European Review for Medical and Pharmacological Sciences 2010; 14: 695-704

Predictors of survival in idiopathic interstitial pneumonia

R. CARBONE[1], G. BOTTINO[2], P. PAREDI[3], P. SHAH[3], K.C. MEYER[4]

[1]Department of Medicine, Respiratory Unit, Regional Hospital Aosta, Aosta (Italy)
[2]DI.MI. University of Genoa, Genoa (Italy)
[3]National Heart and Lung Institute, Royal Brompton Hospital, London (United Kingdom)
[4]Department of Medicine, Section of Allergy, Pulmonary, and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health (USA)

Abstract. – *Aim:* **To evaluate the ability of newly identified clinical factors to predict prognosis and survival in idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP).**

Methods: **Seventy-eight patients referred to the University of Genoa and the Regional Hospital of Aosta between January 1995 and December 2006 were evaluated prospectively. Fifty-nine patients were diagnosed with IPF and 19 with NSIP on the basis of surgical lung biopsy specimens. Gender, age at diagnosis, smoking, New York Heart Association class (NYHA), systolic pulmonary artery pressure (sPAP), Octreoscan uptake index (UI), and therapy were the chosen variables. Primary end-point was survival.**

Results: **With the exception of gender and smoking history, all baseline patient characteristics correlated significantly with the diagnosis (IPF vs. NSIP). Median survival for the entire study group was 52.7 months. Univariate analysis showed poorer survival for the IPF group versus the NSIP group, and survival was significantly lower for older patients ($p<0.001$). Multivariate analysis confirmed the negative prognostic effect of age ($p<0.001$) on survival with a risk of death for older patients (≥66 years old) being more than 4 times higher than that for younger patients (<58 yr.). NYHA class and pulmonary artery pressure were also significant predictors of survival, and all patients with a sPAP ≤35-mm Hg were alive at the end of the follow-up period. There was a good correlation between Octreoscan uptake index and the diagnosis.**

Conclusion: **Diagnosis (IPF vs. NSIP), NYHA class, sPAP, and especially age appear to represent important prognostic indicators in the two most prevalent forms of idiopathic pulmonary fibrosis (IPF and NSIP). Lower Octreoscan uptake values were found in all patients with IPF, suggesting that this test may have a role as a new predictor of survival for differentiating IPF from NSIP.**

Key Words:

Idiopathic interstitial pneumonia, Idiopathic pulmonary fibrosis, Non-specific interstitial pneumonia, Pulmonary artery pressure, Age, Prognostic factors, Survival, Octreotide.

Introduction

Idiopathic pulmonary fibrosis (IPF), also known as idiopathic interstitial pneumonia (UIP), is a disorder of unknown cause[1]. This disorder is the most common subtype of idiopathic interstitial pneumonia (IIP) and is associated with the highest mortality rate. Patients with IPF have a poor prognosis with a median survival rate from diagnosis of 3-5 years, and an average loss of 7 years of life expectancy[2-5].

IPF is becoming an increasingly important respiratory illness in the UK with approximately 4000 new cases diagnosed each year. Equivalent figures for small cell lung cancer, mesothelioma, ovarian and kidney cancers are 6000, 1800, 5600, and 4300 respectively[3].

Studies on mortality in patients with IPF and non-specific interstitial pneumonia (NSIP) have examined a variety of prognostic factors. However, these studies are usually retrospective and often have short periods of observation[6].

The histological pattern can provide important prognostic information for patients with IPF, but this requires an invasive procedure under general anaesthesia, and patients tend to be elderly and have significant co-morbidities in addition to limited respiratory reserve. Hence, it is often not an option for some patients with severe disease to undergo surgical lung biopsy, and other non-invasive measures are needed to provide an accu-

Corresponding Author: Keith C. Meyer, MD; e-mail: kcm@medicine.wisc.edu

rate and confident diagnosis and guide prognosis and treatment. A comprehensive clinical evaluation can provide information that can identify patients who should undergo assessment for transplantation and also for determining when they should be considered in the natural history of their disease. Validation of prognostic factors could help to determine the right moment for lung transplantation and assist in the stratification of patients enrolled in clinical trials[2].

The aim of this prospective study was to enroll patients with IPF and NSIP and examine the impact of a number of markers on survival. The study population consisted of 78 patients referred to the University of Genoa and the Regional Hospital of Aosta who were followed between January 1995 and December 2006.

All diagnoses were based on histological data. The end-point was survival.

