/FVC ratio until 1999. Therefore, we were unable to include these variables. The partial pressure of carbon dioxide (pCO2) and the need for oxygen were also noted. For functional status we gauged the patient's ability to walk more than 150 ft in six minutes and the degree of assistance they required with activities of daily living (ADLs). Although an exact distance walked would be preferred for the 6 min walk test, UNOS only records whether the patient had the ability to walk 150 ft. For co-morbid diseases we focused on the presence of hypertension, COPD, and diabetes. COPD was defined based on the reports of referring centers and not based on UNOS calculated FEV1/FVC ratios. Information regarding the pulmonary capillary wedge pressure (PCWP) and the cardiac index (CI) were collected as well. For each of the variables, the model inputs reflect information available at time of listing.

Sensitivity analysis

Because of the potential for occult left ventricular heart disease and in an effort to control for possible elevations in the PCWP directly contributing to elevations in the mPAP, we conducted a sensitivity analysis in the subgroup of patients with PCWP of < 15 mm Hg. In other words, elevations of the mPAP in this subgroup more properly represent isolated PH.

Statistics

Univariate analyses were performed initially. We employed a Chi-square test to compare categorical variables. Continuous variables followed a non-normal distribution and hence we utilized the Wilcoxon Test for comparisons. All tests were two-tailed, and a p value of <0.05 was assumed to represent statistical significance.

We entered all factors that were significant in the univariate analysis at the ≤ 0.10 level into the model. A backwards stepwise approach was employed. Candidate variables were removed in a stepwise fashion if $p > 0.10$. Co-linearity was assessed via correlation matrices. We assessed the models goodness of fit with the Hosmer-Lemeshow statistic. Ninety-five percent confidence intervals (95% CIs) around odds ratios are also reported. Analyses were done using the SAS 9.1 (Cary, NC).

Results

During the 9.5 year study period 3,457 persons were listed for LT for IPF. The final cohort comprised 2,525 (73.0%) subjects who had RHC data available. Those who had undergone RHC were not systematically different from those who did have a RHC in terms of either demographic characteristics, measures of pulmonary physiology, or assessments of co-morbidities. The mean age of the entire study population undergoing RHC was 53.4 ± 8.7 years and 61.4% were male. Those not undergoing RHC had a mean age of 54.8 ± 6.3 years and 63.3% were male. The mean FVC in both the RHC and non-RHC populations was approximately 50%. Diabetes was reported to occur in nearly

10% of all of these patients, irrespective of whether they had a RHC performed. PH was common affecting 46.1% of all IPF patients listed for LT. Among those with PH the mean PA measured 34.2 ± 9.9 mm Hg. Nearly 1 in 10 subjects had severe PH.

Non-severe PH

Comparisons between those without PH and those with non-severe PH are highlighted in Table 1. Contrasting those without PH to persons with mild and moderate PH (mPAP 25-40 mm Hg) revealed these groups to be comparable with respect to gender distribution while those with mild PH elevations were slightly younger. PH was more frequent among African Americans. Subjects with PH required more assistance with their ADLs. COPD was 1.31 times (95% CI: 1.03-1.67) more prevalent in the PH cohort. Hypertension also occurred more often in persons with PH while there was a trend towards an increased frequency of diabetes in those with PH. Corticosteroid use was common in all subjects.

The pCO2 was marginally higher while the FVC was slightly lower in PH subjects. The FEV1, though, was lower in persons with PH (50.0±16.5% predicted vs. 52.7±16.5% predicted, $p<0.0001$). Similarly, individuals with PH required more supplemental oxygen (2.3±1.9 L/min vs. 2.9±2.1 $p<0.0001$). Furthermore, those with PH in IPF were nearly 80% more likely (OR 1.78, 95% CI: 1.50-2.11, $p<0.0001$) to require more than 3 L/min of oxygen. Results of invasive hemodynamic monitoring indicated that the cardiac index was equivalent between those with and without PH, although the PCWP was higher in the PH cohort.

In multivariate analysis (Table 2), several variables were independently associated with the presence of PH. Need for supplemental oxygen, the PCWP, and the FEV1 correlated with mPAP. Those requiring oxygen were significantly more likely to have concomitant PH (OR 1.22, 95% CI: 1.14-1.30, p <0.001). Similarly, a higher PCWP increased the probability that PH would be present. Neither the FVC nor the CI showed a relationship with PH.

