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Early View

Research letter

Prevalence and Impact of WHO Group 3 Pulmonary Hypertension in Advanced Idiopathic Nonspecific Interstitial Pneumonia

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Prevalence and Impact of WHO Group 3 Pulmonary Hypertension in Advanced Idiopathic Nonspecific Interstitial Pneumonia

Short running title: NSIP PH

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To The Editor:

Pulmonary hypertension (PH) is associated with impaired quality of life, worsened functional status, and increased mortality in idiopathic pulmonary fibrosis (IPF).[1] The prevalence and clinical impact in other idiopathic interstitial pneumonias (IIP) has not been previously reported. Given the prognostic significance of PH in IPF, we sought to determine the prevalence and severity of World Health Organization (WHO) Group 3 PH in a cohort of patients with biopsy-proven idiopathic NSIP. We recognized that the prevalence of PH in this population of patients with advanced NSIP would be an overestimation of the NSIP population at large, but felt that mandating surgical lung biopsy and right heart catheterization (RHC) were the only way to ensure accurate diagnosis of NSIP and PH, respectively.

A retrospective review of patients with idiopathic NSIP diagnosed between 2002 and 2016 at our center was performed. All cases were reviewed at our multidisciplinary pulmonary pathology conference. CTD was rigorously excluded in all patients and RHC was required for confirmation of PH. RHC are not performed standardly on all patients in our clinic, and would have been performed as part of lung transplant evaluation or to confirm PH suggested by clinical parameters or echocardiographic data. PH was defined as a resting mean pulmonary artery pressure (mPAP) of ≥ 25mm Hg and severe PH as mPAP of ≥ 35mm Hg. Patients with a pulmonary capillary wedge pressure (PCWP) > 15 mmHg were excluded from the cohort as they were suspected to have left-heart disease associated (WHO Group 2) PH. Chronic thromboembolic disease was excluded in all patients with ventilation/perfusion scanning. The primary endpoints of this study were the prevalence and impact of WHO Group 3 PH on patient outcomes in idiopathic NSIP. Secondary outcomes included the correlation of FVC and mPAP in idiopathic NSIP patients, as well as the association between other demographics and PH in this population.

Review of records from our multidisciplinary pulmonary pathology meeting identified 95 potential patients with biopsy proven NSIP. Of these patients, 35 met criteria for inclusion in the study.

Eleven of thirty-five patients (31.4%) had WHO Group 3 PH. The mean mPAP for those with and without WHO Group 3 PH were 32.0 ± 10.3 mmHg and 18.1 ± 3.1 mmHg, respectively. Of the thirty-five patients in the study, seven patients (20%) had a mPAP of 25-30 mmHg, two (5.7%) had a mPAP of 31-34 mmHg, and two (5.7%) had a mPAP ≥ 35 mmHg. Figure 1 details the characteristics of the patients with PH versus those without. Percent predicted FVC was similar between the WHO Group 3 PH and no PH cohort, with r=-0.12 suggesting poor correlation between FVC percent predicted and mPAP (p=0.48).

Median transplant-free survival was significantly lower in patients with WHO Group 3 PH at 17.6 months as compared to 47.9 months in the cohort without PH (p=0.05). Severe PH (mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with a low cardiac index) was only seen in two patients (5.7%), both of whom expired without transplant, with an average adjusted survival time of 12.6 months. Both of these patients also suffered from severe functional impairment with a mean 6MWT distance of only 137.2 and 129 m, respectively. A competing risk analysis was performed to determine if the relationship between WHO group 3 PH and survival would persist after taking into account lung transplant as a competing event. The analysis confirmed that the presence of WHO Group 3 PH was associated with an increased risk of death even after considering transplant as a competing risk (HR=3.73, 95% CI 1.32 – 10.55, p=0.013). Additionally, a multivariate competing risk analysis found WHO Group 3 PH was still associated with an increased risk of death after adjusting for age and FVC percent predicted.

We found that WHO Group 3 PH was present in approximately one third (31.4%) of idiopathic NSIP patients who underwent RHC. To our knowledge this is the first and only study to rigorously evaluate PH in NSIP. In fact, no prior study has reported on the prevalence of PH in any idiopathic interstitial pneumonia other than IPF. We feel our study has a number of strengths, including the strict inclusion criteria used to ensure that only idiopathic NSIP patients were included (need for surgical lung

biopsy, extensive CTD serologic evaluation, and review by multidisciplinary pulmonary pathology committee), confirmation of WHO Group 3 PH by RHC, and long-term follow-up.