Methods

The study population consisted of 78 patients with UIP and NSIP who were referred to the Institute of Internal Medicine, University of Genoa, and the Regional Hospital of Aosta, between January 1995 and December 2006. The clinical and radiological features were consistent with a diagnosis of UIP or NSIP in accordance with the American Thoracic Society/ERS Criteria[7]. All patients underwent an open lung biopsy (OLB); 59 patients were diagnosed with UIP and 19 with NSIP. The lingula of the left upper lobe was chosen as a site for lung biopsy in all subjects since it was considered to be technically the easiest lung region to access. Furthermore, recent studies have shown that biopsies from the lingula provide a histological diagnosis compatible to tissue obtained from other sites[8-10]. OLB was not associated with postoperative complications in any of the patients who were followed through December 2006.

Baseline patients characteristics included: gender (male/female), age at diagnosis (divided into the following age groups: <58, 58-65, and ≥66), smoking habits, New York Heart Association classification of dyspnoea (NYHA: levels 0 to 4), systolic pulmonary artery pressure (sPAP) calculated in mmHg (with a cut-off of ≤35, >35-55, and >55 by Trans-Thoracic Doppler-Echocardiography [TTE])[11-13], Octreoscan uptake index (UI) (normal value ≤10)[14,15], and type of therapy.

The efficacy of treatment was evaluated by comparing disease progression and mortality rates in different treatment groups and in subgroups as defined by baseline histological patterns. All 59 patients with IPF were treated with prednisone and cyclophosphamide (CYC). Nine NSIP patients were treated with prednisone plus CYC, and 10 with prednisone alone. Baseline characteristics and comparison among diagnostic groups are listed in Table I.

The research protocol was approved by the Ethics Committee of the University of Genoa School of Medicine and all patients gave their informed consent beforehand.

Octreoscan Protocol

Somatostatin receptor scintigraphy (Octreoscan®-Mallinckrodt Medical, Petten, The Netherlands) whole-body scans were obtained at 4 and 24-hours after 5 mCi of [^{111}In-DTPA-D-Phe1]-Octreotide was administered to all patients. Thoracic images were obtained with single-photon emission computed tomography (SPECT) at the same intervals after injecting the tracer. Whole body acquisition included anterior and posterior views of head, thorax, abdomen, pelvis and legs. Scintigraphic images were acquired with a double-head camera (Prism 2000, Picker USA). The camera had a medium-energy parallel-hole collimator using a 256 × 1024 or a 256 × 256 matrix. Acquisition was performed using both ^{111}In photo peaks (173 and 247 KeV) and a 20% window. The SPECT acquisition was performed with a double Indium photo-peak, 60 projections over 360-° rotation and with a 64 × 64 matrix; slices were reconstructed after back projection, using a Butterworth filter. Octreoscan uptake index (U.I.) was defined as the ratio between normalized accumulation of the tracer in the lungs and thigh. According to this data, the normal value of U.I. at 24-h was fixed at ≤10 U.I. Substantially lower Octreoscan uptake values were found in all patients of this study with IPF.

Statistical Analysis

Comparisons of baseline characteristics were made using unpaired t-tests for continuous variables and Chi-squared test for proportions.

The statistical methodology applied in this study was that generally performed to analyse survival time data and the time endpoint of interest being time to death for non-survivors. Overall survival was calculated from the date of diagnosis until death or last follow-up update.

Table I. Patients characteristics according to histopathologic group (n = 78).

Characteristic	UIP cases (%)	NSIP cases (%)	*p*-value*
Gender			0.238
Male	34 (57.6)	8 (42.1)	
Female	25 (42.4)	11 (57.9)	
Age (year)			< 0.001
Mean ± SD	63.9 ± 9.5	51.3 ± 11.5	
Range	27-79	28 – 75	
Age group (tertiles)			< 0.001
< 58	9 (15.2)	14 (73.7)	
58-65	24 (40.7)	3 (15.8)	
≥ 66	26 (44.1)	2 (10.5)	
Smoking habits			0.231
Non smokers	40 (67.8)	10 (52.6)	
Smokers	19 (32.2)	9 (47.4)	
NYHA			0.002
Mild	14 (23.7)	13 (68.4) 1	
Moderate	29 (49.15)	4 (21.1)	
Severe[2]	16 (27.1)	2 (10.5)	
PAP			0.011
< 35	0 (0.0)	12 (63.2)	
35-54	20 (33.9)	6 (31.6)	
> = 55	39 (66.1)		
Octreoscan U.I.			< 0.001
≤ 10 (Normal)	59 (100.0)	0 (0.0)	
≥ 10 (Altered)	0 (0.0)	19 (100.0)	
Therapy			< 0.001
Prednisone	0 (0.0)	10 (53.6)	
Prednisone + CYC	59 (100.0)	9 (47.4)	
Total	**59 (100.0)**	**19 (100.0)**	

[1]One subject with negative score is included. [2]Two subjects with highly severe score are included. *Fisher's exact test for proportions T-test for means.