Severe PH

Comparisons between those with normal mPAPs and patients with severe PH are also shown in Table 1. Many of the differences seen in the analysis with the non-severe PH subjects were noted in the comparison between those lacking PH and those with severe PH. For example, need for both assistance with ADLs or admission to the hospital at time of listing were more common in severe PH. Hypertension was more often noted in patients with severe PH. Concerningly, race again correlated with PH. Nearly 20% of the severe PH group were African American vs. only 9.0% of non-PH population (OR: 2.37, 95% CI: 1.63-3.46, p<0.001). In terms of physiology, FVC failed to segregate patients with severe PH from those with normal mPAPs and was in fact numerically higher in those with worse mPAPs. The FEV1 did not differ as a function of the mPAP. Interestingly, although the pCO2 was higher in those with mild and moderate elevations of mPAP compared to those with normal mPAPs, the pCO2 was lowest in the severe PH patients.

Multivariate analysis (Table 3) identified several variables independently linked with severe PH. Unlike our observations in the non-severe PH cohort, we noted that race

significantly correlated with the presence of severe PH. Specifically, African Americans were twice as likely to have severe PH compared to Caucasians (OR 1.93, 95%CI: 1.02-3.66, p=0.043). Need for supplemental oxygen also identified subjects more likely to have severe elevations in mPAP. With respect to invasive hemodynamics, PCWP remained a significant factor associated with a diagnosis of severe PH. While cardiac performance did not appear related to severe PH, age, the pCO2, and the FEV1 were independently associated with the presence of severe PH.

Sensitivity analysis

Approximately 18% of entire population had PCWPs of >15. After excluding patients with PCWPs of > 15, the results of the logistic regressions to identify factors independently related to PH varied somewhat from those observed in the entire PH population. Table 4 indicates variables associated with mild to moderate PH not associated with an increased PCWP. As seen in the overall analysis of PH, oxygen use, FEV1, and the PCWP remained significantly correlated with isolated PH. Additionally, need for assistance with ADLs and the presence of hypertension now appeared linked to mild to moderate PH. Table 5 reveals the findings from the multivariate analysis in persons with severe, isolated mPAP elevations. Younger age along with the PCO2 were "protective." In general, factors independently associated with severe PH also correlated with severe, isolated PH. For example, African Americans again faced a nearly 2-fold increased probability of having severe PH. In addition to variables noted in the overall analysis of severe PH, a low six minute walk distance and need for assistance with ADLs additionally were associated with the presence of severe, isolated PH.

Discussion

This large retrospective analysis reveals that PH is common in persons with IPF awaiting LT. Although PH affects approximately 45% of these subjects, severe PH is relatively infrequent. Multivariate analysis indicates that several variables are independently associated with PH and severe PH but only three factors: the FEV1, the need for supplemental oxygen, and an elevated PCWP, consistently correlate with the presence of PH across varying degrees of severity. In the sensitivity analysis of persons who meet the definition for isolated PH (e.g. elevated mPAP and PCWP of <15), the FEV1, need for assistance with ADLs, the PCWP, and oxygen use appear linked to all degrees of this.

Several earlier analyses have gauged the prevalence of PH in IPF. King et al. found that 20% of those with IPF had evidence of PH.[7] However, the presence of PH was only assessed by chest radiography.[7] In a study of 25 persons, Agarwal and colleagues determined that 36% had PH[12] These authors, though, relied only on echocardiography which may overestimate or underestimate the pulmonary artery pressure in persons with interstitial lung disease.[13] In a larger analysis also relying on echocardiography, Nadrous and co-workers concluded that PH was common in advanced IPF and that it correlated with both a lower DLCO and a lower resting PaO2.[8] This study was limited in that there was the potential for substantial selection bias as only 136 of 487 (28%) of patients with IPF had undergone echocardiography.[8] Finally, Lettieri et al. relying on RHC noted that PH was documented in approximately 1/3rd of persons with

IPF.[9] Additionally, these authors demonstrated that even moderate elevations of mPAP (>25 mm Hg) correlated with increased mortality.[9]

The present analysis confirms the findings of these earlier reports and clearly demonstrates that PH is a common complication of IPF. More importantly, our project builds on these efforts, in that our report represents the largest experience with RHC in IPF. As a result, our larger sample size allows more certainty as to the estimation of the prevalence of PH in IPF. Additionally, since we relied only on RHC our estimates of mPAP are likely more accurate than those based solely on echocardiography. All prior studies, moreover, represented the experience of single centers. Because UNOS and OPTN serves as the registry for all US LTs we were able to draw on patients seen at multiple centers.