The major finding from our study was the significant reduction in transplant-free survival seen in idiopathic NSIP patients with WHO Group 3 PH. Median transplant-free survival was over 30 months shorter in patients with WHO Group 3 PH, at a mere 17.6 months. The association of WHO Group 3 PH with increased mortality remained, even after adjusting for age and FVC % predicted and treating lung transplant as a competing risk. The association between the development of PH is consistent with what has been demonstrated in the IPF population, where PH serves as a powerful predictor of mortality.[1,2] Indeed, it appears that once PH develops in NSIP and IPF, outcomes are quite similar suggesting perhaps that PH then becomes the major driver of patients subsequent clinical course. Given this association, it is prudent for clinicians to screen for PH and consider lung transplant listing in NSIP patients who develop complicating PH.

The prevalence of PH in this idiopathic NSIP population is likely an overestimate of what would be seen in a less select, general pulmonary practice population for several reasons. Since our clinic specializes in advanced lung disease and lung transplantation, there is inherent referral bias and the study population represents a more advanced subset of idiopathic NSIP patients as their mean FVC % predicted was 53.3%. In addition, all 35 patients in our study had mixed cellular and fibrotic or fibrotic NSIP pathologically, and thus may represent a more treatment refractory subset of idiopathic NSIP. Lastly, the RHC requirement for inclusion in the study makes the pre-test probability of PH higher as the indication for RHC would typically have been clinical or echocardiographic suspicion of PH or as part of a pre-transplant evaluation. Regardless, given the paucity of data on the prevalence of PH in NSIP, we feel this data is of value to clinicians, particularly those who practice in a clinic with a similar patient population.

Although not the original intention of this manuscript, our study also contributes to the existing literature on survival in idiopathic NSIP. Travis, et al reported a 90% five-year survival for idiopathic fibrotic NSIP.[3] Transplant-free survival in our cohort, even in those without PH, was < 50% at five years. Ours most likely reflects a more advanced population, as noted by the moderately severe mean FVC and its composition of only mixed cellular and fibrotic or fibrotic NSIP patients. In addition, Travis et al. exclusively evaluated death in their survival analysis, not lung transplantation, whereas our study takes into account both outcomes, which likely contributes to the shorter transplant-free survival. Lastly, the methods used to ascertain patient survival differ between the two studies. The Travis study relied upon review of medical records and contact with the referring physician, which may have underestimated the incidence of death compared to our use of the Social Security Death Index, which may be more accurate as patients relocate or are lost to follow-up. Nonetheless, outcomes in our cohort are notably worse than prior reports of NSIP.

In conclusion, we have demonstrated that PH commonly complicates the course of idiopathic fibrotic NSIP. Development of PH in this population is associated with markedly reduced transplant-free survival. Indeed, PH related to NSIP appears to have similar prognostic implications to what has been reported in IPF-PH, supporting the current concept of including both groups in the same clinical trials of therapy.

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Baseline Characteristics of Idiopathic NSIP Patients Stratified by the Presence of Group 3 Pulmonary Hypertension

Characteristic	NSIP Cohort (N=35)	No Pulmonary Hypertension (N=24)	Group 3 Pulmonary Hypertension (N=11)	p value
Age	53.9 (9.8)	52.2 (10.2)	57.8 (8.0)	0.12
Male Gender	17 (49%)	10 (41.7)	7 (63.6)	0.23
FVC % predicted	53.3 (20.4)	56.1 (20.0)	47.2 (20.6)	0.23
DLCO % predicted	33.0 (12.5)	34.9 (13.6)	28.0 (8.9)	0.17
Six Minute Walk Distance (meters)	266.4 (159.2)	281.8 (172.6)	229.5 (120.9)	0.39
Oxygen Requirement	25 (71.4)	15 (62.5)	10 (90.9)	0.08
Mean Pulmonary Artery Pressure	22.5 (9.0)	18.1 (3.1)	32.0 (10.3)	<0.0001
Right Atrial Pressure	5.0 (4.0)	4.3 (3.2)	6.6 (5.3)	0.11
Pulmonary Capillary Wedge Pressure	8.1 (3.5)	7.9 (3.4)	8.5 (3.8)	0.64
Cardiac Index	2.9 (0.7)	2.9 (0.7)	3.1 (0.8)	0.53

Data reported as mean with standard deviation (SD) or percent (%)