Because a preliminary descriptive analysis identified significant differences between the two diagnostic groups with regards to age, therapy and other prognostic factors (Table I), survival analysis was performed separately by diagnosis. Survival curves were generated using the Kaplan-Meier method, and differences in survival between groups were assessed by the log-rank test (LRT), (univariate analysis) and by using various parameters as categorical variables.

The simultaneous effect of each prognostic factor was assessed in a multivariate analysis using the Cox proportional hazard regression model and estimating hazard ratios (HR) with 95% confidence intervals (CI). The Cox proportional hazard model was constructed via backward elimination of variables from the full model. Analysis was carried out using the STATA package.

Results

All the study parameters were significantly correlated with the diagnosis, except for gender and smoking. Overall median survival was 52.7 months. Univariate analysis showed decreased survival rates for the IPF group versus patients with NSIP (Table II A and B) (Figure 1). Gender was of prognostic significance only for patients with NSIP. Smoking habits were similar in both IPF and NSIP patient groups. Survival was significantly decreased with increasing age (LRT $p<0.001$). Higher NYHA classes and sPAP >55 mmHg were predictors of worse prognosis. For the NSIP group, the univariate prognostic value of the analysed variables was quite similar to that observed among patients with IPF (i.e. age, NYHA and sPAP had a significant effect), but smoking had no effect on survival. Gender had a significant effect on survival for the NSIP group, but it

Table IIA. Univariate survival analysis of possible prognostic factors among UIP patients.

Variable	Categories	Events	Censored	Median survival (months)	Log-rank test	*p*-value
Gender	Female	15	10	51.8	1.4	0.2371
	Male	18	16	66.0		
Age (year)	< 58	3	6	–	11.29	0.0035
	58-65	10	14	73.0		
	≥ 66	20	6	27.4		
NYHA	Mild	1	13	–	35.2	< 0.001
	Moderate	16	13	48.7		
	Severe	16	0	15.3		
Smoking habits	Non smokers	23	17	52.7	0.61	0.4354
	Smokers	10	9	48.7		
PAP (echo)	35-55	1	19	–	29.67	< 0.001
	> 55	32	7	28.5		

did not influence survival for the IPF cohort. The histological pattern predicted survival for NSIP; no patients with the cellular subtype died during the observational period in contrast to those with a fibrotic subtype (Table II A and B).

Multivariate analysis confirmed the significant effect of age on prognosis for the entire patient cohort (LLR test $p<0.001$). The risk among older patients (≥ 66 years old) was more than 4 times that estimated among younger subjects (<58 years old) (Table III).

Patients with IPF were older, more likely to have a higher sPAP, and had lower Octreoscan UI scores than patients with NSIP (Figures 2, 3, 4). The correlation of the Octreoscan UI scores with diagnosis demonstrated the utility of the test in predicting the histological findings on surgical lung biopsies as well as prognosis.

Octreoscan UI and sPAP were negatively correlated ($R^2 = 0.189$, $p<0.01$) for the entire study population. Although the two diagnostic groups showed a distinctive Octreotide uptake (high for NSIP and low for UIP), a correlation between Octreoscan UI and sPAP was not found within each diagnostic subgroup ($R^2 = 0.0$, $p>0.1$ for both) (Figure 5).

Table IIB. Univariate survival analysis of possible prognostic factors among NSIP patients.

Variable	Categories	Events	Censored	Median survival (months)	Log-rank test	*p*-value
Gender	Female	1	10	48.7	4.04	0.0445
	Male	6	2			
Age (year)	< 58	3	11	99.4	10.87	0.0044
	58-65	2	1	46.6		
	≥ 66	2	0	38.6		
NYHA	Mild	1	12	–		
	Moderate	4	0	38.6		
	Severe	2	0	23.3	9.71	0.078
Smoking habits	Non smokers	3	7	–	0.3	0.5818
	Smokers	4	5	99.43		
PAP (echo)	< 35	0	1	–	8.68	0.0130
	35-55	1	11	–		
	> 55	6	0	38.6		
Therapy	Pred High dose	2	8	–	1.75	0.1859
	Pred + CYC	5	4	49.7		
Histological features	Cellular	0	8	–	6.23	0.0126
	Fibrous	7	11	48.7		

Table III. Multivariate analysis of prognostic factors.

Factors	Levels	Hazard Ratio	95% CI	
Age	< 58	1.00	(Ref.)	
	58-65	1.63	0.45	5.99
	≥ 66	**4.45**	**1.30**	**15.22**
Sex	Female	1.00	(Ref.)	
	Male	1.32	0.56	3.13
Smoking	Non smoker	1.00	(Ref.)	
	Smoker	0.56	0.21	1.50
NYHA	I	1.79	–	–
	II	0.38	0.16	0.88
	III-IV	1.00	(Ref.)	