Pathophysiologically, the factors independently related to the presence of PH suggest some mechanisms as to the evolution of PH in IPF. The correlation between lower FEV1 and both PH implies that superimposed airflow limitation may accelerate potential elevations in the mPAP. Furthermore, an abnormal pCO2 may mean that underlying gas exchange abnormalities increase the risk for PH. For both of these factors, though, the statistical relationships we observed may not be clinically meaningful -- differences in the mean values for these variables across the strata of mPAPs is small (e.g., 2% difference in FEV1) and thus any correlation is likely speculative rather than causative. It therefore appears likely that in IPF additional causes for elevated mPAPs exist. Other investigators have reached similar conclusions when exploring the mechanisms for PH in COPD. Chaouat et al. performed extensive evaluations in persons with severe COPD and PH.[14] Their data demonstrated that factors other than the extent

of the COPD itself contributed to mPAP increases.[14] With respect to COPD, patients with concurrent IPF and emphysema may be at particularly increased risk for PH. For example, Cottin et al. noted that nearly half of such subjects had PH. Although we did not find an independent association between COPD and PH, the link between FEV1 and PH indicates that patients with both conditions may be at high risk for PH.[15]

Three factors correlated with PH across the range of pressure elevations: the FEV1, need for supplemental oxygen, and the PCWP. In the cohort without elevated PCWPs, assistance with ADLs also appeared important. The interaction between ADLs and PH likely underscores the morbidity burden associated with PH. In other words, inability to perform ADLs does not cause PH but reflects the burden of this on a patient's performance status.[2]

Multiple potential factors could account for the association between need for supplemental oxygen and PH. This may indicate the impact of chronic pulmonary vasoconstriction due to alveolar hypoxia, although the connection between chronic alveolar hypoxia and pulmonary vasoconstriction has not been conclusively demonstrated. It could also represent that, because of regulations regarding use of supplemental oxygen, these patient might simply be more likely to have oxygen prescribed because of underlying cor pulmonale. On the other hand, PH may cause hypoxemia due to both a low cardiac output and low central venous oxygen saturations along with increased perfusion of pulmonary shunt vessels or low V/Q areas.

The interaction between PCWP and PH appears more complicated. The correlation between the two suggests that some component of left ventricular (LV) dysfunction is contributing to PH in IPF. However, several aspects of our data reveal that

more nuanced issues may be involved. First, there was no independent relationship between CI and PH. If LV dysfunction were contributing to PH, one would predict that the CI would be lower in those with PH. Second, despite the association between PH and PCWP, the average PCWPs in the population were, nonetheless, in the normal range. Third, the gradient between the mPAP and the average PCWP in this population was higher than one would expect if this process represented passive congestion. This discordance underscores that some process other than purely LV dysfunction must be contributing to the PH. Similarly, since the population analyzed is relatively selected as these subjects are felt to be candidates for LT, overt congestive heart failure is unlikely to be present. Our sensitivity analysis of patients meeting criteria for isolated PH shows a persistent relationship between mPAP and PCWP. Given that by design these persons have no elevations of the PCWP, one cannot ascribe the elevation in mPAP to passive congestion or occult left ventricular dysfunction.

Some might hypothesize that progressive parenchymal destruction would lead to PH in IPF. We, though, failed to note a strong correlation between FVC and PH. Similarly, the two other studies expressly exploring the nexus between FVC and PH, those by Nadrous et al. and by Lettieri et al. also did not report a positive relationship between FVC and PH.[8,9] Likewise, Leuchte and co-workers in an analysis of the physiology of PH in lung fibrosis did not note a correlation between PH and FVC.[16] Together, these results, along with our data, imply that issues other than decrements in FVC contribute to PH. Alternatively, however, our failure to detect an interaction between FVC and PH may reflect that many subjects already had advanced IPF with low FVC. We doubt this, though, since both the mean FVC and standard deviation around

the FVCs across all three populations studied (normal, mild-moderate PH, severe PH) were similar.