Discussion

IPF is a lung disorder of unknown cause with a high mortality rate, especially when significant secondary pulmonary hypertension (PH) arises as a consequence of the disease process[5,15,16]. Several studies suggest that a confident diagnosis of IPF may be formulated by experienced clinicians on the basis of a consistent clinical presentation combined with a typical radiological pattern of the disease on high-resolution computed tomographic (HRCT) imaging[5,8,17], and patients with a typical clinical presentation and HRCT appearance do not need to be subjected to a surgical lung biopsy. However, Gross et al[18] and Wells et al[8] suggest that surgical lung biopsy may be required when patients are cared for by less experienced clinicians, when the diagnosis is uncertain, and when the clinical diagnosis appears to be inconsistent with IPF. Because the prognosis and treatment for IPF vs. NSIP is significantly different, especially with the cellular form of NSIP, performing a surgical lung biopsy continues to provide a means of attaining diagnostic certainty. Nevertheless, in a recent study by Raghu et al[19] investigating patients with UIP and NSIP, surgical lung biopsy could be performed in only a small percentage of cases (10%) because of advanced disease at the time of recruitment. This underscores the need for the development of non-invasive markers that correlate with specific ILD entities and can provide clinical diagnostic accuracy and obviate the need to proceed to surgical lung biopsy. Moreover, in the eventuality of lung transplantation, which has been shown to significantly prolong survival for IPF and progressive fibrotic NSIP[8], the disease

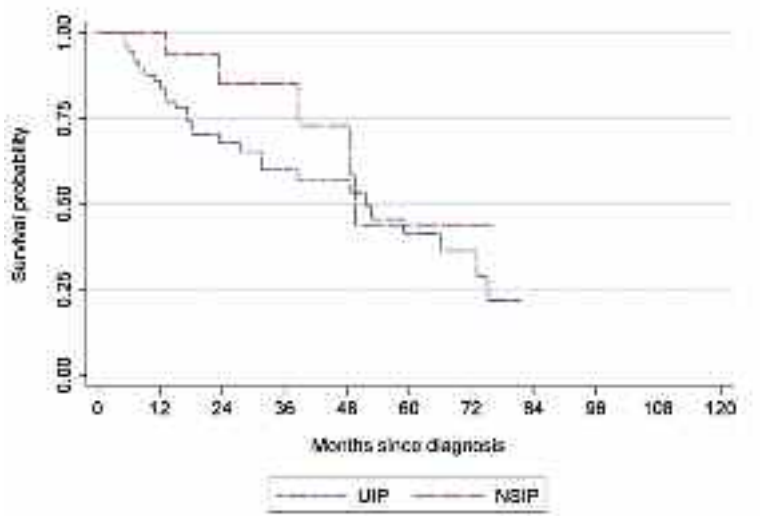

Figure 1. Kaplan-Meier estimates of survival for patients with IIP by diagnosis type.

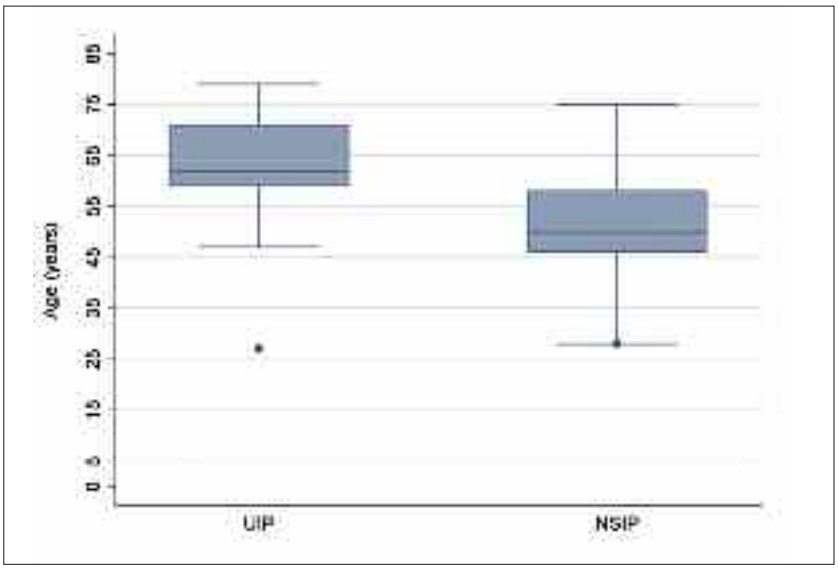

Figure 2. Correlation between age and histological diagnosis in UIP and NSIP patients.

course can nevertheless be quite variable and presents a challenge for predicting the optimal timing of lung transplantation. The use of prognostic factors may assist in decisions concerning the timing of lung transplantation.

Predicting survival via baseline clinical variables has proven challenging, and a number of parameters at the time of diagnosis have been proposed as predictors of worse survival in IPF[2,5,16]. Among the demographic and physiologic variables, patient age at the time of diagnosis appears to be a relatively consistent prognostic marker, but even this parameter can be relatively inaccurate[4] as a prognostic indicator. At present, there are no means for accurately predicting the clinical course for IPF[4], and little is known about survival prediction in NSIP.

We prospectively studied 78 patients who presented between January 1995 and December 2006 and underwent surgical lung biopsy to provide a histopathological diagnosis. Smoking habits and gender of patients in this cohort were of no prognostic value. The role of smoking and its influence on the course of IIP is controversial[20]. Greene et al[21] showed that survival among smokers was better than in non-smokers. The hypothesis that has been advanced to explain this finding was that smokers might have had an underlying obstructive

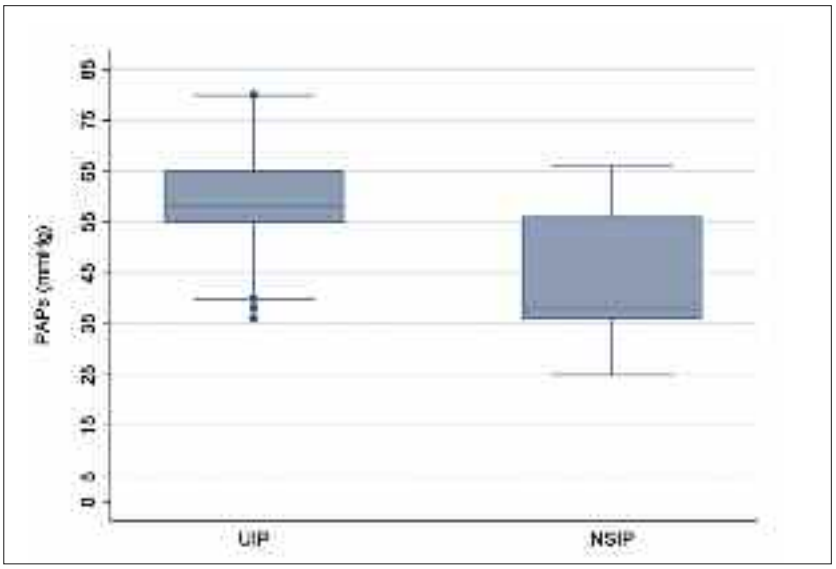

Figure 3. sPAP compared with histological diagnosis in UIP and NSIP patients.

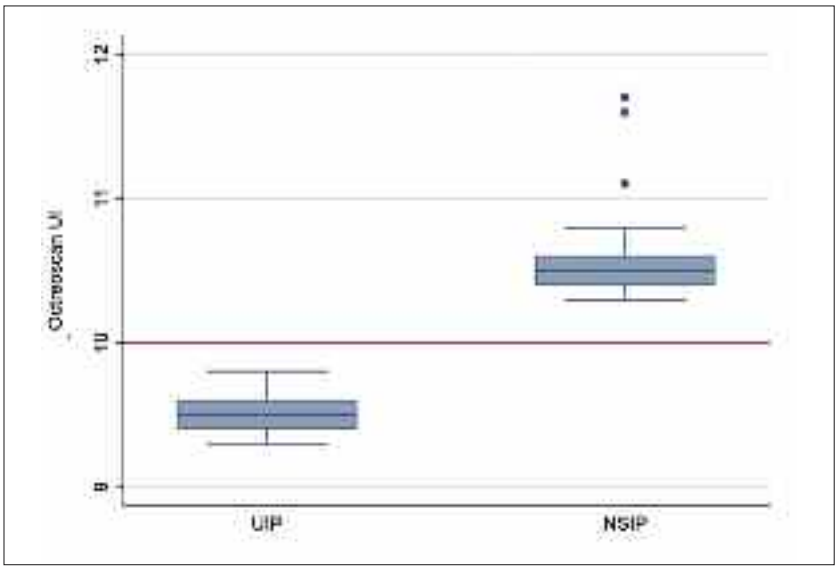

Figure 4. Correlation between Octreoscan UI and histological diagnosis in UIP and NSIP patients.

lung disease, which could have produced symptoms earlier, thereby permitting an identification of the disease in its earlier stages. Baumgartner et al[22] reported a strong correlation between smoking history and risk for IPF with an odds ratio of 2.3 (CI 95%, 1.3 to 3.8) for smokers. Although gender and smoking did not appear to influence survival, this was significantly decreased with increasing age (LRT p <0.001) that was the most significant predictor of survival. The risk of death among older patients (≥66 years old) was more than 4 times higher than that estimated among younger subjects (<58 years old).