African Americans faced a greater probability of suffering from severe PH. This observation is troubling given that earlier analyses noted above show that PH portends worse outcomes in IPF. This connection between severe mPAP elevations and race might reflect later referral during the disease's natural history. That race independently remained strongly associated with severe PH (irrespective of the PCWP) after controlling for other conventional markers of severity of illness and performance status in IPF argues against this conclusion. Differences in access to care may in some way also contribute to this finding and suggests that clinicians must work to ensure that there is not some form of subtle discrimination in our management of African Americans suffering from IPF. Finally, differences in vascular biology, on the other hand, could help explain this finding. African Americans, for instance, have been reported to respond differentially, when compared to Caucasians, to certain vasodilators given in the treatment of heart failure.[17] Future investigations are necessary to explore the meaning and cause of our observation.

Our study has several limitations. The retrospective design exposes the analysis to bias. However, unlike the data generated in other reports dealing with PH in IPF, the UNOS/OPTN registry represents data collected contemporaneously at listing. Thus, recall bias and coding bias are unlikely. Additionally, some of the patients listed for LT for IPF may not have had IPF but some other form of interstitial lung disease. The demographic distribution indicates this is not likely as the cohort resembles the general composition of patients with IPF. We also lacked information on certain variables that

could have been of interest such as the DLCO. Consequently, our noting a relationship between need for supplemental oxygen and PH may simply indicate that need for supplemental oxygen is a surrogate for a lower DLCO. Finally, we studied only patients actually listed for LT. We did not have information on potential subjects not evaluated LT. This limits the generalizability of our conclusions. If the cohort included persons with less advanced IPF, we might have been able to detect a correlation between lung function and PH. Despite these considerations, our study is the largest experience with RHC in IPF.

In conclusion, PH is common in IPF. Generally, the degree of PH in IPF is mild to moderate with few subjects developing severe PH by time of listing for LT. Several clinical variables correlate with the presence of PH. In light of the prevalence of PH in IPF coupled with the absence of highly effective therapies for this disease, clinical trials of agents directed at controlling the mPAP in IPF seem warranted.

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Correlates of Pulmonary Hypertension (n=2525)

Table 1.

Variable	mPAP < 25 mm Hg (n=1363)	mPAP ≥ 25 mm Hg (n=933)	mPAP > 40 mm Hg (n=231)	P (PA > 25 mm Hg vs. ≤ 25 mm Hg)	P (PA > 40 mm Hg vs. ≤ 25 mm Hg)
Demographics					
Age, years	54.0±8.7	53.4±8.5	49.9±9.2	0.040	<0.0001
Male (%)	60.9%	62.8%	58.7%	0.360	0.560
African American (%)	9.0%	11.8%	19.1%	0.030	<0.0001
BMI kg/m^2	27.7±4.8	28.7±5.1	27.7±5.2	<0.0001	0.870
Pulmonary Function					
FVC, % predicted	49.6±15.7	48.4±16.7	51.4±20.8	0.020	0.610
FEV_1, % predicted	52.7±16.5	50.0±16.5	51.5±19.0	<0.0001	0.30
$PaCO_2$, mm Hg	40.5±5.7	41.2±6.9	38.7±7.8	0.150	<0.001
6 minute walk distance < 150 feet, (%)	10.3%	13.9%	21.1%	0.010	<0.0001
Any need for O_2, (%)	75.9%	86.0%	92.8%	<0.0001	<0.0001
Need for ≥ 3 L/min O_2, (%)	37.3%	51.4%	65.4%	<0.0001	<0.0001
O_2 used, L/min	2.3±1.9	2.9±2.1	3.5±2.4	<0.0001	<0.0001
Functional Status					

Some or total ADL assistance (%)	56.7%	63.3%	74.4%	0.001	<0.0001
Hospitalized (%)	3.9%	5.1%	9.7%	0.170	<0.0001
In ICU (%)	1.4%	2.3%	4.0%	0.140	0.010
Co-Morbid Illnesses					
COPD (%)	12.4%	15.7%	16.2%	0.030	0.0130
Hypertension (%)	18.1%	21.6%	22.8%	0.040	0.011
Diabetes (%)	10.4%	13.0%	7.5%	0.060	0.150
Corticosteroids (%)	60.5%	63.4%	58.4%	0.170	0.560
Hemodynamic Monitoring					
Cardiac Index, l/min/m^2	2.8±0.7	2.8±0.8	2.5±0.9	0.82	<0.0001
PCWP, mm Hg	8.3±4.2	12.1±5.5	14.0±8.2	<0.0001	<0.0001