The NYHA class, which reflects cardiac performance, and the sPAP, proved to be accurate, non-invasive markers for survival in-patients with IPF

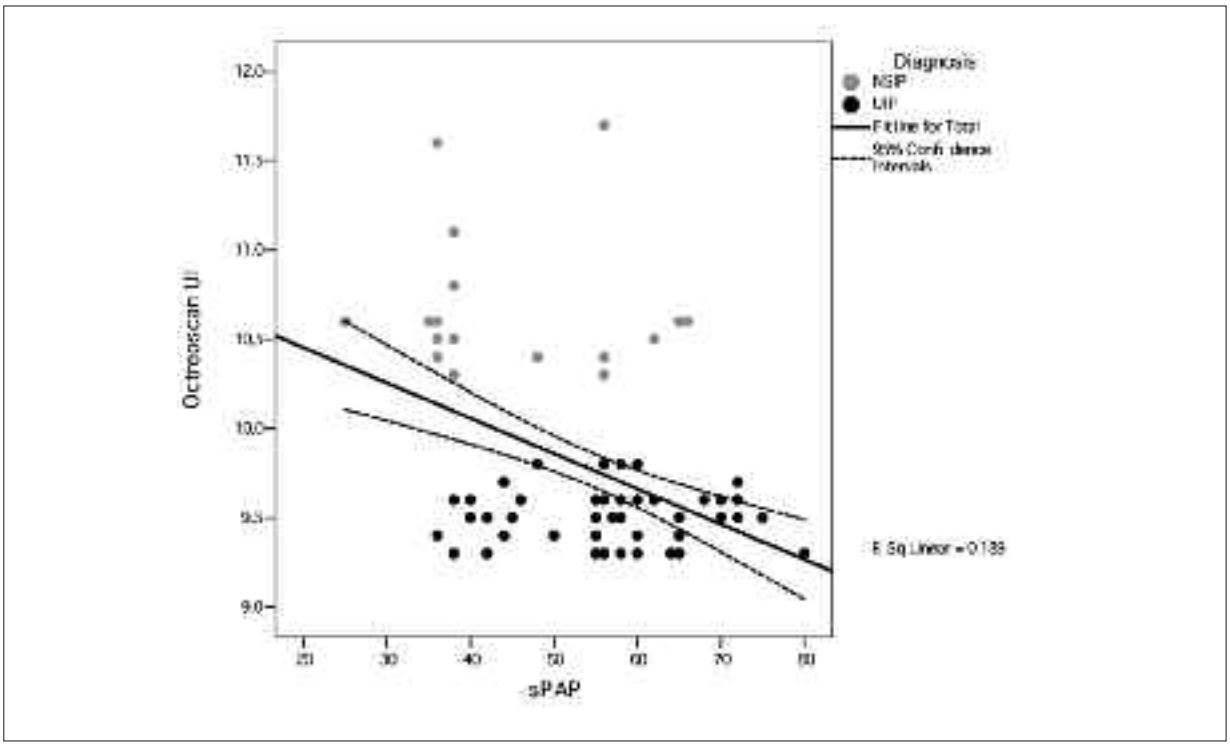

Figure 5. Correlation between Octreoscan UI and histological diagnosis in UIP and NSIP patients.

and NSIP. Higher NYHA classes were highly predictive of a worse prognosis (LRT $p<0.001$). In contrast, all patients with sPAP ≤35 mm Hg were alive at the end of the follow-up period. Lettieri et al[23] reported that PH was the only significant factor that they had identified as a prognostic predictor in their cohort of IPF patients. We found that more advanced age, higher NYHA classes and sPAP >55 mmHg were highly predictive of a worse prognosis in both IPF and NSIP.

Although right heart catheterization provides an accurate estimate of sPAP and other circulatory indexes, the procedure is expensive, invasive, and entails some risk. Doppler echocardiography is a non-invasive technique that has been suggested as an alternative to heart catheterization for the measurement of sPAP via cardiac catheterization[24-26], and transthoracic echocardiography can estimate sPAP with a sensitivity and specificity range of 0.79 to 1.0 and 0.6 to 0.98,

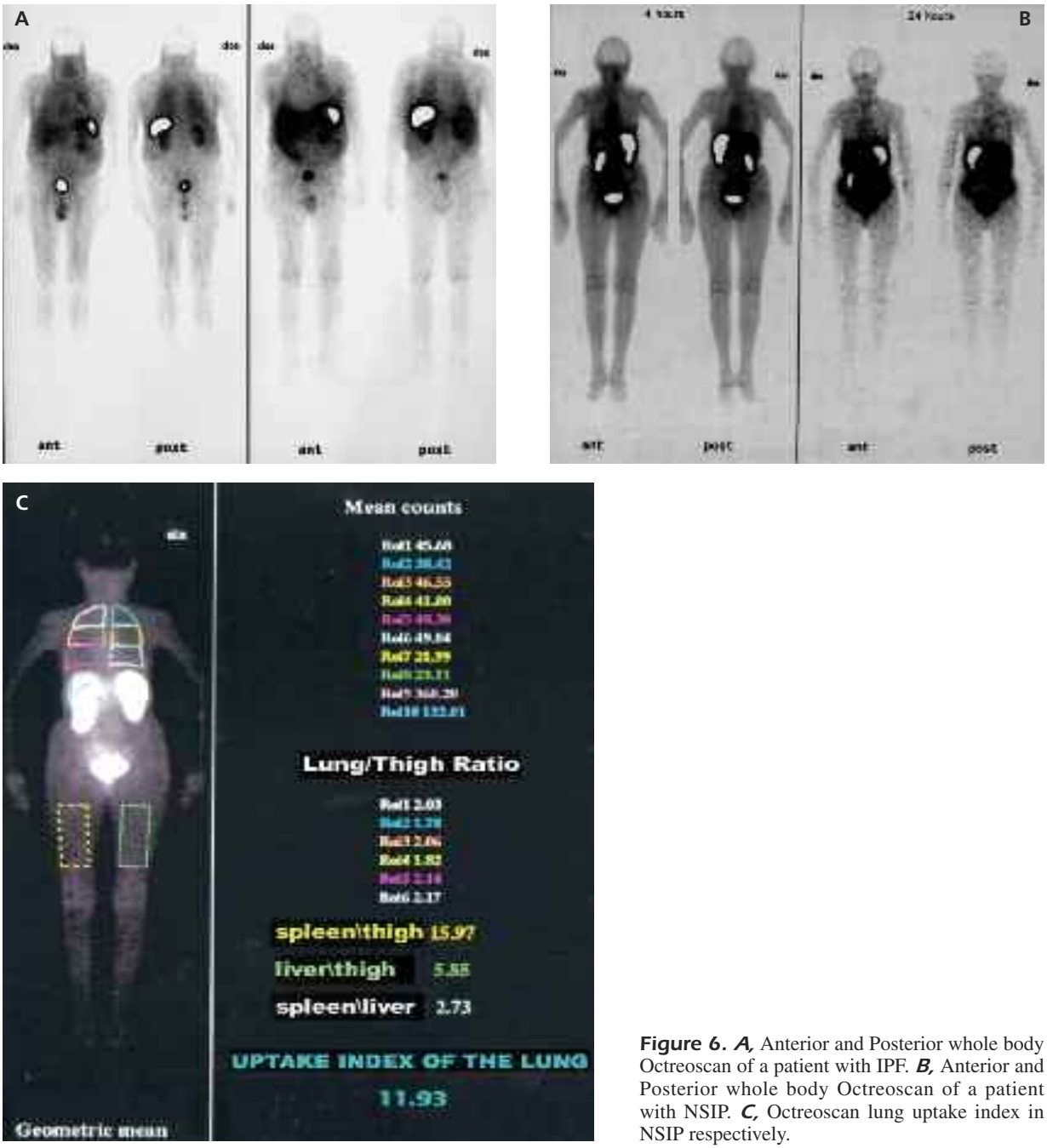

Figure 6. A, Anterior and Posterior whole body Octreoscan of a patient with IPF. ***B,*** Anterior and Posterior whole body Octreoscan of a patient with NSIP. ***C,*** Octreoscan lung uptake index in NSIP respectively.

respectively[27]. However, echocardiography may both over- and underestimates true sPAP as measured via cardiac catheterization[28].

Finally, we found an association of the Octreoscan UI with the diagnostic group, age, and sPAP. The finding of lower Octreoscan UI uptake in patients with IPF compared to NISP suggests that this technique may provide some assistance in the diagnosis and differentiation of these two forms of IIP.

This suggests that Octreoscan U.I. could be useful in differentiating IPF from NSIP (Figure 6, A, B and C), and in monitoring extra-thoracic sarcoidosis. This ancillary test could be a new and accurate method for identifying poor survival in IPF that is characterized by fibrosis, in comparison to NSIP and other interstitial lung diseases, characterized by a considerable lymphocytic infiltrate[14,15].

In summary, we found that age plays a significant role in survival and was the strongest prognostic factor in our cohort of patients with IIP. The risk of death among older patients (≥66 years old) was more than 4 times higher than that estimated among younger patients (<58 years old). The histological diagnosis, NYHA and sPAP also had a significant influence on prognosis. Octreoscan UI was strongly correlated with the histological diagnosis, and showed a lower uptake in all IPF patients, suggesting that this test may potentially be a predictor of survival in the evaluation of patients with IPF compared with NSIP group.