Abbreviations: ADL – activities of daily living, BMI – body mass index, COPD – chronic obstructive pulmonary disease, FEV1- forced expiratory lung volume in 1 second, FVC – forced vital capacity, ICU – intensive care unit, mPAP – mean pulmonary artery pressure, PCWP – pulmonary capillary wedge pressure.

Independent Correlates of Mild to Moderate Pulmonary Hypertension (n=2296)*

Table 2.

Variable	Adjusted Odds Ratio	95% CI	P
Need for any O_2	1.22	1.14 – 1.30	<0.001
PCWP – per 1 mm Hg increase above mean value for cohort	1.19	1.16 – 1.21	<0.001
FEV1 – per 1% increase from mean value for cohort	0.99	0.99 – 1.00	0.050

*Defined as mean pulmonary artery pressure of between 25-40 mm Hg.

Abbreviations: CI – confidence interval, FEV1- forced expiratory lung volume in 1 second, PCWP – pulmonary capillary wedge pressure.

Note: The Hosmer Lemeshow Goodness of Fit test yields a chi-square value of 14.8 (p=0.06).

Independent Correlates of Severe Pulmonary Hypertension (n=1594)*

Table 3.

Variable	Adjusted Odds Ratio	95% CI	P
PCO_2 – per 1 point increase	0.92	0.89 – 0.96	.0001
Age at listing	0.95	0.92 – 0.97	<.0001
FEV1 – per 1% increase from mean value for cohort	0.96	0.93 – 0.99	.003
PCWP – per 1 mm Hg increase above mean value for cohort	1.22	1.17 – 1.28	<0.001
Any O_2 needed	1.29	1.12 – 1.49	0.004
O_2 need > 3 L/min	1.89	1.03 – 3.47	0.041
African American race	1.93	1.02 – 3.66	0.043

*Defined as mean pulmonary artery pressure of > 40 mm Hg.

Abbreviations: ADL – activities of daily living, CI – confidence interval, FEV1 – forced expiratory volume in 1 second; PCWP – pulmonary capillary wedge pressure.

Note: The Hosmer Lemeshow Goodness of Fit test yields a chi-square value of 7.2 (p=0.51).

Independent Correlates of Mild to Moderate Isolated Pulmonary Hypertension (n=1883)

Table 4.

Variable	Adjusted Odds Ratio	95% CI	P
FEV1 – per 1% increase from mean value for cohort	0.99	0.990-0.997	0.006
PCWP – per 1 mm Hg increase above mean value for cohort	1.22	1.18-1.26	<0.001
Need for assistance with ADLs	1.24	1.00-1.54	0.047
Hypertension	1.33	1.03-1.72	0.030
O_2 need > 3 L/min	2.84	2.30-3.50	<0.001

Abbreviations: ADLs – activities of daily living; CI – confidence interval, FEV1 – forced expiratory volume in 1 second, PCWP – pulmonary capillary wedge pressure.

Note: The Hosmer Lemeshow Goodness of Fit test yields a chi-square value of 18.1 (p=0.02).

Independent Correlates of Severe Isolated Pulmonary Hypertension (n=1308)

Table 5.

Variable	Adjusted Odds Ratio	95% CI	P
PCO2	0.88	0.85-0.92	<0.001
Age at listing	0.94	0.92-0.96	<0.001
PCWP -- per 1 mm Hg increase above mean value for cohort	1.26	1.18-1.34	<0.001
6 minute walk distance < 150 feet	1.71	1.00-2.94	0.050
Need for assistance with ADLs	1.78	1.15-2.74	0.010
African American race	1.78	1.02-3.09	0.042
O_2 need > 3 L/min	4.49	2.99-6.74	<0.001

Abbreviations: ADLs – activities of daily living; CI – confidence interval, PCWP – pulmonary capillary wedge pressure.

Note: The Hosmer Lemeshow Goodness of Fit test yields a chi-square value of 5.9 (p=0.66).