Contributors

RC, GB, and KCM participated in the conception of the study design. RC, GB, recruited patients and collected data, PP, PS, and KCM analysed the data. All authors participated in the interpretation of the results. PP, PS, and KCM drafted the manuscript and all authors contributed to the review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

References

1) Hunninghake GW, Schwartz MI. State of the art. Does current knowledge explain the pathogenesis of idiopathic pulmonary fibrosis? The Proceedings of the American Thoracic Society 2007; 4: 449-452.

2) Carbone R, Balleari E, Grosso M, Montanaro F, Bottino G, Ghio R. Predictors of mortality of idiopathic pulmonary fibrosis. Eur Rev Med Pharmacol Sci 2008; 12: 97-104.

3) G. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006; 61: 980-985.

4) Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis 2008; 26: 3-8.

5) Meyer KC, Raghu G. Idiopathic pulmonary fibrosis and associated pulmonary hypertension: genetics, pathobiology, diagnosis, and management. In: Baughman RP, Carbone RG, Bottino G. (eds.) Pulmonary Arterial Hypertension and Interstitial Lung Diseases. New York: Springer 2009; pp. 51-69.

6) Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD, Kitaichi M, Colby TV. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005; 171: 639-644.

7) American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: International Consensus Statement. Am J Respir Crit Care Med 2000; 161: 646-664.

8) Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63(Suppl V): v1-v58.

9) Checani V, Landreneau RJ, Shaikh SS. Open lung biopsy for diffuse infiltrative lung disease. Ann Thorac Surg 1992; 54: 296-300.

10) Temes RT, Joste NE, Allen NL, Crowell RE, Dox HA, Wernly JA. The lingula is appropriate site for lung biopsy. Ann Thorac Surg 2000; 69: 1016-1018.

11) Swigris JJ, Gould MK, Wilson SR. Health-related quality of life among patients with idiopathic pulmonary fibrosis. Chest 2005; 127: 284-294.

12) Olschewski H, Werner S. Diagnosis and classification according to the WHO conference on PPH in Evian (1998). In: Olschewski H, Werner S editors. Pulmonary Hypertension. Pathophysiology, diagnosis, treatment and development of a pulmonary-selective therapy. Bremen: UNI-MED 2002; 4: 40-50.

13) Carbone R, Montanaro F, Ghio R, Monselise A, Baughman R. Cardiac performance in the prognosis of interstitial lung diseases. Sarcoidosis Vascu Diffuse Lung Dis 2006; 23: 237.

14) Carbone R, Filiberti R, Grosso M, Paredi P, Peano L, Cantalupi D, Villa G, Monselise A, Bottino G, Shah P. Octreoscan perspectives in sarcoidosis and idiopathic interstitial pneumonia. Eur Rev Med Pharmacol Sci 2003: 7: 97-105.

15) Carbone RG, Monselise A, Bottino G. Pulmonary hypertension in interstitial lung disease. In: Baughman RP, Carbone RG, Bottino G. (eds.) Pulmonary Arterial Hypertension and Interstitial Lung Diseases. New York: Springer 2009; pp. 13-50.

16) Martinez FJ. Pulmonary hypertension in idiopathic pulmonary fibrosis. In: Baughman RP, Carbone RG, Bottino G. (eds.) Pulmonary Arterial Hypertension and Interstitial Lung Diseases. New York: Springer 2009; pp. 177-194.

17) Flaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004; 170: 904-910.

18) Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med 2001; 345: 517-525.

19) Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006; 174: 810-816.

20) Martinez FJ. Idiopathic interstitial pneumonias: usual interstitial pneumonia versus nonspecific interstitial pneumonia. Proc Am Thorac Soc 2006; 3: 81-95.

21) Greene KE, King TE Jr, Kuroki Y, Bucher-Bartelson B, Hunninghake GW, Newman LS, Nagae H, Mason RJ. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. Eur Respir J 2002; 19: 439-446.

22) Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997, 155: 242-248

23) Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-752.

24) Nadrous IIF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med 2005; 172: 488-493.

25) Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, Mishima M, Kitaichi M, Izumi T. Significance of pulmonary arterial and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 2007; 131: 650-656.

26) McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation 2001; 104: 2797-2802.

27) Ryu JH, Krowka MJ, Pellikka PA, Swanson KL, McGoon MD. Pulmonary hypertension in patients with interstitial lung diseases. Mayo Clin Proc 2007; 82: 342-350.

28) Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Ecocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003; 167: 735-740.

Acknowledgements

We thank Dr. Dario Cantalupi and Dr. Assaf Monselise for additional suggestions for this study.